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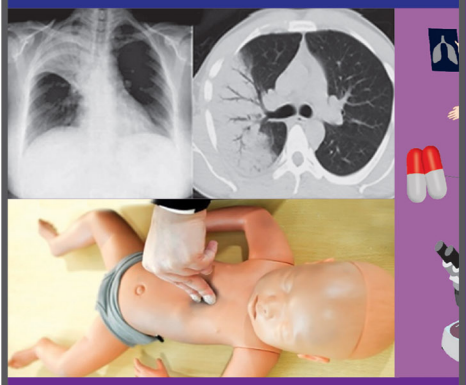

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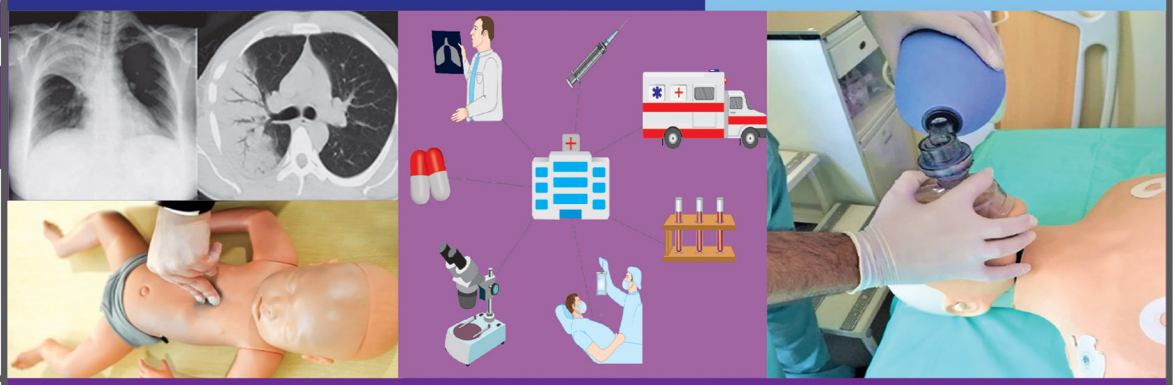

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Volume 1

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Dedicated to

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PREFACE

"*utiṣṭhata* | *jāgrata* | *prāpya varānnibodhata* |
Arise. Awake. And stop not till the goal is reached."

— Swami Vivekananda

We have a passion for improving patient care. Emergency care is all about dealing emergencies in time-bound manner and the emergency department is a place where emergency physician manages most diverse acute conditions in the hospital. On the basis of the typical clinical clues' emergency physician can use accurate diagnostic tools, treatment pathways, and prognostic prediction. The practice of "emergency medicine" continues to evolve, bringing greater expectations of the physicians who provide field care in interhospital shifting by ambulance and medical oversight. The advent of postgraduation program in "emergency medicine", and the continuous broadening of the clinical practice of "emergency medicine" has made the formal study of the art and practice even more essential than ever before. Now we have to show our never-ending commitment to improve patient care across the entire scope of our practice as emergency physicians. The emergency physicians acquiring their knowledge and skills very rapidly to improve the patient care and show their worthiness. We have achieved many milestones along the road of development of the emergency medicine specialty. Our journey starts with Textbook of Emergency and Trauma Care, 1st edition with superb mentors who instilled in us a drive to become excellent clinicians and educators. Now, 2nd edition is updated with "250 Chapters in 22 Sections", extremely useful for emergency physicians, intensivists, family physicians, general practitioners, nurse practitioners, and physician assistants, where clinical clues significantly guide, improve, and expedite diagnosis as well as treatment. It is our most sincere hope that this text serves you well on your journey, wherever the practice of "emergency medicine" may take you.

We thank contributors and readers who have helped to make this 2nd edition possible.

No star is too distant to approach
No mountain too high to climb
No dream is too far to make reality
No quest too difficult to fulfil
No goal is too impossible to achieve
For those who have courage to try several times
So, meet the life challanges with determination
Each time each hour each day
To come out winning honest rewards!!

Devendra Richhariya
Bhawana Sharma

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Section 1: Basic Concepts of Emergency Medicine

1
CHAPTER

Essential Qualities for Emergency Physician

K Hari Prasad

INTRODUCTION

I work in a hospital and have been in and out of emergency most of the times. I guess I have spent most of the part of my career in emergency units. When you are serving the patients, you do not get the time and opportunity most of the times to sit back and think about the scenario. But, if you step back and just stay around in the department for an hour, you can observe so much that would be fulfilling for an almost lifetime experience (provided you do not get scared of witnessing emergency cases and blood at times).

The units are busy 24/7—sometimes more and sometimes less. Staff is always running around dealing with patients' requirements; then an additional pressure of families/friends to continuously update them; police at times; and many other relevant stakeholders. The staff performing to the best of their capabilities to serve and save everyone, relieve everyone of his/her pain through the most compassionate ways.

At all times, it would be apt to say that emergency is the door of any hospital. It brings in patients for the hospitals, so that they could perform their duties righteously. If we consider the other side, that is of the patients, it is right as well. No one wants to come to the hospital by themselves unless it is really called for. Most of the times, we are forced to visit, because it includes an end to our miseries, sufferings, and pain of ours or one of our loved ones. In such a situation, when you are really in need of something, you expect that to be provided to you in the best manner—in the most courteous and efficient way, as expected and deserved by you.

Going to an emergency department of any hospital is never by invitation. But, when we visit someone's home, we expect them to be welcoming us. The first point of contact in any emergency department would ideally be an emergency physician or a nurse. Let us start talking about the emergency physician here first. Emergency medicine is relatively a very new branch of superspecialized medicine that involves training of young doctors to be a "pro" at treating patients under pressure.

It is a job that is under stress and immense pressure of family/friends of patients and too many hopes/expectations of people are set on them and a lot many times—it is also about dealing with difficult situations. Till recent years, we did not have specialized doctors with appropriate skill sets to work in these scenarios. This does not mean emergency units were not running or patients were not treated, but it means that we did not focus enough in this area to train doctors with the right and most fitting competencies.

In India, it is a rapidly progressing field and today many hospitals have specialized doctors in emergency units. They cover the unit 24/7 and provide their services. For such scenarios, hence, they must fit in the work profile and they need to have clarity on expectations—from the patients, family members, colleagues, legal teams, hospital management, and the community. They need to deal with different levels of emotions that each one of them may display in different situations.

QUALITIES OF GOOD EMERGENCY PHYSICIAN

Being the emergency physician is not easy because of too much stressful work, paperwork, irritated patient, and too much competition. So, emergency physician must have professional qualities and should be calm, approachable, passionate, knowledgeable, enthusiastic leader, reliable mentor, efficient learner, and facilitator. Few qualities are described below.

Multitasking

Emergency physician needs to have unique skill sets, multitasking, and the attitude to serve and take up challenges. Every patient that walks into our doors is a challenge many a times—some physically, some emotionally, or some mentally. They may be brought dead, may come in with heart attacks or strokes, road traffic accidents, or even for fever, cough, cold, mild cuts, etc. Everyone's requirements are not the same and so multitasking is the first skill that is required besides the right education on emergency medicine.

Be Efficient and A Team Leader

As said earlier, this is a skill to work under pressure and sometimes with unexpected number of patients (e.g., epidemic or disasters). Some days/nights are worse for them than the others. The laid down policies and guidelines of the department should help him to work more efficiently—the way

staffing is done, resource allocation to name a few. Emergency physician is the chief executive officer (CEO) of the "hospital" (emergency unit) in the hospital. He is responsible to lead the team of his staff members, be prepared and deal with all situations, good clinical outcomes, patient satisfaction, and an administrator. He needs to play the role of being an "example" for his team to look up to him.

Communicator

Communication skills are required in every profession and every work that one does (**Fig. 1**). But here, we are talking about communication being a very different kind of a skill set. It includes being able to communicate happiness about the delivery of a child or safety of the patient. It includes communicating about taking up the next course of action for patients about admission/surgery/follow-up, etc. It could be about breaking bad news about death, bad outcomes, or the actual patient condition that most of the times people are not prepared to listen and accept. The preparation for any such conversation is completely different from one another. Some relatives/family members/patients can understand the situation/outcome, some are irate, some unhappy and some angry. Emergency physician has obviously to deal with all types of these, especially when such things happen in the middle of the night or odd hours and when there is less dependency on others in the hospital.

Compassionate and Empathetic

They need to be compassionate and understand the patient/family's situation—their concern, what they must be going through and then, communicate accordingly. It is said unless you do not fit yourself in their shoes, you do not get the emotion what they must be going through. On the other side, it is also important for him to be firm to be able to handle situations. At the same time, they also need to keep their emotions under control. There are times, due to stressful long hours, they may feel frustrated, tired, and irritated, but these are the testing and most vulnerable times. For a doctor, the patient may be one of many who may have walked-in during his shift, but for that patient or his family, he is the only one. It is a very normal emotion that we face and I also faced many a times, but controlling them is what the best, I learnt over time. Some patients are very impatient and being empathetic helps them to respond even better.

Professional, Confident, and Bold Enough to Take Decisions

Professionalism is expected without even an iota of a doubt (**Fig. 2**). As said earlier, that emergency is the door to the hospital and emergency physician is the first member whom the patient/family meets. Their act of professionalism says a lot and spreads very easily through the word of mouth. Displaying confidence as the head of the family or head of the hospital in that scenario is again very important. The complete body language, behavior, and courage to take decisions in the best interest of the patients are important skills for an emergency physician. Respect must be earned and it could only be earned by our actions and behavior—not by just being there and wearing a white coat with an emergency doctor tag on it.

Work Ethics

No matter what goes on in our personal life or our environment, once I used to wear my white coat in the department and take charge, everything used to take a back seat. I personally feel, this is what we need to do as physicians always. In that situation, only patient is important and just work with a single mind toward good clinical outcomes and patient satisfaction (**Table 1**).

Connecting the Dots

Knowledge of the diseases, clinical pathways, and hospital policies is the most basic required skill set obviously. This also means using the right "mix and match" of knowledge to fit into that patient's condition—to see, evaluate, order the right tests, prescribe, and diagnose it right. Here, attention to details

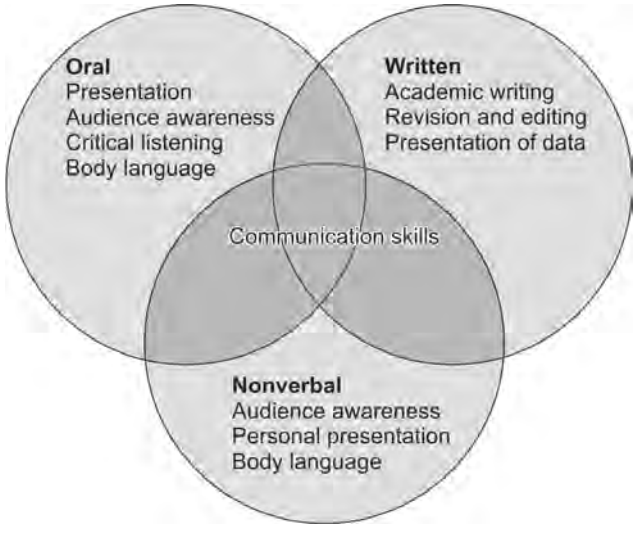

FIG. 1: Components of the communication skills.

FIG. 2: Various aspects of professionalism.

TABLE 1: Do's and don'ts for emergency physician.

Emergency physician should perform	*Emergency physician should avoid*
• Attend and manage all types of emergencies • State authorities should be informed in case of epidemic and fatal communicable diseases • Attend court for medicolegal case	• Advertising • Association with drug manufacturer • Association with patient • Adultery • Addiction, alcohol consumption on duty

and asking the right sets of questions are very important. One simple data point, if missed, may take the complete treatment in a different direction. Connecting the dots and in the right way is the key and this comes with focus, experience, and a positive mind set.

Listen! Listen! Listen!

Keep your eyes and ears open—listen to everything that the patient/family says (**Fig. 3**). They give you the most important piece of information that may help you to move on the first course of action in that short time, when lives matter and time could be controlling that.

Grow and Continue to Learn

Emergency physicians should keep them abreast of the changes in the field of medicine continuously. They need to learn about new technologies, new processes and systems, newer drugs, research, and new clinical guidelines or pathways (**Fig. 4**).

Disaster Management

These are the types of situations that generally emergency physicians face being in the department. Any major external or internal disasters when happen, they automatically play the role of the leader. Handling multiple patients at the same time, managing resources (staffing, equipment, medications, food, water, utilities, etc.), managing the community, press/media, and communicating the right and apt information become challenging.

OTHER BASIC SKILLS

Some of the other basic skills that they are expected to learn and demonstrate are:

- Ability to triage patients as per the most evidence-based guidelines in the time as expected for effective care and good clinical outcomes.
- Being able to obtain history and perform a physical examination. This should also help him to decide the next course of action. You may receive patients with simpler clinical conditions to children who have been abused or drugged or road traffic accidents. The ability to provide accurate care under these circumstances becomes crucial.
- Knowledge of resuscitation and continuously update themselves (at least every 2 years or as and when guidelines change) on basic life support and advanced forms of life support for neonates, pediatrics, adults, and trauma victims.
- He should be able to make an initial diagnosis to consider different investigations that may be required and then interpret the outcomes to establish the plan of care with right measurable goals to achieve.
- Based on the trainings and competencies, hospital may privilege him for the basic emergency procedures that may be required to be done in the department itself, e.g., lumbar puncture, bone marrow aspiration, biopsy, etc.
- Should know the next steps in every situation—outpatient (OP) discharge, brought dead, medicolegal case, admission to ward/intensive care unit (ICU), completing diagnosis, being taken for a surgery/procedure, etc.
- Good documentation is what stands out always. The more details are mentioned, the better care could be given to the patient. It is right to believe that what is not documented is not done.
- Respect patient privacy and confidentiality always.
- Being sensitive to patient's culture, age, gender, and spiritual requirements.

FIG. 3: Careful listening for key information.

FIG. 4: Continuous clinical update by emergency physician.

SUMMARY

Emergency medicine is a relatively new academic field in India. Emergency is a situation or condition of any life-threatening consequences requiring immediate intervention. As the medical field is an ever-growing field, and emergency medicine is rapidly progressing, a good emergency physician is a need of Indian healthcare. A dedicated emergency medicine faculty is the key factor in developing emergency care workforce. Good emergency faculty should be expert in resuscitation and able to treat each disease of almost every specialty.

"I have gone through this and I see them in my hospitals daily, it is not an easy task. Doctors are made by God especially to serve the mankind, but I believe emergency doctors are especially crafted by God to screen and be at the first level to save lives."

—Dr K Hari Prasad

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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2 CHAPTER

Designing and Staffing of Emergency Department

Saleh Fares, Omar Ghazanfar

INTRODUCTION

The emergency department (ED) plays a central role in providing vital access to acute healthcare to the public. An ED is also an important gateway to many inpatient and outpatient services offered by the hospital. In addition, a major proportion of acute admissions to inpatient beds are via ED. The major characteristics which make the ED unique include:

- Emerging and novel models of ED care and design
- Varying levels and types of staffing models
- Undifferentiated case mix including critical and life-threatening illnesses, major trauma, dependent on the hospital status, and a wide spectrum of age groups from pediatrics to geriatrics.
- The presence of patients and relatives with varying levels of anxiety
- High patient turnover
- Variable admission and discharge pathways
- Medical services provided largely by specialist emergency physicians, supported by junior doctors, and allied nursing and other health professionals.

CHALLENGES FOR EMERGENCY DEPARTMENT IN INDIA

- There is mismatch between the capacity of healthcare facility and population of that area resulting in overcrowding at the limited number of available facilities.
- Lack of funds or poor planning leads to poor Infrastructure at the existing healthcare facilities.
- Unawareness of National Standards and Guidelines leads to inadequately equipped healthcare facilities.
- Inadequately skilled manpower—suboptimal quality care at the existing health facilities
- Unawareness of standard operating procedures regarding managing a patient
- Lack of quality care as nonaccountability and lack of monitoring mechanisms

EMERGENCY DEPARTMENT FUNCTION

The primary function of the ED is to receive, resuscitate, and provide acute healthcare to patients. It should also be equipped to handle disasters and mass causalities. Varied patient population requiring varying medical inputs includes, but the list is not exhaustive: Major trauma, geriatrics, pediatrics, mental health disorders, patients with abuse (any age group), custodial patients, patients with infectious diseases, and mass causalities (to include chemical, biological, and radiological contaminants).

REQUIREMENTS FOR CREATING NEW INFRASTRUCTURE AS EMERGENCY DEPARTMENT

There are a number of factors which must be considered, when structuring an ED. This will include both staff requirements and patient needs and demographics. The needs of these varying patient groups can be addressed through, for example, suitably placed furniture and art, adequate access to information and communications technology, and appropriately designed rooms and equipment that are suitable for use by particular patient population.

While the needs of patients and relatives are highly important, it is also necessary that a healthy working environment for staff is facilitated by the design of the ED. These needs can be catered to through the use of well-placed staff bases, staff rooms large enough to accommodate the maximum number of possible users, and ensuring that staff facilities are located separately from clinical areas, in order to promote effective breaks from patient care.

Designing of an efficient ED should look at certain elements, which will aim to make the department efficient, reliable, and cost-effective. The design needs to be practical and reflect the needs of the professionals who run the department and treat patients with varied needs and requirements.

The structure and design should reflect the spatial relationships between staff and patients and improve the flow and continuity of care from the front door of the hospital to admission or discharge of patients. It should be kept in mind that the ED functioning is very fluid with ebb and flow of patients changing during a 24-hour/7-day week, and flexibility is needed to enable reallocation of treatment spaces as required.

The ED should aim to create a healthy environment through proper application of occupational health standards to ensure a safe working environment. The well-being of patients and staff should be an important consideration through proper and safe use of design and space.

GENERAL CONSIDERATIONS FOR DESIGNING EMERGENCY DEPARTMENT

- Emergency department design should be smooth, rapidly accessible to from all areas with a minimum cross traffic.
- The resuscitation area, triaging areas, and treatment areas should be close enough, as staff may require to rush from one place to another.
- Visitor and patient access to all areas should not traverse through clinical areas.
- Patient protection of privacy should be considered while designing at the same time, the need for observation of patients by staff should also be considered.
- Emergency department design should accommodate radiological imaging, laboratory, and other diagnostic services of hospital with the close proximity of the ED.
- Appropriate signs consistent with the applicable regulations and laws should indicate the direction of the accident and ED from major thorough fares along with broad outline of services available.
- Safety of the ED staff, patients, and visitors must be top priorities while designing and implementation.
- The entrances of the ED should be clearly visible from all possible sides and should be located on the ground floor for easy accessibility.
- It should be close to public transport.
- Adequate bilingual signage should be available to ensure ease-of-way finding.
- Illuminated signage is required for some signs to ensure visibility at night. The use of graphic and character display "EMERGENCY" is recommended.
- Car parking should be well-lit and available exclusively for patients and their relatives and staff should be close to the entrance.
- Undercover parking should be available for appropriate number of ambulances. This will be determined by case load.

OTHER REQUIREMENTS

- *Bed spacing*: In the acute treatment area, there should be at least 10 feet of clear floor space between beds.
- *Lighting*: Clinical area should have exposure to daylight, helpful in minimizing the disorientation in patient as well as in staff also. Provision of high standard focused examination light should be done in all treatment areas. Each examination light should have a power output of 30,000 lux, illuminate a field size of at least 150 mm and be of robust construction.
- *Sound control*: Designed so as to minimize the transmission of sound between adjacent treatment areas.
- *Service panels*: Service panels should be minimally equipped as follows:
  - Centralized oxygen outlet
  - Centralized suction outlet
  - Sockets
  - *Physiological monitors*: Each acute treatment area bed should have access to a physiological monitor which should include a minimum of:
    - Electrocardiogram (ECG)
    - Noninvasive blood pressure (NIBP)
    - Temperature
    - Oxygen saturation (SpO_2)
- *Cabling*: Adequate cabling should be provided to ensure availability of sockets to all clinical and nonclinical areas. Cabling of telephone and computers should be nearer to workplace, where these are necessary.
- *Medical gases*: All patient care areas should be internally piped for medical gases.
- *Doors*: All doors measurement is appropriate enough to accommodate a full hospital bed.
- *Corridors*: Adequate width of corridors is necessary, allows the cross passage of two hospital beds or a hospital bed and linen trolley without difficulty. There should be adequate space for trolleys to enter or exit any of the consulting rooms and to be turned around. Storage of equipment, linen, waste, or patients should not be kept in standard corridors.
- *Air conditioning*: Infectious disease isolation room in ED should have special flow and filtering requirements—heating, ventilation, and air conditioning (HVAC) system.
- *Information/Communications support*: Telecommunications and information technology is one of the important parts of ED. All staff stations and all consultation areas should be equipped with telephones, intercoms, and public address system that can reach all areas of the ED. Public telephones should be available in the waiting area. Direct communication should be installed between the ambulance service and the ED.
- *Patient call facilities*: All patient care areas including toilets and bathrooms require individual patient call bell facilities. Emergency department bed spaces should be equipped with call buttons, easily accessible to patient on the ED trolley.
- *Handwashing facilities*: Adequate handwashing facilities should be available. Hands free taps should be available in clinical areas. Treatment area should be equipped with basins for handwashing at a ratio of 1:8 in observation area and at the ratio of 1:1 for every procedure/consulting room/triage/isolation area. Standard infection prevention precautions should be taken and sufficient quantities of personal protective equipment (PPE) should be present for all the staffs.
- *Emergency power*: Backup emergency power must be available to all lights, ventilators, and computer terminals in the resuscitation and treatment/observation areas of the department. All areas should be equipped within emergency lighting. In the event of a total power failure, sufficient space and power points should be available to enable a backup system.
- *Wall finish*: Hospital beds, ambulance trolleys, and wheelchairs may cause damage to walls, so all wall surfaces

in areas, which may come into contact with mobile equipment, should be reinforced.
- *Floor covering*: The floor covering of all patient-care areas and corridors should have following features:
  - Nonslip surface
  - Impermeable to water and body fluids
  - Durable
  - Easy to clean
- *Wall clocks*: Clinical areas and waiting areas should be equipped with wall clocks and should be visible to all patients. Time clocks are desirable in the resuscitation, procedure, and plaster rooms. Time displayed in all areas and on computers must be synchronized.

PATIENT FLOW

The ED has a wide case mix and varying volume of patients presenting with various pathologies and different part of the day and the week. Many different models have been used successfully internationally taking into account both staff and patients to aid the flow of care through the emergency service. No single system works for all hospitals as this is largely dependent on patient needs and adequate and safe staffing. Some of the concepts of patient care that affect flow within the ED include:
- *Medical-led triage with senior nursing staff*: Triage done by senior nurse to make definitive investigations and decision making on the patient's arrival to the ED.
- *Traditional models of care* which filtered patients on the basis of their primary complaints. This was a medical-surgical model, which still exists in some healthcare systems.
- *Rapid assessment team (RAT) for critically ill patients*: Senior doctor, nursing staff, administrative staff, phlebotomist, and scribe.

This team may either be mobile within the department or be stationed in specific assessment areas and can be mobilized as per needs and requirements.

DEDICATED AREA WITHIN EMERGENCY DEPARTMENT

As part of the structural design of an ED, a variety of considerations needs to be taken into account. These include dedicated clinical areas for ED staff, access to the main hospital, multidisciplinary team areas, staff facilities, and areas for special and specific clinical requirements. These are summarized in **Table 1**. Patient and staff experience is essential in designing and developing an ED and various factors need to be taken into account to facilitate this. This is summarized in **Table 2**.

NEW CONCEPTS IN EMERGENCY DEPARTMENT DESIGN

The breathing emergency department: Studies conducted to determine the benchmark size for an ED patient unit indicate that smaller EDs with fewer visits function more efficiently and have higher patient satisfaction rates than larger EDs. These studies suggest that the functional ED patient unit should be of 13 beds to enable better management of patients and tasks. However, as patient visits increase, the majority of EDs increase their footprint and number of beds, decreasing efficiency. There are a few models designed to divide the department into smaller, more manageable units, including *the fast-track approach* (focused on lower acuity flow, discussed below). This design divides an ED into two separate departments based on patient acuity. Another option to help reduce unit size *is the breathing emergency department*, which subdivides the department into smaller units and opens and closes them based on the cyclical cycle of peak patient visit times.

STAFFING MODEL FOR EMERGENCY DEPARTMENT

Medical and practitioner staffing in emergency departments: Correct staffing is the key to delivering timely and high-quality care in the ED. There is no one-size-fits-all staffing model for ED. Intelligent staffing models will also allow for rota patterns that are realistic and sustainable and will involve the use of clinicians from a range of professional backgrounds. A tiered approach to staffing is, therefore, necessary with consideration of sustainability for each tier. Correct staffing in EDs results in safer care with improved quality, better performance, increased efficiency, and happy and resilient workforce.

How to staff an emergency department? Staffing an ED is a complex and demanding job and requires input from a variety of different internal and external factors. In essence, staffing is a function of: *(1) Capacity, (2) Capability, (3) Sustainable working, and (4) Resilience.*

Capacity: Required capacity can be calculated on the basis of predicted demand. Demand needs to be considered in terms of volume, case mix, and segregated work streams. Capacity calculations need to be considered. EDs should be staffed to meet variation in demand, aiming to cope with normal demand variation.

Capability: A capable system does what it is supposed to do. This essentially means that the right number of clinicians with the appropriate skill mix is needed at the right time. Senior and experienced clinicians generally more efficient while junior clinicians generate additional work for senior colleagues. There is a natural desire to specify the productivity of different groups of clinicians. The best estimate of local productivity is local data (**Table 3**).

Tier 1 clinicians (interns) or clinicians with enhanced supervision requirements, e.g., doctors in difficulty may have minimal or even negative productivity due to the senior input required on cases they see. *Tier 2 doctors* (junior residents/rotating doctors) are generally thought to see about one patient per hour, perhaps slightly more on minors, although this depends on the case mix seen. A consultant *(Tier 5)*, supervising a department, may see no new patients in order to maximize their efficacy in the command and control role and to avoid potentially disadvantaging patients, they do see through interruptions and multitasking. The productivity of the remaining groups (senior residents and other senior ED physicians) will vary between about 1 and 3 patients per hour, depending on variables such as experience, professional development, case mix, the effectiveness of efforts to maximize workforce efficiency, the requirement to move between physical areas, procedures undertaken, and supervisory demands.

TABLE 1: The dedicated areas within an emergency department.

Hospital access areas	*Clinical areas*	*Multidisciplinary team areas*	*Special areas*	*Administrative areas*
• Proximity to main entrance • Streamlined access to investigative areas • Close or cohabited areas for other acute services • Helipad • Angiography • HDU/CCU/ICU • Operating theaters • Clear route to wards • Outpatient access • Communication hub • Areas for disaster management	• Entrance, waiting room, and reception area • Triage • Resuscitation area • Mental health assessment area Clinical consultation area to include fast track, subacute minors or ambulatory care • Acute treatment area • Investigative areas—X-ray, short stay, investigation room, etc.	• Equipment storage • Refreshment areas • Physiotherapy, OT assessment area • Staff and amenities areas	• Eye/ENT/gynecology/plaster rooms • Storage areas • Disposal room • Medication room • Office space • Staff room • Ambulance offloading area • Decontamination area • Ambulatory/Urgent care	• Storage • Drug preparation room • Clean and dirty utility • Teaching and research areas • Patient amenities • Toilets

(CCU: cardiac care unit; ENT: ear, nose, and throat; HDU: high-dependency unit; ICU: intensive care unit; OT: operation theater)

TABLE 2: Factors to consider in the design to improve staff and patients experience in the emergency department.

Staff experience	*Patient experience*
• Comfortable seating areas at staff bases and bedside • Easy and ready access to equipment • Efficient workflow design with good access to all work space areas • Design which limits overcrowding • Confidential discussion rooms • Air quality with ventilation control • Good staff rest facilities with appropriate amenities and storage facilities • Overnight facilities for staff	• Clear signs for pathways and facilities • Information about ED process to include triage and/or waiting times • Multilingual signs • Public health educations leaflets • Friendly staff • Security personnel • Clean and well presented • Information desks • Appropriate waiting areas ideally with color coding • Availability of refreshments

(ED: emergency department)

All EDs require a senior doctor, immediately available at all times. Larger departments will require several senior doctors on duty to manage the supervisory workload, to see the sickest and the most complex patients, and to undertake dedicated tasks such as rapid assessment. Larger departments may be able to develop specific areas led predominantly by *Tier 2* or *Tier 3* clinicians.

Sustainable working and sustainable staffing: There are significant concerns around attrition rate in EDs. Sustainable working requires attention to specific details taking into account and work-life balance due to the antisocial nature of shift work. These include the following:

- Workload and work intensity, when on duty
- A balanced mix of clinical, nonclinical, and academic activity, particularly for senior clinicians
- Professional development
- Physiological and physical limitations of staff (e.g., age, chronic illness, or disability)
- Compensation for late night/overnight working

Rotas for individual tiers can be combined provided attention is paid to skill-mix. Sustainable working leads to more effective working. Tired or burned-out staffs are less safe, less efficient, and less effective. Sustainable working is also the key to building an emergency medicine (EM) workforce for the future. Furthermore, many emergency physicians are concerned how they will work in EDs as they get older, and in particular, how they will cope with intense, late, and overnight working. Constructing sustainable working for an aging workforce, while ensuring development within the consultant role into the third and fourth decades of consultant life, is key consideration for workforce planning. Alongside sustainable working, consider sustainable staffing. This means paying attention to recruitment and retention. Retention is the first part of recruitment. Permanent workforces are more safe and more efficient than using locums or relying on staff to internally cover gaps and vacancies.

Consider how to keep your staff happy and fulfilled. This is partly about how you set up the workforce in general:

- Enough staff of the right skill-mix, doing work they enjoy.
- Develop a culture that genuinely values staff (rather than paying lip service to the concept).
- Provide a reasonable and healthy working environment.
- Offer terms and conditions that recognize the intensity and demands of ED shift work.
- Invest in professional development.

TABLE 3: The different (TIER classification) tiers working in an emergency department.	
Tier 1	Require complete supervision. All patients must be signed-off before admission or discharge e.g., interns/ junior residents
Tier 2	Require access to advise or direct supervision, or practice independently, but with limited scope doctors, some primary care clinicians, and junior residents
Tier 3	More senior/experienced clinicians, requiring less-direct supervision. Generally fewer limitations in scope of practice. Senior residents and experienced practioners
Tier 4	Senior clinicians able to supervise a department alone with remote support possess some extended skills. Full scope of practice
Tier 5	Senior clinicians with accredited and advanced qualifications in EM/full set of extended skills. Consultants in EM

(EM: emergency medicine)

Resilience: Staffing models need build in resilience to contributes toward sustainable working and research. Further research is needed into:

- Staffing models for EDs of different sizes
- The relationship between appropriate staffing and patient safety
- Decision making density and interruptions within EDs
- The combined effects of age, time of day, and shift patterns on safe decision making in clinicians
- Recruitment and retention in acute specialties

Action is needed to build an EM workforce fit to meet the demands of the future. This includes attracting people into EM and then retaining them. This comes down to providing professionally satisfying workplaces, sustainable working patterns, attractive terms and conditions, and professional development.

DECIDING FACTORS FOR STAFFING IN EMERGENCY

- Patient volume
- Patient acuity
- Patient length of stay
- The capabilities of physicians
- The role of nonphysician staffing
- The hospital's expectations
- Nursing expectations
- Financial goals and expectations

REQUIREMENTS OF EMERGENCY PHYSICIAN FOR EMERGENCY DEPARTMENT

In three shifts during 24 hours at the rate of approximately 25 patients/shift, total patients = 75

- 75 patients/24 hours = 2 medical officers/shift (total 6 medical officers during 24 h)
- 75–100 patients/24 hours = 3 medical officers/shift (total 9 medical officers during 24 h)
- More than 100 patients/24 hours = 4 medical officers/shift (total 12 medical officers during 24 h)

It is assumed that morning and evening shift is of 6 hours and night shift is of 12 hours. All medical officers should be supervised by consultant/senior consultant in each shift. As per predefined roster, all the specialists to be available on call round the clock.

REQUIREMENTS OF STAFF NURSE IN EMERGENCY DEPARTMENT

When triaging nursing staff is separated from other clinical staff:

- More than 75 patients/24 hours = 4 staff nurses/shift (total 12 staff nurses during 24 h)
- For every additional attendance of 25 patients, add 2 more staff nurses in 24 hours
- For emergency ward—1:4 per shift + 15% leave reserve

EMERGENCY MEDICAL TECHNICIANS

One emergency medical technician (EMT), trained nursing assistant/ambulance/shift, they can assist nursing staff or staff posted in minor, when they are not accompanying ambulance. Duration and number of shifts may vary depending upon workload.

STAFF FOR MINOR OPERATION THEATER

- For the workload of less than 25 patients/24 hours = 1 operation theater (OT) technician and/or dresser/shift (total 3 OT assistants/dresser during 24 h) for dressings, splint applications, and suturing of minor injuries.
- 25–50 patients/24 hours = 2 OT technician and or dresser/ shift during morning shift and 1 OT assistant and/or dresser during evening and night shifts.
- 50–100 patients/24 hours = 2 OT assistants and/or dresser/shift during morning and evening shifts and 2 OT assistants and/or dresser during night shift.

OTHER STAFF

- *Registration clerk*: A dedicated person to be present for registration of patients in all shifts.
- *Data entry operator*: A dedicated person for computerized medicolegal record entry in all shifts.
- *Laboratory technician (LT)*: For emergency sample collection center:
  - Less than 75 samples/24 hours = 1 LT/shift (total 3 LT during 24 h)
  - 75–150 samples/24 hours = 2 LT/shift (total 6 LT during 24 h)
- *Security staff*: For a workload of:
  - 75–100 patients/24 hours = 1 security staff/shift (total 3 security staff during 24 h)
  - 100–150 patients/24 hours = 2 security staff/shift (total 6 security staff during 24 h)

- *Housekeeping staff*: For a workload of:
  - 75–100 patients/24 hours = 1 housekeeping staff/shift (total 3 housekeeping staff during 24 h)
  - 100–150 patients/24 hours = 2 housekeeping staff/shift (total 6 staff during 24 h)
- *Group D staff*: For a workload of:
  - Less than 100 patients/24 hours = 1 group D staff/shift (total 3 group D staff during 24 h)
  - More than 100 patients/24 hours = 2 group D staff/shift (total 6 group D staff during 24 h)

SUMMARY

Emergency department design and structure works hand-in-hand in conjunction with the staffing structure to provide a safe, productive, efficient, and reliable service to provide ultimate and immediate care to the unscheduled and undifferentiated patient population which presents to the emergency healthcare services.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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3

CHAPTER

Observation and Isolation Unit

Devendra Richhariya

INTRODUCTION

Emergency services are becoming more organized in India, and by adopting best practices in the emergency department (ED), it is now possible to provide the best quality care. One of the best practices is the establishment of an observation unit (OU) in the ED , a dedicated area for observation of a patient which provides safe and efficient care. The concept of the emergency department observation unit (EDOU) is now well developed and clearly described. Knowledge of the various types of OUs, their locations, sizes, designing, staffing, and development of protocols can be implemented while establishing and managing the OU , and leadership can sustain service excellence for their patient in the OU.

OBSERVATION UNIT DESIGN AND LAYOUT

While designing the OU in the ED, the clinical effectiveness and financial viability are the top priorities. Various types of OU designs have been described by Ross and colleagues.

Types of Observation Units

The first type of OU is protocols-driven that is termed *type 1 OU*. Another type of OU is that managed by clinical direction given by an individual clinician (not based on protocols) termed *type 2 OU*. In *type 3 OU*, patients can be observed in any hospital bed but care is protocol-based. In *type 4 OU,* the patient is observed in a nonprotocolized manner in any hospital bed.

Open or closed unit: Another classification of OU is a closed or an open OU. In a closed OU, the patient is managed under a single group or specialty, such as an emergency medicine specialist. In the open OU, the patient is managed by individual clinician directives. Evidence shows that protocol-driven and closed OUs are much superior and also commonly designed. Protocol-based type 1 OUs are superior because of:

- Unified leadership
- Condition-specific protocol
- Inclusion and exclusion criteria
- Timely interventions
- Inpatient and discharged criteria

Other than these points, appropriate patients are placed in the OU, there is better adherence to time-bound protocols, and targeted feedback and education can be provided because of the closed unit which can enforce accountability and quality.

Hybrid Unit

Sometimes, for a smaller hospital, it is not justifiable to create an OU in view of the extra cost incurred in the salary of nursing and other support staff. In these situations, the "hybrid" OU is also used as a recovery unit and observation patients, as well as patients of elective procedure, can also be recovered and discharged afterward. The hallmark of a hybrid OU is to maximize the operational capacity. In case of extreme hospital census, a hybrid unit can also be used to hold the patient, who is waiting for inpatient beds, though these practices should be avoided because long waiting hour for the patient in ED results in lack of beds for acute care and this results in vicious cycle.

Location

The location of OU is critical from the logistic and patient points of view. Placement of OU away from the ED causes difficulty in clinical re-evaluation, communication, and transport. Placing this OU within or just adjacent to the ED gives the following benefits:

- Highest patient comfort
- Minimal disruption of the process
- Close proximity to clinicians
- Close proximity to supply and equipment
- Cost-saving

Volume Capacity

After identifying the space for the OU, another important part in establishing the OU is deciding the capacity of the unit. Various studies suggest that 5–10% of all the ED patients can be good candidates for OU care or a new facility OU should be started with a minimum of five to eight beds with a 1:5 or 1:4 nursing ratio.

Observation Unit Layout

Careful designing of OU and utilization of physical space are required to optimize clinical care. Other factors such as allocated funds, state, city, and health regulations influence the OU design. Structuring the space in which the patient–clinician

interaction is maintained is important, so a curtained cubical which faces the nursing station is generally recommended. Curtained cubical and closed room have their own advantages and disadvantages. A semicircular nursing station facing cubical provides direct visualization of the patient and allows the patient to feel better cared for during his/her stay. Areas such as medication preparation area, consultant workplace, nursing workplace, and utility rooms are equally important parts of an OU layout.

Time Cut-off

Patient length of stay (LOS) cutoff is an important consideration for a successful EDOU. Most of the EDOUs use a 24-hour maximum cutoff; during this time frame, a decision for safe discharge or for further in-hospital hospitalization is taken.

PROTOCOL DEVELOPMENT

Phases of Emergency Department Observation Unit Protocol Development

Once the EDOU is established, clinical pathways and protocols are required for successful medical and surgical acute care. Pathways and protocols enable a clinician to select an appropriate patient for EDOU and manage him/her with evidence-based diagnostics and interventions. There are five main phases of protocol development (**Fig. 1**):

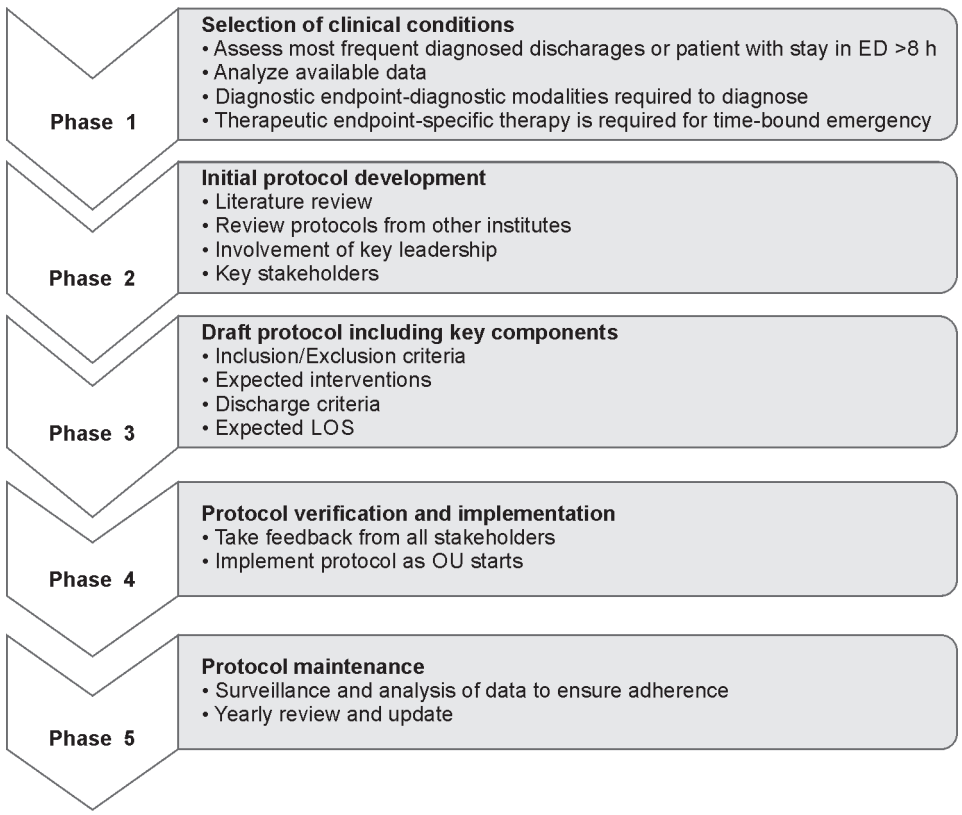
1. Selecting the clinical condition
2. Initial protocol development
3. Draft the protocol with key components
4. Verification and implementation of protocol
5. Maintenance of protocol

Selection of clinical condition: Since many decades, chest pain was the focus while establishing a protocol in the ED; later on, transient ischemic attack (TIA), stroke, asthma, atrial fibrillation, syncope, heart failure, and pulmonary embolism were also included. Other conditions such as abdominal pain, dehydration, renal colic back pain, pyelonephritis, cellulitis, chronic obstructive pulmonary disease (COPD), community-acquired pneumonia, deep vein thrombosis (DVT), electrolyte imbalance, and psychiatric emergencies are also managed in EDOU. The next important area is a discussion with key leadership and analyzing the hospital data regarding the most frequent diagnosis and discharges from the inpatient team and their LOS. After leadership approval and guided decision-making, EDOU is started with widely established pathways and later other conditions are included through further analysis.

It is a matter of discussion whether a patient with behavioral health problems such as a patient with suicidal tendency should be included in OU care or not. Each institution should examine its own policy, security, resources, and discussion with the psychiatrist and take the decision.

Diagnostic and therapeutic endpoints: For any given clinical situation, necessary diagnostic modalities are selected to diagnose a particular condition in EDOU. Similarly, therapeutic protocols are selected so that necessary time-bound therapies are delivered.

Protocol development: After the conditions and diagnostic and therapeutic endpoints are selected, the next step is the development of a protocol which enables the clinicians


Phase 1
Selection of clinical conditions
• Assess most frequent diagnosed discharages or patient with stay in ED >8 h
• Analyze available data
• Diagnostic endpoint-diagnostic modalities required to diagnose
• Therapeutic endpoint-specific therapy is required for time-bound emergency
Phase 2
Initial protocol development
• Literature review
• Review protocols from other institutes
• Involvement of key leadership
• Key stakeholders
Phase 3
Draft protocol including key components
• Inclusion/Exclusion criteria
• Expected interventions
• Discharge criteria
• Expected LOS
Phase 4
Protocol verification and implementation
• Take feedback from all stakeholders
• Implement protocol as OU starts
Phase 5
Protocol maintenance
• Surveillance and analysis of data to ensure adherence
• Yearly review and update

(ED: emergency department; LOS: length of stay; OU: observation unit)

FIG. 1: Phases of protocol development for observation unit.

in selecting the patient for OU management. The process starts with literature review and discussion with the various institutions who have an established protocol. Further, relevant stakeholders such as EDOU leadership and appropriate consultant are included for the joint development of EDOU pathways. A well-developed protocol should include inclusion and exclusion criteria, expected intervention in EDOU and disposition criteria, expected LOS, and medical records. Patients should be avoided for OU management who clearly require inpatient treatment or can be discharged home safely. Disposition criteria are helpful in maintaining the appropriate patient flow and efficiency within the EDOU. LOS is variable in each patient depending on the condition, but the expected time for discharge is also helpful in maintaining the flow of the OU.

Protocol verification, implementation, and maintenance: During this process, feedback is obtained from all stakeholders. After sufficient review and editing, the protocol can be operational in EDOU. Protocol development is a dynamic process and not static, so the final phase of protocol development is maintenance. The protocol can be updated yearly to ensure optimal use of EDOU.

OBSERVATION UNIT MANAGEMENT

Leadership

Successful management of OU depends on strong leadership which consists of the clinical director, nursing director, and operation director who works in coordination and are accountable for efficient patient care. This group of leadership is responsible for implementing protocols, monitoring utilization and quality, and encouraging research and educational activities.

Individual responsibilities: The clinical director is primarily responsible for monitoring the physical activities and workflow and developing protocols for new conditions. The nursing director monitors nursing interventions, care coordination, and case management. The operational director is responsible for finances, interfacing with hospital administration, workflow metric reporting, and compiling the annual report and overall return on investment of the EDOU. Another important role of the leadership trio is a strong commitment to the hospital leadership and a quarterly meeting with the organization's leadership where the annual report can be reviewed. Communication among all the leadership and the frontline staff is necessary to ensure success. Usually, 6–9 months are allocated for the development of the OU. This timeline allows planning, construction, staffing, and protocol development in a smooth fashion. Creating and implementing new protocols take several months. Communication should be established and several meetings are required with the various departments, which will get impacted with the opening of the OU, to explain its purpose and gain their support.

Staffing

Clinician, support staff, ancillary support: For effective management of OU, appropriate staffing is essential. Staffing of OU consists of physician, nurses, and medical assistants. For managing the OU, a popular model exists in which the physician and nurses take all the responsibilities of each patient in OU. Critical decisions are taken by a physician in the presence of a decompensated patient or if there is any concerning diagnostic or imaging report. From a nursing point of view, OU is staffed by skilled and trained nursing staff. A newly developed OU does not necessarily require all new staffing; rather the existing staff of inpatient care can be given responsibilities and the patient–nursing ratio can be similar to that in the inpatient floor, i.e., one nurse is allocated per shift—1:4 or 1:5 (one nurse in every four patients or one nurse in every five patients). Apart from physician and nurses, additional staff such as care coordinator, unit clerk, and medical assistant are important who play a key role in disposition of decision to maintain good flow through OU. One clerk and one nursing assistant are required in every eight beds of OU. A care coordinator (a nurse by training) should be available from 7 AM till late evening who helps the patient going to rehabilitation, requiring home services, going to home, or getting admitted.

Consulting or referral services enable smooth delivery of care process and management within OU and afterward in an outpatient setting also. So, in every clinical pathway, priority access should be clearly established for the consultant attending to the patient for appropriate investigations and follow-up. Primary consultants for OU include cardiologist, neurologist, gastroenterologist, general surgeon and urologist and further depend on the patient population.

Imaging Modalities

For efficient and effective care in OU, access to key imaging modalities is essential. Communication and agreement over the turnaround time with cardiology and radiology should be the focus of effort. Computed tomography (CT), magnetic resonance imaging (MRI), echocardiography, and stress testing are the imaging modalities in priority.

Workflow

Smooth workflow of OU which is essential for optimizing patient care depends on various factors such as LOS documentation and communication. According to various studies, approximate LOS is 15 hours. Patient population with LOS of 8–15 hours is best managed and those who require more than 24-hours' LOS, it is better to admit them in inpatient facilities for efficient management. Taking rounds with the attending physician and nurse along with documentation of the initial examination and management is the initial minimum requirement. Further documentation of decision-making, results of test and imaging, and plan of care should also be documented in the patient's chart or in the electronic medical record. Orders are placed in OU which enables a hospital for billing for appropriate hospital services. A progress note is entered in electronic medical records for optimal patient care and a discharge summary should also be maintained and one copy should be given to the patient which includes physical examination, clinical course in the OU, diagnosis, follow-up advice, and schedule for an outpatient visit.

QUALITY ASSURANCE PROCESS AND METRICS

To optimize the use of EDOU and to maximize safety and efficiency of OU key metrics are important concerns for leadership. Important metrics of focus include:

- LOS
- Occupancy rate
- Discharge to home
- Inpatient conversion rate
- Revisit to ED rate
- Patient satisfaction

For the LOS assessment tracking, LOS <6 hours hours, LOS >24 hours, LOS >36 hours, LOS >2 midnights as well as LOS as per the patient's conditions should be noted. The appropriate standard for occupancy rate is 60–75% which may increase further depending on additional patient volume on ED and inpatient services. The discharge to home and inpatient conversion rate benchmarks are 80% and 20%, respectively. Close monitoring of these indicators is helpful in the following ways:

- Maintaining effective patient flow through ED.
- More effective way of disposition can be generated.
- Lessen both ED and inpatient overcrowding.

Effective OU and patient care should be paramount over all other management issues and financial concern.

Dashboard

Data are collected from different sources, and key performance indicators are summarized in a visual presentation. The focus should be on choosing the best data, which should be easy to read and interpretable. Monthly updates in the dashboard are helpful in continuous quality improvement, and this can be used across the healthcare. It is important to develop a dashboard during the planning process itself and not once the operation has started.

Policy Manual

Developing and maintaining the policy manual for OU is one of the best practices, which provides a unified solution to any key issue to staff members. The policy manual is helpful in addressing the problem with a clear path for resolution. It consists of specific processes and documentation expectations in detail, and the staff feels more secure and confident while performing their duties. The policy manual should be developed in the early phase of management and should be updated every 6–12 months.

Annual Report

At the end of the fiscal and calendar year, a formal annual report should be prepared and discussed with departmental and hospital leadership to highlight EDOU contribution, hospital bed-hours saved, safety record, patient satisfaction, and revenue generation.

GUIDELINES FOR SETTING UP AN ISOLATION UNIT

In view of the recent COVID-19 outbreak, the World Health Organization has declared the COVID-19 (SARS-CoV-2) outbreak as a public health emergency of international concern. Preparedness for COVID 19 outbreak includes containment, including active surveillance, early detection, isolation and case management, contact tracing, and prevention of the onward spread of SARS-CoV-2 infection. The mainstay of outbreak containment is the isolation of cases and quarantine of contacts. Quarantine and isolation are helpful in breaking the chain of transmission in the community and are important mainstays of cluster containment.

Quarantine: Individuals (who are not yet ill) but exposed to infectious diseases/COVID-19 are separated from nonexposed people, because they have the potential to become ill. Home quarantine of contacts of suspect/confirmed cases can also be done as per the government guidelines.

Isolation: Individuals who are ill and suspected or confirmed of infectious disease/COVID-19 are separated. These individuals are hospitalized and kept in isolation (designated area in a hospital) till they are tested negative. Positive cases remain hospitalized till the time two of their samples are tested negative or as per the government guidelines.

Patients may develop lower respiratory involvement (pneumonia in 15%), and a few of them may require ventilatory support (5%). Hence, intensive care beds are also identified with the support of a dialysis facility and extracorporeal membrane oxygenator (ECMO) facility for managing the respiratory/renal complications/multiorgan failure. If these facilities are not available, then the nearest tertiary care center is identified and it becomes a part of the plan. There are various ways of isolating the patient. Single-isolation rooms or negative-pressure rooms with 12 or more air changes per hour are recommended. Alternatively, all positive COVID-19 cases can be cohorted in a ward with good ventilation in a resource-constrained setting. Likewise, all suspect cases should also be separated into different wards. However, at least 1-m distance between two beds needs to be maintained and patients need to wear a triple-layer surgical mask at all times. Infection prevention control practices should be followed strictly in all health facilities because nosocomial infections in patients and attending healthcare personnel are well documented in the current COVID-19 outbreak as well. To ensure that all healthcare personnel are well aware of infection-prevention practices, Infection Prevention and Control committees should be formed.

The designated hospitals will ensure that personal protective equipment (PPE) and other logistics (hand sanitizer, soap, water, etc.), are in place and that all healthcare staff have been trained in washing of hands, respiratory etiquettes, donning/doffing, proper disposal of PPEs, and biomedical waste management (BMWM). Three-layered surgical masks and gloves are necessary at all times for doctors, nurses, and paramedics working in the clinical areas. Full complement of PPE should be worn by the medical personnel working in isolation and critical care facilities (including N95 masks) and also by the support staff engaged in cleaning and disinfection. Environmental cleaning should be done twice daily which should consist of damp dusting and floor mopping with Lysol or other phenolic disinfectants and cleaning of surfaces with sodium hypochlorite solution. Detailed guidelines available on the Ministry of Health and Family Welfare (MoHFW) website guideline can be followed.

Setting up an Isolation Facility/Ward

An isolation room/area helps in controlling the airflow in the room, so the number of airborne infectious particles is also reduced to a level where cross-infection to other people within a healthcare facility is highly unlikely. This may be achieved by:

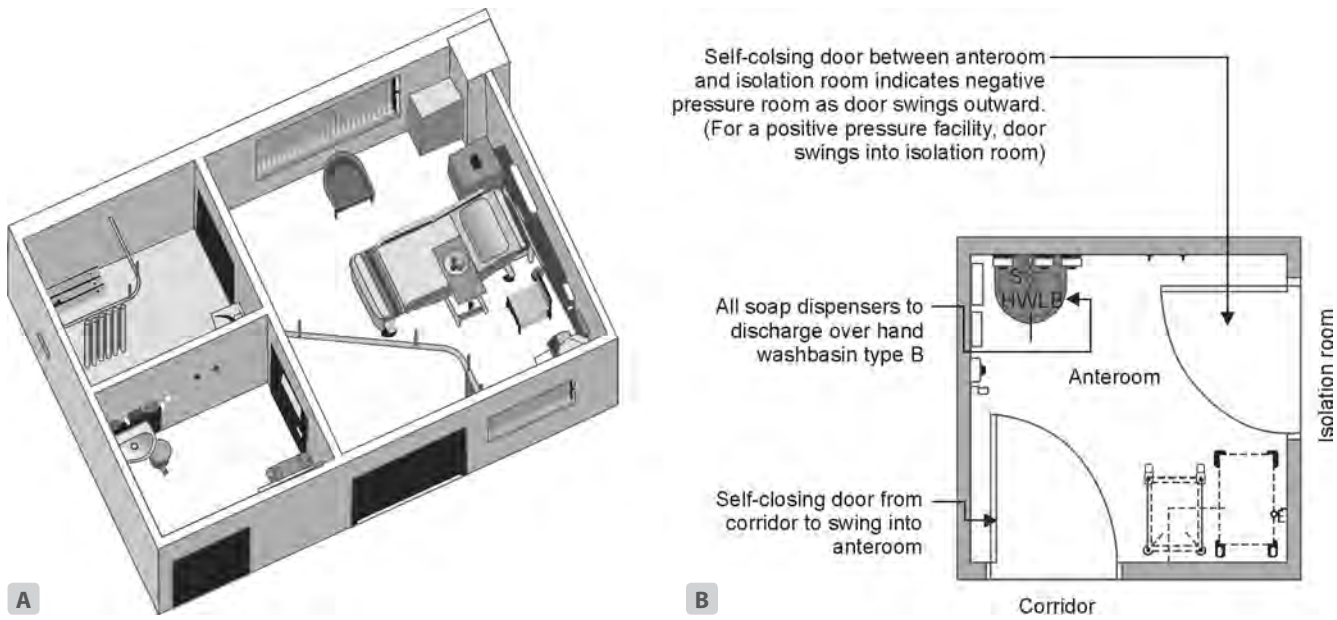
- Controlling the quantity and quality of the intake or exhaust air.
- Maintaining different air pressures between the adjacent areas.
- Designing airflow patterns for specific clinical procedures.
- Diluting infectious particles with large air volumes.
- Air filtration—high-efficiency particulate air (HEPA) filters, etc.

A state-level isolation facility should have at least 50 beds and a district-level isolation facility should have 10-bed isolation wards. Well-illuminated/visible signages on the door indicating that the space is an isolation area should be posted. Only essential furniture in the room that can be easily cleaned (does not retain dust or moisture) should be kept. A single room is preferred for COVID-19 patients. Single-room availability is not always present in a healthcare facility, so a 10-bed facility can be created with a minimum space of 2,000 sqft with the beds being separated from each other by at least 1 m (3 feet). The isolation area should be away from postsurgical wards/dialysis unit/sick newborn care unit (SNCU)/labor room, etc., and preferably have separate entry and exit. The isolation area should be accessed through separate stairs and lift, with restriction of visitors.

In most of the healthcare facilities, visitors' entries are unavoidable as they are anxious to see their family members. Hospital guidance should be provided for proper use of PPE and hand hygiene practices prior to entry into the isolation room/area. A communication setup should be installed within the isolation area; a dedicated smartphone should preferably be provided in the isolation area so that video calls can be arranged with family members. This may reduce family members' entry into the isolation area.

Isolation room entry should be through a double door, equipped with adequate PPE waste disposal bins and anteroom (for changing PPE) for doctors and nurses (**Figs. 2A** and **B**). BMWM guidelines should be used for disposal of PPE. A checklist may be useful to ensure that all equipment is available. Use a touch-free bin and place appropriate waste bags in a bin. Ensure that bins and a puncture-proof container for sharps disposal remain inside the isolation room which should be managed as per the BMWM guidelines. Water bottles and cups, tissue wipes, and all items necessary for personal hygiene should be within the patient's reach. The personal belongings of the patient should be minimum. If possible, a stethoscope, thermometer, blood pressure cuff, and sphygmomanometer should be dedicated for the patient or else should be thoroughly cleaned and disinfected before use.

Room ventilation should be adequate. Ensure 12 air changes/h and filtering of exhaust air, if the room is air-conditioned. Patients requiring aerosolization procedures (intubation, suction, nebulization) a negative pressure in isolation rooms is desirable. These rooms may have standalone air-conditioning. Isolation areas should not be a part of the central air-conditioning. If air-conditioning is not available, negative pressure could also be created by installing three to four exhaust fans which drive the air out of the room. In a hospital where large spaces with natural ventilation are available, a natural unidirectional flow of air is maintained through large windows on the opposite walls of the room. The principle of natural ventilation is to allow and enhance the flow of outdoor air by natural forces from one opening to another to achieve the desirable air change per hour. A separate toilet with proper cleaning and supplies is the priority for an isolation area. A checklist is important to keep things updated (**Box 1**). For possible outbreak investigation and contact tracing, keep a roster of all staff working in the isolation areas. Appoint dedicated doctors, nurses, and paramedics to the isolation facility and they should not be allowed to work in other patient-care areas. Portable X-ray, ultrasound and other equipment should be dedicated to the isolation area only.


A
Self-colsing door between anteroom and isolation room indicates negative pressure room as door swings outward. (For a positive pressure facility, door swings into isolation room)
All soap dispensers to discharge over hand washbasin type B
HWLB
Anteroom
Isolation room
Self-closing door from corridor to swing into anteroom
Corridor
B

FIGS. 2A AND B: (A) Typical isolation room; (B) Typical anteroom.

Wearing and Removing Personal Protective Equipment

Before entering the isolation room or area: Collect all equipment needed. Perform hand hygiene with an alcohol-based hand rub. Put on PPE in the order that ensures adequate placement of PPE items and prevent self-contamination and self-inoculation while using and taking off PPE; an example of the order in which to don PPE when all PPE items are needed is hand hygiene, gown, mask or respirator, eye protection, and gloves.

Leaving the isolation room or area: Remove PPE in the anteroom or, if there is no anteroom, make sure that the PPE should not contaminate other parts of isolation or other people.

General principles for removing PPE: Removal of PPE should be such that it prevents self-contamination or self-inoculation. Perform hand hygiene immediately after removing gloves. Remove the mask or particulate respirator last. Discard disposable items in a closed rubbish bin. Perform hand hygiene with an alcohol-based hand rub (preferably) or soap and water whenever ungloved hands touch contaminated PPE items. Details of PPE are given in Chapter 10.

BOX 1: Checklist for isolation rooms.

- Eye protection (visor or goggles)
- Face shield (provides eye, nose, and mouth protection)
- Gloves reusable, vinyl or rubber gloves for environmental cleaning, latex single-use gloves
- Particulate respirators (N95, FFP2, or equivalent)
- Medical (surgical or procedure) masks
- Gowns and aprons, single-use, long-sleeved, fluid-resistant
- Alcohol-based hand rub
- Plain soap (liquid if possible, for washing hands in clean water)
- Clean single-use towels (e.g., paper towels)
- Sharps containers
- For disinfection of surfaces, appropriate detergent disinfectant
- Large clinical waste bags, linen bags

Classification of Isolation Rooms

Isolation rooms are broadly classified into four classes (**Table 1**):

1. *Class-S standard pressure rooms*: For the patient with contact and droplet isolation. A normal air-conditioned room is appropriate.
2. *Class-N negative pressure rooms*: Used for airborne droplet nuclei isolation. It is also known as "airborne infection isolation" or "infectious isolation unit." The negative pressure gradient is maintained from the room to the anteroom as well as the ambient air. The air change rate should be 12 air changes/h.
3. *Class-P positive pressure rooms*: Rooms are positive pressure relative to ambient air used for an immuno-compromised and transplant patient.
4. *Class-A alternating pressure (negative/positive) rooms*: Room with alternate negative and positive pressure. Usually, these are not recommended as there is difficulty in maintaining the appropriate airflow.

Transport of Infectious Patients

Transfer and movement of the infectious patients should be limited and only on advice by clinicians, e.g., for diagnostic or treatment purposes. In cases where infectious patients are required to be transported to other units within the hospital or outside, the following precautions may be implemented. The patient should be dressed in a mask and gown, covered with sheets, and transferred to a protective environment isolation room.

To ensure suitable accommodation on arrival, the destination unit should be contacted and notified prior to the transfer. It is preferred that the patient is not transported through public access corridors but by dedicated corridors and lifts. During planning stages, design can assist the transfer of infectious patients by providing service corridors and strategically placed lifts, capable of separation from other lifts. The nominated lift may be isolated from public and staff transit through access control measures and cleaned following transit of the infectious patient. A designated floor for horizontal bed transfers of infectious patients away from busy clinical areas

TABLE 1: Classification of the isolation room.

	(S) standard	*(N) negative*	*(P) positive*	*(A) alternate*
Ventilation criteria	No pressure difference between room and adjacent corridor	Air pressure is less in the room than the adjacent corridor	Air pressure is more in the room than the adjacent corridor	Pressure can be adjusted either positive or negative
Indication	Contact or droplet	Airborne	Immunocompromised/Transplant patient, prevention of infection from the outside environment	Not recommended
Examples	• VRE • Gastroenteritis • Meningococcal disease • Hepatitis A • Cutaneous anthrax	• Measles • Chicken pox • Suspected or proven pulmonary/laryngeal tuberculosis	Prevention of infection in bone marrow transplant patient	Not recommended
Pressure	NA	Room –ve 30 Pa Ensuite –ve 30 Pa Anteroom –ve 15 Pa	Room +ve 30 Pa Ensuite +ve 30 Pa Anteroom +ve 15 Pa	NA

(VRE: vancomycin-resistant enterococci)

should be considered. The designated floor may be located at mid-level in the hospital. A combination of nominated lifts, corridors, and a bed transfer floor would assist in the movement of infectious patients through the hospital and minimize the risk of spread of infection.

SUMMARY

The design, location, layout, and process of EDOU are carefully selected to enable optimal care and finances. Several acute medical and surgical conditions are amenable to the OU clinical pathway; developing and maintaining protocols to guide patient selection and clinical care are critical; collaborative leadership model, appropriate staffing, and a robust monitoring system for quality, safety, and finances are required for ongoing strong OU management. Department and hospital leaders can generate and sustain service excellence for their observation patient population with a better understanding of these principles of OU establishment and management. Healthcare facilities should develop, implement, assess, and revise infection-control policies and practices that are appropriate to their particular needs based on the patient population demography and the facility's specialties. In view of the present pandemic of COVID-19, healthcare facilities requiring larger isolation areas to accommodate patients at the same time should take all measures to prevent the transmission also.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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4 CHAPTER

Observation Medicine

M Rajadurai, Akmal Areeb, Devendra Richhariya

INTRODUCTION

Observation medicine deals with care of patients managed in the emergency department (ED) who require a short period (<24 h) of stay for evaluation and treatment in the dedicated observation unit (OU). These patients are managed using focused, condition-specific, and accelerated diagnostic or therapeutic protocols, which help to prevent inappropriate discharges or admissions while improving healthcare resource utilization. Observation care in such OUs has better outcomes than inpatient admission in terms of shorter length of stays, lower costs, lesser diagnostic uncertainty, and improved patient satisfaction. An ideal OU should have the following characteristics:

- Located within or immediately adjacent to ED and referred to as emergency department-based observation units (EDOUs)
- Comprises about 5–10% of all ED patients or a minimum of five to eight beds
- Protocol driven
- A strong collaborative and leadership model consisting of a physician director, a nurse director, and an administrative operations director
- Appropriate staffs consisting of physicians, physician assistants, and nurses
- Follows a robust monitoring system for quality, safety, and finances
- Prioritized support of consulting services such as cardiology, neurology, general surgery, urology, and gastroenterology and imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and echocardiogram.

CLINICAL DECISION RULES

Clinical decision rules (CDRs), also known as decision, are evidence-based tools or protocols to assist the emergency physician/clinicians in decision-making for common complaints in ED. These CDRs are often helpful in the ED setting to identify patients who might be at a higher risk for serious conditions, such as pulmonary embolism (PE) or subarachnoid hemorrhage (SAH), or to prevent overuse of unnecessary testing.

Although CDRs are termed "rules," these are not the replacement of critical thinking from experienced practitioners. In fact, many of the CDRs are compared with clinician gestalt or clinical practice, and they do not always fare better. In fact, some rules actually adopted clinician gestalt whereas, a rule cannot be applied unless the pretest probability (based on a physician's judgment of the likelihood of the disease) is below a predetermined threshold. Also, CDR is only useful for the practitioner, if it is practical. If a CDR has too many complicated variables, it is unlikely to be successful in a busy clinical environment of ED. CDRs must be applied appropriately.

Evolution and Validation of Clinical Decision Rules

Clinical decision rules evolve through a process of derivation to validation to impact analysis of the tool. After the tool is derived (level 4 evidence), the tool is validated in a limited patient setting (level 3 evidence), then a broader validation setting (level 2 evidence), and, finally, the impact of the tool is assessed (level 1 evidence). The tool must be validated in a patient population with similar characteristics to the clinician's patient population. For example, the tool may not perform the same (have the same sensitivity and specificity) if the prevalence of the disease is different between the study and actual patient populations. Also, the clinicians/emergency physicians must be familiar with the *inclusion and exclusion criteria* for a particular CDR. The tool could be misused, if the tool is derived and validated for over 18 years of the patient population and if used inappropriately in a pediatric setting.

Purpose of the Clinical Decision Rules

The practitioner must also understand the purpose of the CDR and whether, it is a *one-way or two-way rule.* As noted by Green, for example, the Ottawa Ankle Rules are intended to be a two-way rule; if the patient meets criteria, you do an X-ray. If they do not meet criteria, you do not do an X-ray. There are two paths you can take after you apply your CDR. Alternatively, the pulmonary embolism rule-out criteria (PERC) demonstrate a one-way rule. This tool was developed to identify a subset of patients at very low risk for PE such that no further testing needs to be done. If the patient is "PERC positive," this should

not imply that further testing for PE such as a D-dimer should be done. Whether or not additional testing should be done remains up to the practitioner and depends on many variables including whether an alternate diagnosis is much more likely. PERC was simply designed to help "rule out" the diagnosis of PE and not "rule in." This rule only guides you down one path, potentially to do no testing; it makes no judgment as to what you should do if the patient is "PERC positive."

Other Risk Stratification Tools

In addition to CDRs, there are many risk stratification tools or scales that are currently used for serious conditions such as PE and acute coronary syndrome (ACS). Others are being developed for use in the ED setting for common conditions such as congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and transient ischemic attack (TIA) to identify patients at higher risk for acute severe complications. From a practical perspective, the ED physician will often use these risk stratification devices to help determine which patients require admission. However, these tools are less prescriptive in that they are not rules that suggest what an emergency physician should or should not do; rather, they help the emergency physician more objectively look at the risk for an individual patient. Then the emergency physician must decide what level of risk he/she comfortable with in regard to inpatient or outpatient management, which may greatly depend on the resources available in those environments such as in the OU. Most of the risk stratification tools encompass multiple variables with more complicated scoring systems; as they are not easily memorized, most of these would typically be used by ED physicians with real-time access to a computer or smartphone with appropriate apps.

Benefits of Implementation of Clinical Decision Rules

Given the many pitfalls noted above regarding CDRs, the goals of using evidence-based medicine to reduce practice variability, maximize the use of resources, and help identify and diagnose high-risk conditions are important. It is equally important that the ED physician critically appraise these tools and selectively apply them in appropriate ways. *MDCalc.com* provides a summary of the most common tools that are being used with easy-to-use online calculators, additional information on inclusion and exclusion criteria, and pearls and pitfalls for each tool. This chapter reviews the most commonly used CDRs in the EDOU.

CHEST PAIN

Patients presenting with chest pain to ED with normal electrocardiogram (ECG) and cardiac markers on arrival should be observed for a period of 6–12 hours before ruling out ACS (**Table 1**). Simultaneously, other life-threatening causes of chest pain such as PE, tension pneumothorax, cardiac tamponade, and aortic dissection should be considered high risk based on clinical presentation and managed and admitted immediately. In EDOU, performing serial ECG/cardiac biomarkers and stress tests helps to identify ACS or patients at risk who would benefit from timely intervention to reduce their risk of a major adverse cardiac event (MACE). *TIMI (thrombolysis in myocardial infarction) score* (**Table 2**) and *HEART score* (**Table 3**) are used for risk stratification in chest pain. Managing low-risk chest pain in EDOU and *Vancouver Chest Pain Rule* for safe discharge are summarized in **Flowchart 1**.

TABLE 1: Patient selection criteria to treat in observation unit—chest pain.

Inclusion criteria	*Exclusion criteria*
Low-risk unstable angina patients 8–12 h after presentation who: • Are symptom free • Have normal serial cardiac markers/ECG • Have no signs of heart failure	• AMI within 2 days • High-risk unstable angina • Left main coronary artery stenosis • Hypertrophic cardiomyopathy • Uncontrolled symptomatic heart failure • Uncontrolled cardiac tachyarrhythmias or bradyarrhythmia • Acute pulmonary embolism or pulmonary infarction • Acute myocarditis or pericarditis • Endocarditis • Symptomatic severe aortic stenosis • Acute aortic dissection • Severe arterial hypertension (>200/110 mm Hg) • Acute noncardiac issue (sepsis and toxicologic) • Electrolyte abnormalities • Mental or physical impairment leading to inability to exercise adequately
Stress tests—aid in identification of inducible myocardial ischemia by use of stressors and help rule out CAD before the discharge of at-risk patients presenting with chest pain. • Exercise stress test (treadmill test) using Bruce protocol • Stress echocardiography using dobutamine—indicated if the patient cannot exercise • Myocardial perfusion imaging	

(AMI: acute myocardial infarction; CAD: coronary artery disease; ECG: electrocardiogram)

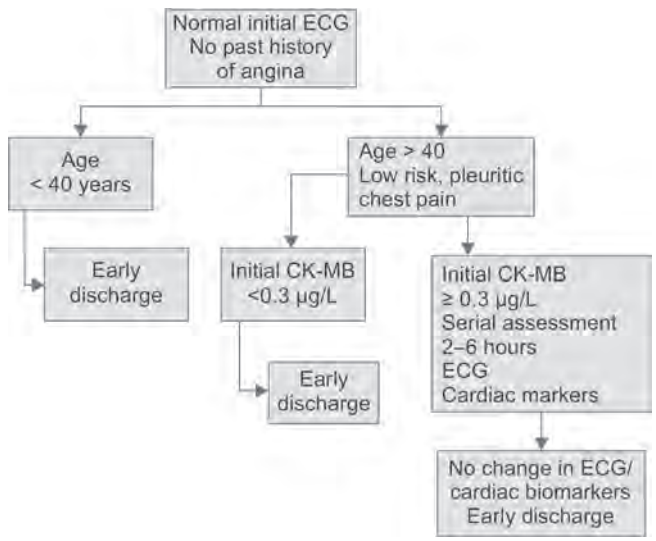
TABLE 2: Risk stratification—TIMI score—1 point for each positive score.

History	Age > 65 years
	Three or more risk factors for CAD
	Known CAD
	Aspirin use in the past 7 days
Presentation	Recent (<24 h) severe angina
	Positive cardiac biomarkers
	ST deviation > 0.5 mm
Higher *TIMI scores* mandate admission. Predicts risk of an adverse cardiac outcome within 14 days of presentation with unstable angina or non-STEMI. *Vancouver Chest Pain Rule*—used to determine very low-risk chest pain patients and help in early discharge.	

(CAD: coronary artery disease; STEMI: ST-segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction)

TABLE 3: Risk stratification—HEART risk score for chest pain patients in the emergency department.		
History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST depression	2
	Nonspecific repolarization changes	1
	Normal	0
Age	>65 years	2
	45–65 years	1
	<45 years	0
Risk factors	>3 risk	2
	1 or 2	1
	No risk	0
Troponins	>3 × normal limit	2
	1–3 × normal limit	1
	<normal limit	0
Heart score	**Risk of MACE**	**Recommendations**
0–3	0.9%	ED discharge
4–6	12%	Observation
>6	65%	Cardiology admission

(ED: emergency department; MACE: major adverse cardiac event)



(ECG: electrocardiogram; CK-MB: creatine kinase myocardial band)

FLOWCHART 1: Managing low-risk chest pain and safe discharge from observation unit (Vancouver Chest Pain Rule).

ATRIAL FIBRILLATION

Atrial fibrillation is the most common clinically significant arrhythmia and its incidence increases with age which required a new and innovative management strategy. The patient should be carefully selected for the OU (**Table 4**). Protocol-based management is started for atrial fibrillation. Risk stratification is important before starting the anticoagulation therapy by *CHA_2DS_2-VASc scoring* and *HAS-BLED* (*hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol*) *scoring* system (**Table 5**). A stepwise systematic approach (**Flowchart 2**) is required to be implemented in the management of atrial fibrillation as the patient has a risk of developing the stroke, if not managed properly.

ACUTE HEART FAILURE

Recommendations on risk stratification as well as EDOU management of acute heart failure (HF) syndrome are published by The Society of Chest Pain Centres (now the Society for Cardiovascular Patient Care). Most of the patients with acute HF are not appropriate for observation care. High-risk patients can be identified by multiple risk stratification schemes. These patients are at high risk for inpatient morbidity or mortality and not be good candidates for observation management. Therefore, it is important to identify those patients who are completely inappropriate for care in the OU. Most of the patients with acute symptoms of HF presenting to the ED should be admitted to an inpatient unit because these patients require initial workup and management which generally surpass the recommended 24-hour observation time. The summary of EDOU recommendation for acute HF is given in **Table 6**.

SYNCOPE

For syncope, multiple risk stratification rules are published, but a physician's judgment is more important because none of the published rules demonstrated an improvement in outcome because syncopal episodes are generally considered as the precursor to sudden cardiac death in patients with cardiovascular history and frequently admitted to the hospital. The most common markers of risk factors include family history of sudden cardiac death, severe cardiac disease [including dilated cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, or left ventricular (LV) outflow disease], ECG abnormalities (such as preexcitation syndrome, Brugada syndrome, QT interval abnormalities, or conduction blocks), or exertional syncope. Patients who are considered low risk should usually be discharged. Syncope management in EDOU is summarized in **Table 7** and **Flowchart 3**.

VENOUS THROMBOEMBOLISM

Acute venous thromboembolism (VTE) disease, which includes deep venous thrombosis (DVT) and PE, is a frequent reason for patients to present to the ED and require hospitalization. The therapeutic strategy for VTE has remained unchanged for decades: Anticoagulation (**Table 8**) to prevent clot propagation, new or recurrent PE, secondary pulmonary hypertension, and, in the case of DVT, mitigate longer term and nonlethal complications, such as post-thrombotic syndrome. Historically, treatment of VTE mandated hospital admission for unfractionated heparin (UFH) infusion while vitamin K antagonists (VKAs) were administered. The availability of low-molecular-weight heparin (LMWH), which can be administered subcutaneously with a predictable therapeutic effect,

TABLE 4: Patient selection for the management of AF in EDOU.

Protocol for AF relies on algorithms incorporating anticoagulation, rate and rhythm control, and mechanisms to ensure rapid outpatient follow-up.

Ideal patients	**Contraindicated patients**
• Hemodynamically stable patients • No signs of cardiac ischemia • Onset of AF of <48 hours' duration	AF secondary to the underlying causes such as sepsis, pulmonary embolism, gastrointestinal (GI) bleed. Unstable AF patients

Relative contraindications

- Acute renal insufficiency
- Pregnant patients
- Unknown time of AF onset
- Expected length of stay >36 h due to comorbidities
- Patients having poor health literacy
- Patients lacking close follow-up
- Inability to adhere to a treatment

- Risk factors for immediate stroke following cardioversion of AF
- Unknown time from onset
- History of transient ischemic attack (TIA) or stroke in last 6 months
- History of valve disease

Management of AF in EDOU anticoagulation—based on economic considerations

Warfarin—Vitamin K antagonist

- Requires frequent monitoring of INR
- Interacts with many foods and medications
- Requires bridging or overlapping therapy with UFH/LMWH for 3–5 days

DOACs

- Edoxaban, dabigatran—require additional lead in therapy with UFH/LMWH for 5 days
- Apixaban rivaroxaban—do not require bridging/lead in therapy with parenteral anticoagulation
- Preferred over warfarin in:
  - Patients with nonvalvular AF
  - Patients who cannot be relied upon to get their INR levels checked or
  - Patients who cannot adhere to diet restrictions required when taking warfarin
- Cardiology consultation
- Echocardiography—to rule out valvular heart disease

Anticoagulation

- Long-term anticoagulation following cardioversion or rate control should be initiated in individuals at risk of stroke and thromboembolism. The risk stratification is done with CHA2DS2-VASc score and prior to initiating anticoagulation patients' bleeding risk must also be assessed using HAS-BLED score simultaneously

Discharge criteria

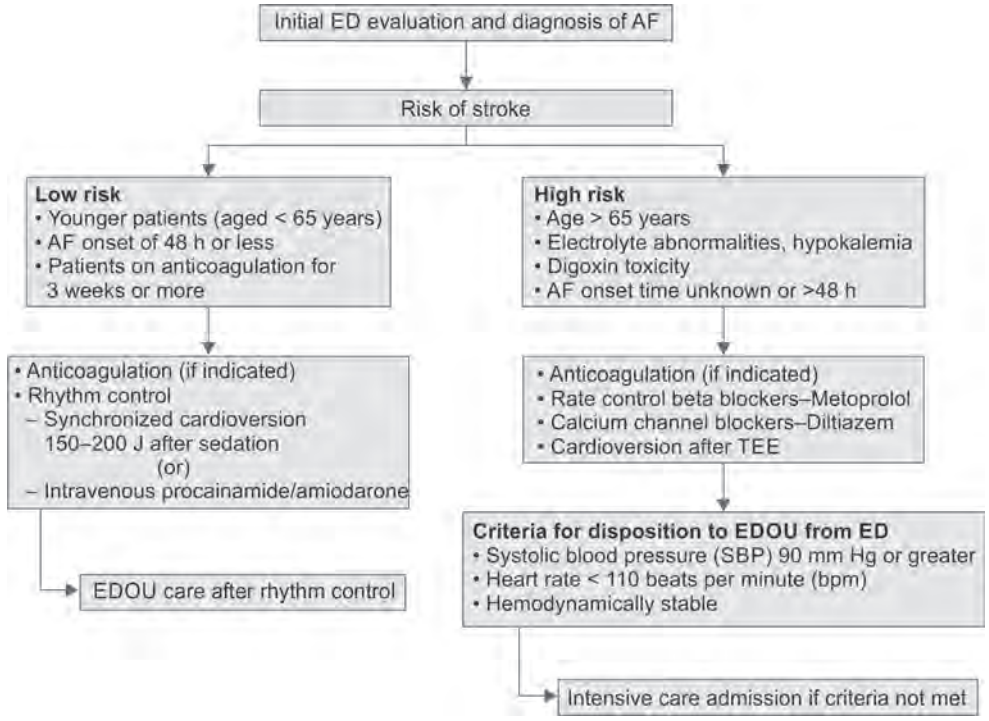
- AF rate controlled or rhythm converted to normal sinus for at least 1–2 h
- Negative serial cardiac biomarker tests if ACS is suspected
- Discharge advice
- Cardiology follow-up in 3–5 days
- Prescribe 30 days of anticoagulation if indicated
- Prescribe the lowest long-acting oral dose of rate control medication equivalent to what they received in EDOU, if discharged on rate control medications
- Educate patients and family about risks of bleeding or stroke, medication side effects, and dietary precautions

(ACS: acute coronary syndrome; AF: atrial fibrillation; DOAC: direct oral anticoagulant; EDOU: emergency department-based observation unit; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol usage; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin)

TABLE 5: Risk stratification for anticoagulation therapy in atrial fibrillation patients.

CHA_2DS_2-VASc scoring system		***HAS-BLED score***	
Components	*Score*	*Components*	*Score*
Congestive heart failure	1	Hypertension	1
		Abnormal liver and kidney	1
Diabetes	1	Stroke	1
Hypertension	1	Bleeding predisposition	1
Stroke/TIA/thromboembolism	2	Labile INR	1
Age > 75 years	2	Elderly >65	1
Age 65–74 years	1	Drugs (use of antiplatelet and alcohol)	1
Sex: Female	1	A score of 3 or greater indicates a high risk of bleeding	
Total maximum score 9: AHA recommends oral anticoagulation for a score of 2 or greater. Aspirin is recommended in known CAD patients even with a score of 0			

(AHA: American Heart Association; CAD: coronary artery disease; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol usage; INR: international normalized ratio; TIA: transient ischemic attack)



(ED: emergency department; EDOU: emergency department-based observation unit; TEE: transesophageal echocardiography)

FLOWCHART 2: Stepwise systematic approach to atrial fibrillation.

shifted the initial management of uncomplicated DVT toward the outpatient setting. The diagnosis of PE, however, remained a reason for hospital admission for anticoagulation and monitoring for hemodynamic compromise.

Patients with underlying HF, pulmonary disease, or active cancer have significantly higher mortality rates in the setting of acute PE and may, therefore, require higher levels of care than patients without such comorbidities. Scoring systems, such as the *PESI (pulmonary embolism severity index), sPESI (simplified pulmonary embolism severity index), Hestia score*, and *Geneva score*, incorporate medical history and clinical criteria into a score that establishes patients at either low or very low risk for adverse outcomes. Both the PESI and the sPESI have demonstrated sufficient sensitivity to indicate outpatient or observation management in patients with low scores (**Table 9**). Likewise, a Hestia score of 0 indicates low risk (**Box 1**).

ACUTE ABDOMINAL PAIN

Gastrointestinal (GI) emergencies, such as abdominal pain, are one of the common symptoms in ED. The traditional teaching for a patient with abdominal pain is to perform a rapid diagnostic workup with pain management. After

TABLE 6: Patient selection for EDOU care acute heart failure.

Exclusion criteria	*Patient management*	*Disposition*
• Newly diagnosed HF patients • HF with new ischemic ECG changes or elevated troponins • HF with unstable cardiac arrhythmia • HF with cardiogenic shock/ symptomatic hypotension • Difficulty weaning off NIV or persistent respiratory distress • BNP > 1,000 pg/mL or NT-pro BNP > 5,000 pg/mL • HF with impaired renal function	• Record weight and oxygen requirement on arrival • Strict input and output measurement • Cardiac monitoring for early detection of malignant arrhythmias • Measurement of electrolytes, serial troponins • Diuretics and fluid restriction to reduce fluid overload • Consider initiation of a synergistic thiazide diuretic, if there is an inadequate response to the initial intravenous diuretic dose • Initiate vasodilators with caution as hypotension occurs following initial diuresis • Identify the trigger for HF and educate the patient • Look for medication noncompliance	• *Home* • Hemodynamic stability • Resolution of dyspnea and edema • Admit into hospital • No improvement in fluid balance, oxygen requirement, vital signs • The decline in cardiac, pulmonary, or renal function

Discharge advice

- Educate patient and family members regarding medication and diet compliance
- Dietary restriction of sodium to 1,500 mg/day
- Educate patients and families to look out for and recognize signs and symptoms of worsening HF such as increasing dyspnea, increased weight gain, and increasing fatigue

(BNP: brain natriuretic peptide; HF: heart failure; NIV: noninvasive ventilation; NT-pro BNP: N-terminal pro-brain natriuretic peptide)

TABLE 7: Patient selection for observation unit treatment—syncope.

Transient loss of consciousness due to cerebral hypoperfusion, the cause for which can be life-threatening or benign	
Suspected cause of syncope	EDOU monitoring/management
GI bleed	Serial hemoglobin, hematocrit
Dehydration	• Rehydration with fluids • Assessment of metabolic panel
Cardiac	• Serial troponin measurements • BNP measurement • Continuous cardiac monitoring
• EDOU management • Vitals monitoring • Clinical/laboratory reassessments based on the suspected cause	
Discharge • Severe disease ruled out • Patients discharged without a clear diagnosis—advice to follow up with a physician • Outpatient cardiac monitoring (Holter monitoring and Loop recorders) in consultation with cardiology—if cardiac arrhythmia suspected but could not be confirmed during EDOU stay	

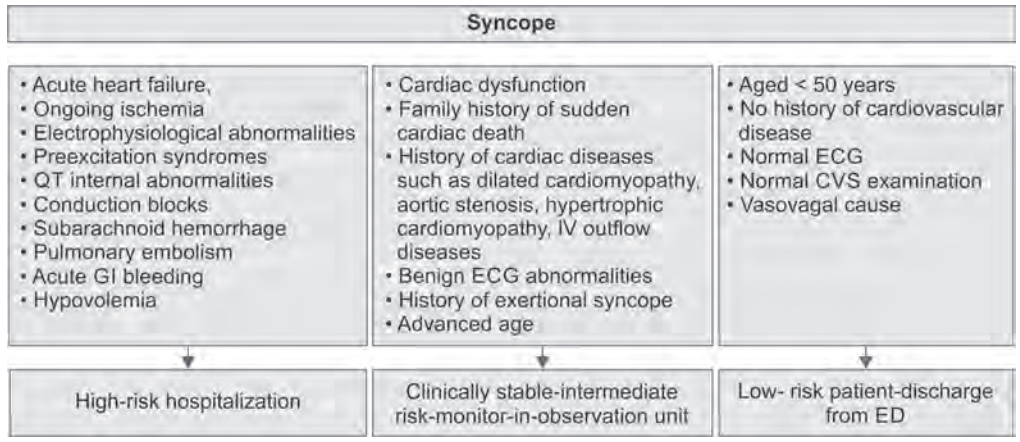
(BNP: brain natriuretic peptide; EDOU: emergency department-based observation unit; GI: gastrointestinal)

the initial ED workup, patients are either discharged home or admitted to a surgical or medical inpatient service (**Box 2**). Rapid and accurate diagnosis and treatment of patients increasingly rely on early radiographic testing. EDOUs are helpful in improving the patient experience by using appropriate imaging modalities. EDOU management is helpful in reducing the morbidity and mortality and health care expenditures. Inclusion and exclusion criteria related to GI complaints for EDOU protocols may remain the same. Three levels are considered for inclusions and exclusions: (1) Healthcare system level, (2) general patient level, and (3) within the specific patient protocol. Capacity constraints, availability of required resources, unit factors, and team factors are important at the level of the healthcare system.

APPENDICITIS

In patients who present to the ED with abdominal pain, the most common diagnosis that is suspected is appendicitis, which requires surgery. History, physical examination, and laboratory evaluation are included in the initial ED, although no single laboratory value can rule in or rule out the diagnosis of appendicitis. Risk scores and imaging scoring systems are included in the evaluation of patients with suspected appendicitis. Alvarado score, also known by its mnemonic MANTRELS (Migration to the right iliac fossa, Anorexia, Nausea/Vomiting, Tenderness in the right iliac fossa, rebound pain, Elevated temperature (fever), Leukocytosis, and Shift of leukocytes to the left) score, is commonly used in addition to the history, physical, and laboratory values. Eight predictive factors are used in the Alvarado score (**Table 10**) given a point value of 1 or 2 based on diagnostic weight.

Pediatric appendicitis score, appendicitis inflammatory response score, Raja Isteri Pengiran Anak Saleha appendicitis score, and the adult appendicitis score are the other scoring systems that may be used to categorize the patients into low, intermediate, and high risk for appendicitis. Imaging studies are obtained if the clinical scoring system places the patient in the moderate to high-risk group. The approach to a patient with appendicitis in EDOU is summarized in **Flowchart 4**.


Syncope
• Acute heart failure,
• Ongoing ischemia
• Electrophysiological abnormalities
• Preexcitation syndromes
• QT internal abnormalities
• Conduction blocks
• Subarachnoid hemorrhage
• Pulmonary embolism
• Acute GI bleeding
• Hypovolemia
• Cardiac dysfunction
• Family history of sudden cardiac death
• History of cardiac diseases such as dilated cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, IV outflow diseases
• Benign ECG abnormalities
• History of exertional syncope
• Advanced age
• Aged < 50 years
• No history of cardiovascular disease
• Normal ECG
• Normal CVS examination
• Vasovagal cause
High-risk hospitalization
Clinically stable-intermediate risk-monitor-in-observation unit
Low- risk patient-discharge from ED

(CVS: cardiovascular; ED: emergency department; GI: gastrointestinal)

FLOWCHART 3: Approach to syncope in observation unit.

TABLE 8: Patient selection for observation unit treatment—venous thromboembolism (DVT + PE).

Inclusion criteria	*Exclusion criteria—DVT*	*Exclusion criteria—PE*
• Stable patient • No comorbidities • Low-risk PE or DVT based on risk stratification scores	• Critical limb ischemia • Large iliac/pelvic DVTs • Decompensated comorbidities • Require inpatient monitoring	• Hemodynamically unstable—hypotension, shock, acute cardiac arrest • Presence of RV dysfunction • Elevated BNP or NT-pro BNP levels • Elevated troponin level • Patients with comorbidities—heart failure, pulmonary disease, active cancer
Risk stratification • PESI, sPESI • Hestia score		
Patient management • Anticoagulation—based on economic considerations • Establish follow-up with the physician • Educate about dietary restrictions and monitoring therapy if initiated on VKAs • Educate patients and caregivers about the disease and bleeding risks		

(BNP: brain natriuretic peptide; DVT: deep venous thrombosis; NT-pro BNP: N-terminal pro-brain natriuretic peptide; PE: pulmonary embolism; RV: right ventricular; VKAs: vitamin K antagonists; PESI: Pulmonary Embolism Severity Index; sPESI: simplified Pulmonary Embolism Severity Index)

TABLE 9: Assessing risk score for managing VTE patients in an observation unit.

Characteristics	*PESI*	*sPESI*
Age	1 point per year of age	1 point if aged >80 years
Male sex	10 points	–
Cancer	30 points	1 point
History of HF	10 points	1 point if either/both
Chronic pulmonary disease	10 points	
Heart rate > 100	20 points	1 point
SBP < 100 mm Hg	30 points	1 point
Respiratory rate > 30	20 points	–
Temperature < 36°C/96.8°F	20 points	–
Altered mental status	60 points	–
Oxygen saturation < 90%	20 points	1 point
• *sPESI score*: 0—low-risk patient; *PESI score*: <65 years—very low 30-day mortality risk • Low PESI and sPESI indicate outpatient or observation management • Hestia score of 0 indicates low risk		

(HF: heart failure; PESI: pulmonary embolism severity index; sPESI: simplified pulmonary embolism severity index; SBP: systolic blood pressure)

BOX 1: Hestia risk stratification score (any one positive response requires inpatient management).

- Hemodynamically unstable
- Indication for fibrinolysis or thrombectomy
- At high risk for bleeding:
  - GI bleeding within the last 14 days
  - Stroke within 4 weeks
  - Surgery within 2 weeks
  - Bleeding diathesis
  - Thrombocytopenia (<75–109/L)
  - Uncontrolled hypertension (SBP > 180 mm Hg, diastolic blood pressure > 110 mm Hg)
- Supplemental oxygen required for oxygen saturation > 90%
- PE occurred while on anticoagulation
- Parenteral pain medication required
- Medical or social reason necessitating inpatient admission
- Creatinine clearance < 30 mL/min
- Severe hepatic impairment
- Pregnant
- History of heparin-induced thrombocytopenia

(GI: gastrointestinal; PE: pulmonary embolism; SBP: systolic blood pressure)

BOX 2: Patient selection for observation unit treatment—abdominal pain.

- Exclusion criteria
- Unstable vital signs
- Surgical abdomen
- Severe sepsis
- Immunocompromised
- Diagnostic workup reveals any emergent surgical condition
- Differential diagnosis of abdominal pain ranges from very low-risk conditions, such as constipation, to catastrophic conditions, such as a ruptured abdominal aortic aneurysm. EDOUs may be used for evaluation and possible treatment of conditions such as appendicitis, GI bleeding, and pancreatitis
- Several emergent conditions may initially appear to have a GI etiology such as epigastric pain of an inferior wall, acute myocardial infarction, right upper quadrant pain of hepatic congestion in congestive heart failure, generalized abdominal pain with nausea and vomiting in diabetic ketoacidosis, back and flank pain in pulmonary embolism

(EDOUs: emergency department-based observation units; GI: gastrointestinal)

TABLE 10: Patient selection for treatment of appendicitis in observation unit.

Diagnosis is considered based on history, physical examination, and laboratory values

Alvarado score/MANTRELS score—used to risk stratify suspected patients

Suspected appendicitis patient with:

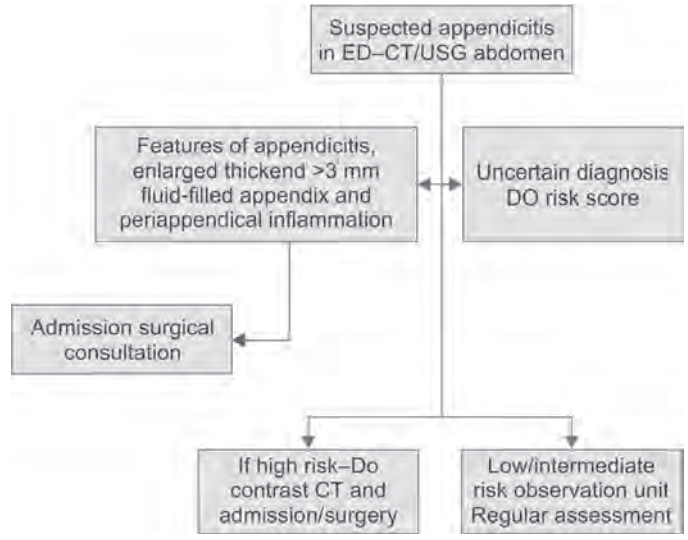
- Negative or indeterminate initial imaging results
- Diagnostic uncertainty and lower risk scoring

Nonoperative treatment of appendicitis should not be considered in EDOU

Alvarado scoring system for appendicitis

Characteristics		***Points***
Symptoms	Nausea and/or vomiting	1
	Anorexia	1
	Migration of pain to right lower quadrant	1
Signs	Tenderness in the right lower quadrant	2
	Rebound	1
	Temperature > 37.3°C (99.1°F)	1
Laboratory tests	>10,000/dL	2
White blood cell count	Left shift	1

Score	**Risk**	**Management**
1–4	Low risk	• Observation • Serial clinical reassessment and laboratory studies • Repeat risk assessment with Alvarado score
5–6	Intermediate risk	
7–10	High risk	• Admission • Contrast-enhanced CT of abdomen


Suspected appendicitis in ED–CT/USG abdomen
Features of appendicitis, enlarged thickend >3 mm fluid-filled appendix and periappendical inflammation
Uncertain diagnosis DO risk score
Admission surgical consultation
If high risk–Do contrast CT and admission/surgery
Low/intermediate risk observation unit Regular assessment

(ED: emergency department; USG: ultrasound)

FLOWCHART 4: Approach to appendicitis in EDOU.

GASTROINTESTINAL BLEEDING

Gastrointestinal bleeding (GIB) is usually classified as upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB). This categorization is done anatomically at the ligament of Treitz, the ligament that suspends the duodenojejunal flexure and inhibits the reflux of gastrointestinal contents distal to this site. Bleeding from

the upper GI tract indicates hematemesis. Clinical severity, risk of mortality, treatment requirements, length of stay, and cost are different in each and every patient who present with gastrointestinal bleed. Clinical risk scores such as Glasgow Blatchford Score and Clinical Rockall Score (**Table 11**) are used and helpful for an emergency physician in recognizing and managing these factors.

ACUTE PANCREATITIS

Acute pancreatitis (AP) is a frequent cause of abdominal pain. The diagnosis of AP requires the presence of two out of three features: (1) Abdominal pain consistent with AP, (2) serum lipase or amylase at least three times the upper limit of normal, or (3) characteristic findings on abdominal imaging, generally

TABLE 11: Patient selection for observation unit treatment—GI bleed.

Exclusion criteria for observation care	***EDOU strategy in GI bleed management***
• Hemodynamic instability • Persistent orthostasis despite 1-L intravenous fluid bolus, syncope • Evidence of active bleeding in ED—frequent episodes of hematemesis, melena, bright red blood per rectum • Coagulopathy • Known esophageal varices • Transfusion requirement • Comorbidities such as heart failure, ischemic heart disease, renal failure, liver failure, disseminated malignancy	• Keep patient NPO • Place two large-bore I catheters • PPI • Frequent reassessments—vital signs, pallor, orthostasis, repeat Hb/PCV • Identify the source of bleeding • Gastroenterology consultation for OGDScopy or colonoscopy within 24 h ideally • Bowel preparation if planned for colonoscopy

	Upper GI bleed	***Lower GI bleed***
Clinical features	• Melena • Past history of UGIB • Positive nasogastric tube aspirate	• Blood clots in stool • Hematochezia • Past history of LGIB
Laboratory value	BUN to Cr ratio >30	BUN to Cr ratio <30
Common causes	• Peptic ulcer disease • Variceal bleeding • Esophagitis • Mallory–Weiss tear	• Diverticular bleeding • Hemorrhoids • Polyps • Colorectal cancer • Intestinal ischemia • Colitis

Glasgow Blatchford criteria—low-risk GI bleed Clinical Rockall score—low-risk bleed		
BUN	<18.2 mg/dL	Age <60 years
Hemoglobin	Men >13 g/dL	Blood pressure > 100 mm Hg systolic
Hemoglobin	Women >12 g/dL	Pulse < 100/min
SBP	>109 mm Hg	• No syncope, melena, liver disease, heart failure • No heart failure, ischemic heart disease, renal failure, liver failure, disseminated malignancy, or other major comorbidities
Pulse	<100 beats per minute	

Low-risk GI bleed patients meeting Glasgow Blatchford criteria can be observed in OU

Discharge criteria
- Clinically stable
- Stable hemoglobin/hematocrit level
- No evidence of rebleeding
- No concern of high risk of rebleeding on endoscopy
- Discharge advice
- Avoid NSAIDs, anticoagulants, alcohol consumption
- Timely follow up in outpatient service

(BUN: blood urea nitrogen; ED: emergency department; GI: gastrointestinal; Hb: hemoglobin; LGIB: lower gastrointestinal bleeding; NPO: nil per oral; NSAIDs: nonsteroidal anti-inflammatory drugs OGD: oesophago-gastro-duodenoscopy; OU: observation unit; PCV: packed cell volume; SBP: systolic blood pressure; UGIB: upper gastrointestinal bleeding)

contrast-enhanced CT. The Atlanta Classification of AP most recently modified its classification of AP into two phases: (1) Early and (2) Late. Further classification is based on severity. Mild AP has no organ failure, or local or systemic complications, and often resolves within the 1st week, which may be ideal for EDOU management. Moderately severe AP is defined by the presence of transient organ failure, local complications, or exacerbation of the comorbid disease. Severe AP is defined by persistent organ failure for >48 hours. The Atlanta Classification is used to provide nomenclature regarding the severity of AP, but it does not provide an assessment of risk. Several scoring systems providing an assessment of risk have been published. Some of the most commonly known scores are the Ranson criteria, Glasgow score, and the APACHE II (acute physiology and chronic health evaluation II) score, which are based on clinical variables. Limitations of these scores at the time of ED disposition include that the Ranson criteria and the Glasgow score require the input of clinical variables at 48 hours, whereas the APACHE II is very complex and not specific to AP.

More recent risk predictors may provide critical information earlier in the course of the presentation of AP (**Table 12**). The *HAPS (harmless acute pancreatitis score)* is made up of three parameters and is used to help identify patients with AP who would not require intensive care unit (ICU) level of care and could potentially not require inpatient treatment at all. The HAPS could provide utility in the evaluation of AP to determine if hospitalization or an OU stay is needed or if the patient may be a candidate for discharge home. Another modern risk score, the *BISAP (bedside index of severity in acute pancreatitis) score*, is currently used to determine AP severity. Calculation of this score depends on five parameters that are easily attainable in the ED. The BISAP score is simple to use and is an accurate method for identifying patients at increased risk for in-hospital mortality. Several publications have compared the BISAP score with other risk scores in predicting the severity of AP and have noted its usefulness in determining AP severity earlier than other scoring systems. The BISAP score may be a useful tool to help divert appropriate patients to an EDOU. Exclusion criteria, management, and discharge criteria of AP for EDOU management are given in **Table 13**, and a summary of managing the AP is given in **Flowchart 5**.

TRANSIENT ISCHEMIC ATTACK/MINOR STROKE

Transient ischemic attack: Transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. *Minor stroke*: Patients with neurological dysfunction presenting after 24–48 hours and able to perform their activities of daily living at home and being ambulated unassisted in the ED.

Transient ischemic attack presents without any residual deficit and patients appear clinically normal; most patients do not have any event during or after the TIA so these are the ideal candidates for OU workup. TIA is the risk factor for subsequent

TABLE 12: Risk scores used for initial evaluation of acute pancreatitis.

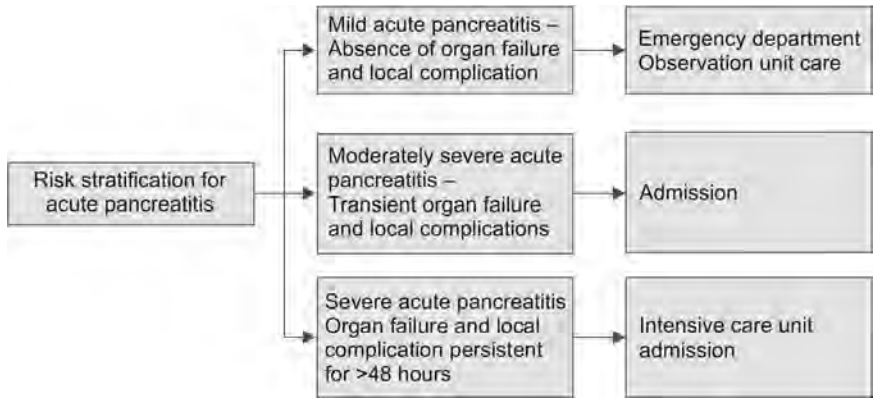
Risk score	*Clinical parameter*	*Scoring*	*Utility for EDOU*	*Purpose*
BISAP	• Obtained within first 24 h • BUN > 25 mg/dL • Impaired mental status • SIRS • Age > 60 years • Pleural effusion	• 1 point for each parameter Maximum score = 5 • Score = 0: 0.1% mortality • Score ≤ 2: 1.9% mortality	• Easily calculated before EDOU disposition • Could consider patients with BISAP score 2	Predicts mortality from acute pancreatitis
HAPS	• Initial evaluation • No rebound tenderness • Normal HCT Cr <2 mg/day	• 1 point for each parameter • Maximum score = 3 • Score = 0 not requiring hospitalization	• Easily calculated before EDOU disposition • Patients with a score of 0 could be discharged or placed in EDOU	Predicts mild course of acute pancreatitis

(BUN: blood urea nitrogen; BISAP: bedside index of severity in acute pancreatitis; EDOU: emergency department-based observation unit; HAPS: harmless acute pancreatitis score; HCT: hematocrit; SIRS: systemic inflammatory response syndrome)

TABLE 13: Exclusion criteria management and discharge criteria for acute pancreatitis in an observation unit.

Exclusion criteria for EDOU care	*EDOU management*	*Discharge criteria and advice*
• Gallstone pancreatitis • Blood urea nitrogen > 20 mg/dL • Hematocrit > 44% • Acute kidney injury • Pleural effusion • Pulmonary infiltrates • Extra pancreatic collections • Altered mental status	• Early aggressive hydration with IV Fluids (caution in elderly, cardiac, or renal patients) • Regular assessment of clinical status, vital signs, urine output, and laboratory values • Monitor for complications—fluid overload, abdominal compartment syndrome, etc. • Bowel rest with early oral feedings as appropriate beginning with clear liquids • Pain control with intravenous opioids • Antiemetics	• Stable vital signs • Tolerates solid diet and analgesics orally • Advice discontinuation of alcohol or medication which triggered the development of pancreatitis • Provide outpatient follow-up

(EDOU: emergency department-based observation unit)


Risk stratification for acute pancreatitis
Mild acute pancreatitis – Absence of organ failure and local complication
Emergency department Observation unit care
Moderately severe acute pancreatitis – Transient organ failure and local complications
Admission
Severe acute pancreatitis Organ failure and local complication persistent for >48 hours
Intensive care unit admission

FLOWCHART 5: Summary of management of acute pancreatitis in emergency department-based observation unit.

vascular events. The main objective of the initial evaluation of the management of TIA patients in EDOU are early detection and prevention of stroke, detection of causes of TIA, and prevention of future strokes. Causes of TIA may be vascular (extracranial or intracranial), cardioembolic, and cryptogenic. Evaluation of TIA includes a history of duration of symptoms assessing the vascular risk factors and other suspected etiology, and examination includes a structured stroke examination, such as the NIHSS (National Institutes of Health Stroke Score), to improve the clinical detection of small, subtle strokes. ECG and cardiac monitoring are important for the detection of atrial fibrillation. Laboratory testing should include a complete blood count, serum glucose, electrolytes, and prothrombin time. Brain imaging, with either CT or MRI, should be obtained if possible. Epilepsy, postictal paralysis, complex migraines, such as hemiplegic or ocular migraines, cervical disc disease, transient global amnesia, intracranial lesions, such as subdural hematomas and mass lesions, inner ear disease with vertigo, and metabolic derangement of the serum glucose, sodium, or calcium are the few conditions which commonly mimic the TIA.

There is no gold standard for diagnosing TIA. False-positive diagnostic rates range from 25% to 38%. To improve diagnostic performance, scores have been developed. The most common tool used for TIA risk stratification is ABCD2 score recommended by the American Heart Association (AHA). Admission or discharge of the patient is based on a total score more than or less than 3. However, further studies revealed that patients with ABCD2 less than 3 even detected high levels of carotid stenosis, atrial fibrillation, and other cardiac sources of embolism. Based on these studies, the American College of Emergency Physicians (ACEP) in 2016 recommends that physicians should not rely on the ABCD2 score for discharging the patient directly from the ED.

"Get up and Go" test: Objective measure is to assess the mobility of the patient in which the patient is asked to stand from a seated position, walk a short distance, turn around, walk back, and sit down. It is graded on a five-point scale in which a score of 1 indicates no need for assistance or risk of falling and a score of 5 indicates that the patient fell or almost fell during the test. A score of 3 indicates a risk of falling and should be given if the patient exhibits undue slowness, hesitancy, or stumbling. Although this test has not been validated in this population, the provider needs to perform some functional assessment on patients before selecting the patient for EDOU care. *ED goals*: Early detection and prevention of stroke, detection of alternate causes of TIA/stroke, *ED screening, bedside* dysphagia test, mobility test

These patients should be carefully selected on the basis of criteria given in **Table 14** for managing in OU and a stepwise approach should be followed as shown in **Flowchart 6**.

DIZZINESS/VERTIGO

Dizziness/vertigo is one of the common presenting waxing and waning symptoms in ED, with very broad differential and underlying etiology. It may involve many different organ systems as well as pharmacologic and environmental factors. Dizziness has peripheral, vestibular, or brainstem pathology. Evaluation of neurogenic dizziness focused on two main anatomic regions: (1) The cerebellum (central) or (2) The vestibular system (peripheral). An attempt should be made to determine if the cause is central or peripheral (**Table 15**). Patients with cerebellar dysfunction may present with ataxia or falls, and neurologic examination should include cerebellar and gait testing, whereas those with vestibular dysfunction may present with vertigo, and evaluation peripheral cause of vertigo should include Dix–Hallpike maneuver to test for nystagmus. Many patients may require laboratory testing and imaging.

A complete blood count and chemistry panel will screen for anemia, infection, or electrolyte abnormalities, such as hyponatremia, which can contribute to their symptoms. Consider serum vitamin B12 and folic acid levels in those presenting with ataxia of insidious onset, especially if they are at risk for malnutrition. A noncontrast head CT is indicated as the initial test for patients with a suspected central cause of neurogenic dizziness. This will rule out mass lesions, intracranial hemorrhage, subacute ischemic strokes, or cerebellar atrophy. Patients with vertigo that is clearly the result of a peripheral cause do not need imaging. ED treatment of peripheral causes of vertigo is mainly supportive and can include intravenous (IV) fluids, benzodiazepines, antiemetics, and antihistamines, such as meclizine. The Epley maneuver can resolve benign paroxysmal peripheral vertigo and may be performed by the ED provider or neurology consultant. The EDOU can be considered for continued diagnostic or therapeutic care of ED patients with vertigo (**Table 16**). Ideal patients for the EDOU are those whose symptoms are likely peripheral. Patients with concern for a central process based

TABLE 14: Patient selection for EDOU care—TIA minor stroke.

Exclusion criteria	*Inclusion criteria*	*EDOU intervention*
• Persistent acute neurologic deficit or crescendo TIAs • Disabling stroke (new gait disturbance, unable to perform ADLs, fails dysphagia screen and mobility test) • Nonfocal symptoms—confusion, weakness, seizure, transient global amnesia, depressed mental status • Known extracranial embolic source (history of atrial fibrillation, cardiomyopathy, prosthetic heart valve, mural thrombus, recent myocardial infarction, endocarditis) • Presence of active comorbidities • Poor social support • History of prior large stroke • Positive head CT/MRI • Known carotid stenosis (>50%)	• *Transient ischemic attack (TIA):* Resolved acute deficit • *Nondisabling stroke*: Will not require nursing home or inpatient rehabilitation on discharge • Independent with ADLs • Passes bedside dysphagia screen and mobility test (get up and go) • No high-risk conditions • CT brain negative for hemorrhage/mass lesion (unless prompt MRI planned) • Workup can be completed within 18 h	• Neuro checks every 2 h to detect stroke, crescendo TIA by trained nurses, emergency physicians • Neurology consult to detect occult stroke • Evaluate the size of stroke: MRI brain with and without contrast • Evaluate for embolic sources • MR angiography/CT angiography of head and neck vessels or Doppler of neck vessels • 2D echocardiography • Cardiac monitoring for at least 12 h for paroxysmal atrial fibrillation • Evaluate for contributing factors: Lipid panel, HbA1c level • Antiplatelet therapy: Aspirin ± clopidogrel • Stroke-preventive education (lipids, smoking, diabetes mellitus, hypertension, obesity, alcohol, stroke)

Disposition

Home	**Hospital**
• No recurrent deficits/Improved • Able to do daily routine work • Reassuring testing/negative workup • Clinically stable • Initiated on antiplatelet therapy	• Recurrent symptoms/need for rehabilitation • Evidence vascular disease stenosis of neck vessels • Evidence of embolic source requiring treatment (e.g., heparin/coumadin); for example, mural thrombus, paroxysmal atrial fibrillation • Unable to complete workup or safely discharge patient within the time frame • Physician/neurology judgment

Get up and go test

Score	**Description**
1	Normal: No assistance required; no evidence of falling
2	Very slightly abnormal
3	Mildly abnormal: fall risk; patient exhibited undue slowness, hesitancy, abnormal movements of the trunk or upper limbs, staggering or stumbling
4	Moderately abnormal
5	Severely abnormal: At risk of falling during the test

(ADLs: activities of daily living; HbA1c: glycated hemoglobin; TIA: transient ischemic attack)

Source: Mathias S, Nayak USL, Isaacs B. Balance in elderly patients: the get-up and go test. Arch Phys Med Rehabil 1986;67:387-9.

on history or physical examination should be admitted for further workup.

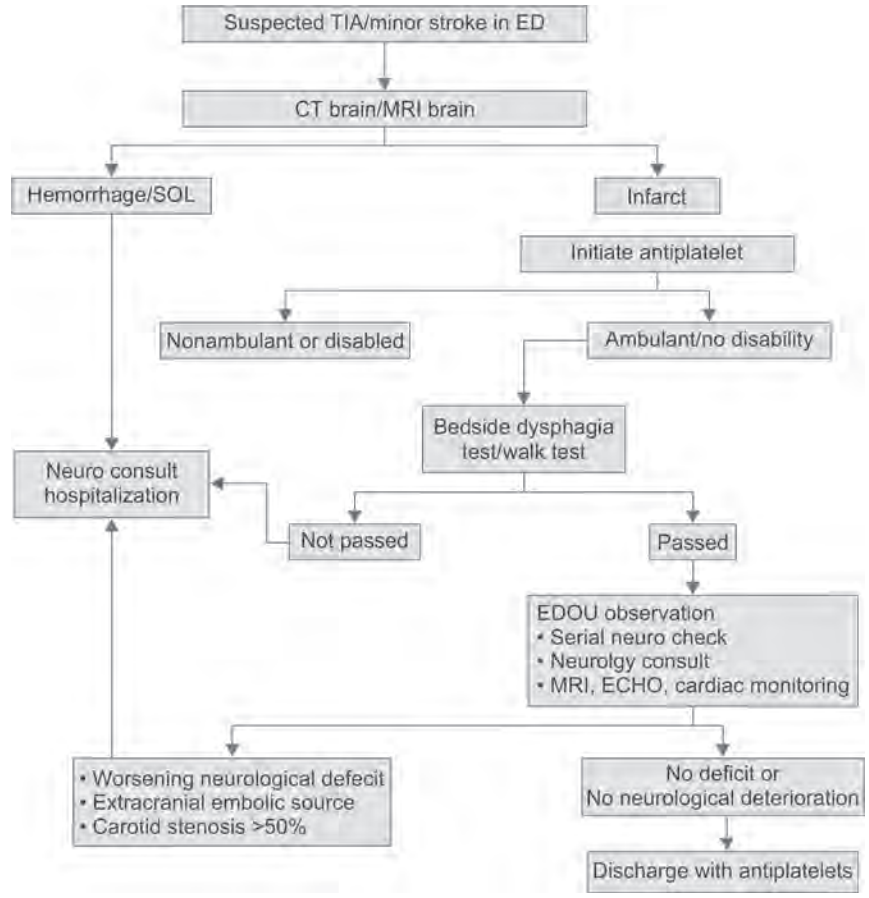
BACK PAIN

Back pain is the most common musculoskeletal complaint in the ED. Most of the patients presenting to the ED will have a benign cause for their back pain. But ED physicians must be aware of life-threatening causes of back pain as well as cases in which neurologic deficit exists while evaluating the patient. ED evaluation should focus on to rule in or rule out high-risk causes of back pain, such as abdominal aortic aneurysm, spinal cord compression, and pain management.

Patients should be assessed for neurologic deficit as well as for possible urinary or fecal incontinence, traumatic etiology, or IV drug use history. A careful examination must be performed to detect weakness and numbness as well as to determine if the weakness is due to pain or if it is a sensory change in a dermatomal distribution. Ancillary tests, such as laboratory tests or imaging, are only performed in patients with red flags on history or physical for malignancy, fracture, infection, or epidural compression syndrome. The goals of EDOU care (**Table 17**) for patients with acute back pain are to treat pain for patients with intractable symptoms in the ED and to obtain advanced neuroimaging for patients at mild to moderate risk for lumbar radiculopathy.

HEADACHE

Headache is also a common complaint in ED. Headache with benign conditions is usually discharged to home following ED treatment. A few patients will require additional



(ADLs: activities of daily living; ECHO: echocardiogram; ED: emergency department; EDOU: emergency department-based observation unit; HbA1c: glycated hemoglobin; SOL: space-occupying lesion; TIA: transient ischemic attack)

FLOWCHART 6: Approach to patients with TIA/stroke.

TABLE 15: Vertigo.

	Cerebellar dysfunction	***Peripheral vestibular dysfunction***
Presentation	Ataxia or falls	Vertigo
Examination	• Gait assessment • Cerebellar signs	Dix–Hallpike maneuver—look for nystagmus
Treatment	Admission Neuro consult	EDOU management: • IV fluid • Benzodiazepines • Antiemetics • Antihistamines—meclizine • Epley maneuver

(IV: intravenous)

diagnostic and therapeutic interventions, making them ideal EDOU candidates. ED evaluation of patients with headache has two primary goals: (1) To rule out life-threatening causes of headache, such as SAH or meningitis, and (2) to start appropriate therapy. A thorough history and examination will be helpful in narrowing down the differential diagnosis and in giving a better understanding about the characteristics of the current headache, e.g., tension headache or migraine, which can be treated with oral analgesia and discharged after appropriate pain relief is obtained.

Patients who are vomiting or appear in distress may require IV fluids, analgesia, and antiemetics. Noncontrast head CT is not recommended for routine evaluation of patients with an headache but is a recommended initial step to rule out SAH or mass lesion.

There are two groups of patients with headache who may benefit from care in an EDOU (**Table 18**). Each of these conditions requires coordination with ancillary services, specifically neurology, before the initiation of an headache protocol to ensure efficient care. The first group is patients with benign headache who need better pain control and the second is patients in whom there is a concern for idiopathic intracranial hypertension (IIH), previously known as pseudotumor cerebri.

Patients with an established diagnosis of migraines can be chosen for EDOU management or whose current headache is similar to their previous episodes. Patients with fever, neurologic deficits, and other comorbidities should be excluded. EDOU care for patients with tension/migraine consists of continued supportive care, such as a quiet, dark room where they can rest, routine analgesia, and antiemetics. Usual medications are nonsteroidal anti-inflammatory medications (NSAIDs) or steroids. Neurology consultation may be necessary for headache that are difficult to abort, as they can recommend other abortifacient medications, such as valproic acid. Some patients may require further imaging, such as MRI/MRA. Disposition patients whose headache have been aborted and are at their neurologic baseline may be discharged home.

TABLE 16: Selection of patient for observation unit care—dizziness/vertigo.

Inclusion criteria for observation care	*Exclusion criteria*	*Potential interventions in EDOU*
• Likely peripheral vertigo • Normal CT/MRI of brain • Normal cerebellar and cranial nerve examination	• Acute hearing loss, double vision, fixed neurologic deficits • Severe headache, head injury • Hemodynamic instability • High clinical suspicion for central vertigo or stroke	• Symptomatic control • Rule out differential diagnosis—anemia, hyponatremia, B12/folate deficiency, sepsis • MRI and neurology consultation

Disposition	
Home	**Hospital**
• Stable vital signs • Able to ambulate and care for self safely • Able to take oral medications/food	• A positive finding on testing (MRI or laboratory) • Consultant recommendation • Persistent symptoms, inability to ambulate

(EDOU: emergency department-based observation unit)

TABLE 17: Selection of patient for observation unit—back pain.

Inclusion criteria for EDOU care	*Exclusion*	*EDOU intervention*
• Inability to control pain in the emergency department • No known malignancy or injection drug use • No history of trauma • No fracture seen on imaging	• Frequent visits for back pain • Bowel/bladder incontinence or saddle anesthesia • Inability to stand or walk due to neurologic deficit • Fever, suspected discitis, or spinal epidural abscess	• Pain management • MRI or CT to rule out spinal stenosis, malignancy • Frequent reassessment • Neurology or neurosurgery consultation

Disposition	
Home	**Hospital**
• Able to ambulate and care for self • Tolerates oral analgesics	• Worsening neurologic examination • Inability to walk, care for self • Intractable pain • Consultant recommendations • Abnormal imaging • Requires surgical intervention

(EDOU: emergency department-based observation unit)

TABLE 18: Selection of patient for observation unit care—headache.

Inclusion	*Exclusion*	*EDOU interventions*
• Tension headache • History of migraine—similar episodes in past • Drug-related headache • No focal neurologic signs • Normal CT brain scan	• Focal neurologic signs • Meningismus • Elevated intraocular pressure • Abnormal CT scan • Hypertensive emergency • Suspected temporal arteritis • Blocked ventriculoperitoneal shunt • Frequent ED visits	• Serial examinations including vital signs • Neurology checks: Level of alertness, speech, motor function • Analgesics • Neurology/ophthalmology consult as indicated • MRI with MR angiogram/venogram imaging if indicated

Disposition criteria
• Home—pain resolved • No clinical deterioration • The primary goal of ED evaluation of headache is to rule out life-threatening causes such as subarachnoid hemorrhage or meningitis and to begin appropriate therapy

(ED: emergency department; EDOU: emergency department-based observation unit)

TABLE 19: Selection of patient for observation unit care—seizure.

Inclusion criteria for EDOU care	*Exclusion*	*EDOU interventions*
• Known seizure disorder • No active seizure within past 2 h • New-onset seizures with a normal neurology examination, normal brain imaging, normal laboratory values (electrolytes, blood glucose)	• Ongoing seizures or postictal state • Persistent focal neurologic deficit • Suspected meningitis or stroke • Delirium due to other causes • Seizures due to toxic exposure of drugs, hypoxemia • Pregnancy beyond first trimester/eclampsia • New findings on neuroimaging • Cardiac arrhythmias	• Appropriate anticonvulsant therapy • Seizure precautions—position, NPO/oral intake with caution • Cardiac and oximetry monitoring • Serial (every 2–4 h) neurology checks and vital signs • Toxicologic testing as needed • EEG • Neurology consultation

Disposition	
Home	**Hospital**
• No clinical deterioration • Anticonvulsants initiated • Correction of abnormal lab parameters • Resolution of postictal or benzodiazepine-related sedation	• Clinical/neurological deterioration • Identification of other causes of seizure • Recurrent seizures or status epilepticus

(EDOU: emergency department-based observation unit; EEG: electroencephalogram; NPO: nil per oral)

Patients should be admitted if they have a change in their neurologic examination, unrelieved pain, or need further workup [e.g., electroencephalogram (EEG), lumbar puncture].

SEIZURES

Seizures are a common reason for patients to present to the ED. It can be difficult for the emergency physician to determine if the present episode is due to seizure or by conditions that mimic seizures, such as syncope or psychiatric conditions.

The initial ED management of active seizure is ensuring that the seizure has stopped and keeping the patient safe during the postictal period. Patients who receive benzodiazepines from prehospital providers or in the ED need to have their airway and cardiovascular status closely monitored. In patients with no history of seizures, ED workup is indicated. This should include a complete blood count and basic chemistry to screen for infectious or metabolic precipitants for the seizure. In addition, brain imaging should be obtained to rule out structural brain abnormality. For patients with epilepsy, there should still be an attempt to isolate the precipitant for the seizure. This can include infectious or metabolic conditions as well as noncompliance with anticonvulsant medications. Patients whose seizures followed their usual pattern and have returned to their baseline may not need any workup other than determination if drug levels are therapeutic in cases in which levels can be obtained in a timely manner. Patients with evidence of head trauma, fevers, or altered mental status likely need laboratory tests and imaging to ensure that another condition does not exist. Neurology consultation may be helpful for establishing the diagnosis of seizures and in deciding whether to start anticonvulsant medications. Occasionally, patients presenting after a seizure will need further workup or therapeutics beyond their ED visit. The EDOU is an ideal location for patients who need to be loaded with anticonvulsant medications, obtain an MRI or EEG, or have a formal evaluation by a neurologist (**Table 19**).

ASTHMA/CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The Global Initiative for Asthma defines asthma as "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation." Asthma is one of the most common conditions of all ages managed in an OU. The EDOU is an ideal place for asthma care and COPD care because this gives an extended period of observation of 24 hours (corticosteroids therapy may not reach full effect for up to 6 h), for patient teaching and preventative treatments that may lead to decreased recurrence, admissions, morbidity, and mortality. On the basis of vital signs and physical examination, asthma severity can be classified as mild, moderate, or severe. Patients selected for EDOU are those who have mild-to-moderate asthma and have not improved with initial therapy and hence cannot be discharged to home. Keeping the patient in EDOU under cardiac monitoring and pulse oximetry allows time for full medication effect, and final disposition can be done after repeated clinical assessment (**Table 20**). Various scoring systems are also used to assess the severity such as pediatric asthma severity score, pulmonary index score, and pediatric respiratory assessment measure (respiratory rate, accessory muscle use, decreased breath sounds) score. But no scoring system is a well-accepted and sufficiently validated scoring system. Chest radiograph as part of the workup is performed in the EDOU. Patients and caregivers should be educated about asthma medications, inhaler and peak flow meter use, and smoking cessation because patient education is helpful not only in the management and prevention of asthma but also in reducing the number of revisits.

TABLE 20: Patient selection for EDOU care asthma/chronic obstructive lung disease.

Inclusion criteria	*Exclusion criteria*	*EDOU interventions*
• Alert and oriented with stable vital signs • Intermediate response to β2 agonist nebulizers and steroid therapy in ED—improving but still wheezing • Chest X-ray—no significant acute findings	• Unstable vital signs • Clinically unstable—severe dyspnea, confusion, drowsiness • Poor response to initial ED treatment • Persistent use of accessory muscles, tachypnea (RR > 40), or excessive effort • ABG—respiratory acidosis, requires BiPAP • O_2 saturation < 92% on room air • Suspected acute coronary syndrome, congestive heart failure, or pneumonia • High-risk patient—prior intubation/admission in ICU • Frequent ED visits (>3/years) or hospitalizations (>2/years) • Recent steroid use or steroid dependence • Comorbidities such as cardiovascular disease, chronic lung disease, psychiatric disease	• Serial nebulization—β2 agonist and ipratropium • Systemic steroids • Frequent reassessment (every 2–4 h) of vital signs, response to therapy, and mental status • Pulse oximetry and cardiac monitoring

Discharge criteria	
Home	**Admit**
• Acceptable vital signs: HR < 100, RR < 20 after ambulation • Pulse oximetry > 93% on room air • Resolution of bronchospasm • Discharge on steroids, nebulizers • Follow-up in outpatient care • Smoking cessation counseling	• Progressive deterioration in clinical status or vital signs • Failure to resolve bronchospasm within 15 h • Hypoxic despite therapy

(ABG: arterial blood gases; BiPAP: bilevel positive airway pressure; ED: emergency department; EDOU: emergency department-based observation unit; HR: heart rate; ICU: intensive care unit; RR: respiratory rate)

COMMUNITY-ACQUIRED PNEUMONIA

Pneumonia, an infection of the lung parenchyma caused by bacteria, viruses, and fungi, is commonly seen in the ED. Pneumonia is frequently classified based on the location where it was presumed to have been acquired. Hospital-acquired (nosocomial) pneumonia is diagnosed after a minimum of 48 hours of hospital admission. Ventilator-associated pneumonia is defined by the development of pneumonia >48 hours after endotracheal intubation. Community-acquired pneumonia (CAP) is pneumonia that is neither hospital-acquired (nosocomial) pneumonia nor ventilator-associated pneumonia.

The British Thoracic Society developed the *CURB-65 (confusion, uremia, respiratory rate, BP, age ≥65 years) score*, a validated scoring system that assigns 1 point for the presence of each of the following variables: Confusion, uremia (blood urea nitrogen ≥ 19 mg/dL), respiratory rate ≥ 30 breaths per minute, blood pressure (systolic < 90 mm Hg or diastolic ≤ 60 mm Hg), and age 65 years or older. Patients with a score of 0 and 1 are low risk and have low mortality rates (0.6% and 2.7%, respectively).

The *SCAP (severe community acquired pneumonia) score* was developed in 2006 in an effort to develop a clinical prediction rule that could be calculated easily using only variables readily available in the ED. This system assigns various points for major (arterial pH < 7.3, systolic blood pressure <90 mm Hg) and minor [confusion, uremia (blood urea nitrogen > 30), respiratory rate > 30 breaths per minute, chest radiography (bilateral or multifocal infiltrates), PaO_2 < 54 mm Hg or PaO_2/FiO_2 < 250, age ≥80 years] variables and risk stratifies patients into low-, medium-, and high-risk groups. One drawback to this score is the use of arterial pH, which is not always measured.

In a prospective validation study of the three scoring systems—(1) PSI, (2) CURB-65, and (3) SCAP—patients considered low risk by all three had similar low risks of mortality. These scoring systems may underestimate illness severity, which should be taken into consideration when making disposition decisions. The ACEP's CAP clinical policy recommends the use of scoring systems in decisions for disposition.

The use of EDOU-specific protocols for the treatment of CAP ensures appropriate and timely administration of antibiotics and timely recognition of potential patient deterioration (**Table 21**). CAP protocols have been associated with improved overall quality. Management of CAP patients in the EDOU includes regular monitoring of vital signs with the assessment of pulse oximetry, respiratory status, and mentation. The patient should be reassessed serially for the need for parenteral antibiotics, IV fluids, and other potential interventions. Respiratory care may include suctioning of secretions with isolation measures. The patient should be counseled for smoking cessation.

INFECTIONS

An emergency physician commonly deals with infectious conditions in the ED. Managing infectious diseases in ED is very challenging with the emergence and spread of drug-resistant organisms, especially community-acquired

TABLE 21: Patient selection for EDOU care pneumonia.

Inclusion	*Exclusion (All features suggestive of Severe CAP)*	*Potential interventions*
• Pneumonia on chest radiograph or on CT scan or on clinical presentation • CURB-65 score 2–3 • Stable vital signs • Pulse oximetry > 90% on room air • Normal mental status	• Respiratory failure requiring positive-pressure ventilation • Severe respiratory distress—respiratory rate > 40, use of accessory muscles, severe intercostal retractions, cyanosis • Altered mental status—new-onset • Pulse oximetry < 90% on room air • Unstable vital signs • CURB-65 score of 4 or 5	• Serial vital signs, pulse oximetry • Serial clinical examinations—respiratory rate, use of accessory muscles, retractions, wheeze on auscultation, mental status assessment • Give supplemental oxygen • Initiate antibiotic therapy
CURB-65 score—1 point for the presence of each [confusion, uremia, respiratory rate > 30/min, blood pressure (systolic < 90 mm Hg or diastolic < 60 mm Hg)/age > 65 years]		
Discharge criteria		
Home: • Significant clinical improvement • Acceptable, stable vital signs • Pulse oximetry > 90% on room air • Able to tolerate oral intake and oral medications	*Admit:* • Deteriorating clinical condition: Worsening vital signs, alteration of mental status, respiratory distress, or respiratory failure • Hypoxia pulse oximetry < 90% on room air	
Antibiotic therapy for community-acquired pneumonia		
Outpatient treatment Previously healthy—macrolide, doxycycline Comorbidities: • Respiratory fluoroquinolone/β-lactam + macrolide/ amoxicillin-clavulanate • Ceftriaxone, cefpodoxime, cefuroxime + doxycycline/ macrolide Select an alternative antibiotic from a different antimicrobial drug class if antibiotic used within the prior 3 months	*Inpatient treatment* Non-ICU treatment—respiratory fluoroquinolone/β-lactam + macrolide/ doxycycline Preferred β-lactam agents—cefotaxime, ceftriaxone, ampicillin	

(CAP: community-acquired pneumonia; CURB-65: confusion, uremia, respiratory rate, BP, age ≥ 65 years; ICU: intensive care unit)

methicillin-resistant *staphylococcus aureus* (CA-MRSA). A recent challenge for the emergency physician is pandemic infection such as severe acute respiratory syndrome-2 (SARS CoV-2) or Covid-19 The choice of antibiotics and their response is not very straightforward and patient needs more time to stay in the ED (**Table 22**). So, OU in ED is a safe area for monitoring a patient with infection (**Flowchart 7**).

ACUTE TRAUMATIC CONDITIONS

Emergency department-based observation units are always used to manage trauma patients of various grades of severity which also reduce the hospital overcrowding and improve the outcome also. Various studies are also supportive for use of EDOU for all types of trauma. Trauma code trauma protocols are used to investigate and treat the patient in the OU, which is considered as a safe, cost-effective alternative to routine inpatient admission for the short-term management of injured patients (**Table 23**).

METABOLIC AND ENDOCRINE CONDITIONS

An observation unit is ideal for the care of many metabolic conditions, such as hypokalemia hyperkalemia, hyponatremia, hypoglycemia (**Table 24**), and hyperglycemia (**Table 25**). Electrolyte abnormality conditions can be best managed by therapeutic protocols with little or no diagnostic uncertainty. The care in the unit is often straightforward (**Box 3**). Carefully selected patients are included for OU care with the minor manifestation of their chronic condition.

ADDITIONAL CLINICAL CONDITIONS

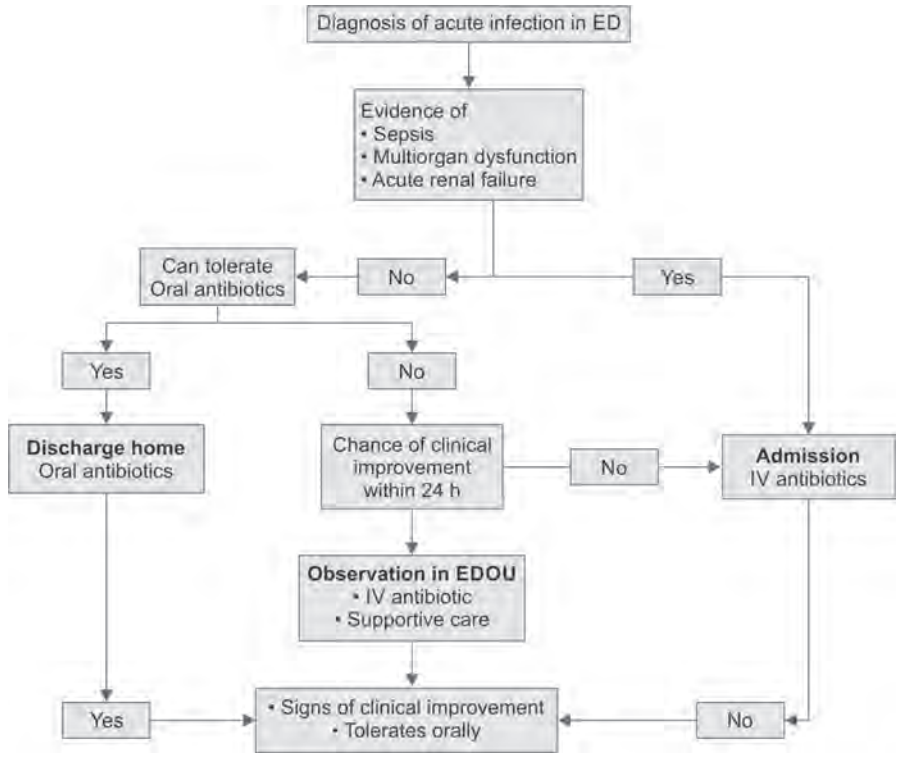
There are many conditions that do not fit into larger protocols that can be managed in the EDOU. The condition that complies with the definition of medical observation where the patient is 70–80% likely to be discharged in 15–18 hours is appropriate, e.g., abnormal uterine bleeding (**Table 26**), allergic reaction (**Table 27**), alcohol intoxication (**Table 28**).

TABLE 22: Management of infections in EDOU.

Infection	*Preferred antibiotic therapy*	*Nonpharmacological interventions*
Skin and soft-tissue infections		
Purulent infection Mild-to-moderate	Oral clindamycin, doxycycline	• Culture and sensitivity • I&D of abscess • Limb elevation
Severe	Intravenous vancomycin, linezolid	
Nonpurulent infection Mild-to-moderate	Oral cephalosporin, dicloxacillin, clindamycin	• Limb elevation
Severe	Intravenous cefazolin, clindamycin, oxacillin	
Hand and foot infections		
Superficial	Oral clindamycin, TMP-SMX	
Deep infections, necrotizing fasciitis	Intravenous vancomycin, piperacillin-tazobactam	• Surgical debridement • Splinting • Elevation
Animal bite wounds	Oral amoxicillin/clavulanate, IV ampicillin/sulbactam	• Irrigation • Vaccination
Peritonsillar abscess	*Intravenous:* • Ampicillin/sulbactam 3 g 6th hourly or • Clindamycin 900 mg 8th hourly • Oral • Amoxicillin/clavulanate 875 BD or • Clindamycin 300 mg 4 times/day	CT/oral US, ENT consult Needle drainage of abscess Look for complications: • Airway obstruction • Aspiration pneumonia • Septicemia • IJV thrombosis and thrombophlebitis • Carotid artery rupture and pseudoaneurysm • Mediastinitis • Necrotizing fasciitis
Pelvic inflammatory disease	Single-dose IM ceftriaxone or 3rd generation cephalosporin + oral doxycycline 100 mg BD ± metronidazole 500 mg BD for 2 weeks	• Pregnancy test • Radiological imaging with US/CT to rule out complications/peritonitis • Gynecology consult • Consider serologic testing for human immunodeficiency virus (HIV) and NAATs for gonorrhoeae/ trachomatis infection • STI counseling
Acute pyelonephritis	*Intravenous:* • Ciprofloxacin 400 mg BD • Levofloxacin 70 mg OD • Ampicillin/sulbactam 3 g 6th hourly • Piperacillin/tazobactam 4.5 g 8th hourly • Oral (for 1 week) • Ciprofloxacin 500 mg BD • Levofloxacin 750 mg OD	• Urinalysis and urine culture sensitivity before initiating antibiotics • Radiological imaging with CT/renal US in case of: ○ Immunosuppression ○ Persistent symptoms ○ Recurrent infections ○ Sepsis ○ Diabetes ○ Prior urogenital surgery
Suspected ESBL UTI	• IV meropenem 500 mg 8th hourly	

Disposition from EDOU	
Home • Clinical stable and improved • Able to take/tolerate the oral antibiotic	**Hospitalization** • Inability to take oral medication • Severe sepsis—hypotension, increased lactates, organ failure • No improvement/worsening of clinical condition • Inconclusive diagnostic workup • Need for surgical intervention • Presence of comorbidities/complications

(CAP: community-acquired pneumonia; CURB-65: confusion, uremia, respiratory rate, BP, age ≥ 65 years; ICU: intensive care unit)



(ED: emergency department; EDOU: emergency department-based observation unit)

FLOWCHART 7: Management of infection in observation unit.

TABLE 23: Managing trauma in observation unit.

Conditions	***Criteria for observation***	***EDOU management***
Mild traumatic brain injury	Neurologically intact with CT brain finding of: • Solitary contusion < 5 mm diameter • Localized subarachnoid hemorrhage < 1 mm thick • Isolated pneumocephaly • Closed depressed outer table skull fracture Anticoagulated patient with normal CT	Analgesics Neurological observation Neurosurgeon consult
Traumatic orthopedic conditions	Nonoperative orthopedic trauma and extremity fractures	Pain control Bracing
Compartment syndrome	Young men with fractures of: • Tibial diaphysis • Forearm diaphysis • Distal radius	Observe for development of compartment syndrome Emergent fasciotomy SOS
Trauma in pregnant patients	>20 weeks' gestation	Cardiotocographic monitoring (CTG) for 6 h
	High-risk conditions: • Uterine tenderness • Significant abdominal pain • Vaginal bleeding • Frequent contraction more than once per 10 minutes • Rupture of membranes • Fetal tachycardia, bradycardia • High-risk mechanism of injury	CTG for 24 h Obstetrics consultation
Other traumas	Rhabdomyolysis Rib fractures Abdominal contusions Minor burns Soft-tissue injuries	Pain management Hemodynamic monitoring Trauma surgeon consult

TABLE 24: Selection of patient for observation unit care—hypoglycemia.

Exclusion criteria for EDOU Care	*Management in OU*	*Disposition*
• Hypoglycemia secondary to drug overdosage as part of attempt at self-harm • Inability to tolerate oral intake • Blood glucose < 80 mg/dL after initial ED treatment • Underlying serious etiology • Nondiabetic	• Adequate dietary intake and hydration • Serial clinical examinations • Bedside glucose measurement 2nd hourly • Diabetic education	• Discharge • Resolution of symptoms • Bedside glucose > 80 mg/dL • Resolution of precipitating factor • Arrange follow-up with physician • Admission • Deterioration of clinical signs • Persistent neurological deficit • Bedside glucose consistently <80 mg/dL

(ED: emergency department; EDOU: emergency department-based observation unit; OU: observation unit)

TABLE 25: Selection of patient for observation unit care—hyperglycemia.

Inclusion	*Exclusion*	*Management in OU*
• Blood sugar > 300 mg/dL and <600 mg/dL after ED treatment • Normal pH and CO_2 level • Readily treatable cause (e.g., noncompliance, urinary tract infection, abscess)	• New-onset hyperglycemia • Diabetic ketoacidosis • Altered mental status	• IV hydration crystalloids at 150–250 mL/h • Bedside glucose monitoring 2nd hourly • Sliding-scale insulin • Treat precipitating causes • Diabetic counseling

Disposition

Home	**Admit**
• Blood glucose < 250 mg/dL • Symptoms resolved • Normal vital signs • Tolerating oral fluids • Primary care follow-up in 48 h • Patient education provided	• Worsening symptoms • Development of diabetic ketoacidosis or hyperosmolar hyperglycemic state • Inability to tolerate oral fluids

(ED: emergency department; OU: observation unit)

BOX 3: Selection of patient for observation unit care—electrolyte abnormalities.

- Minor electrolyte abnormalities with stable vitals and without any clinical complication can be corrected safely in EDOU
- Exclusion criteria for EDOU care
- Unstable vital signs of cardiovascular compromise
- Mental status changes
- Associated causes requiring long-term treatment
- Hyperkalemia level > 5.0 mEq/L with ECG changes
- Hypokalemia level < 2.5 mEq/L or >2.5 mEq/L with ventricular ectopy
- Hyponatremia level > 120 mEq/L with abnormal mentation <120 mEq/L SIADH
- Hypernatremia level >155 mEq/L, <155 mEq/L with altered mental status
- Hypercalcemia level >7.0 mEq/L (ionized calcium
- Hypocalcemia level <1.0 mEq/L (ionized calcium)
- Hypomagnesemia level <2.0 mEq/L associated with electrolyte abnormalities
- >2 acute electrolyte disturbances

(EDOU: emergency department-based observation unit; SIADH: syndrome of inappropriate antidiuretic hormone secretion)

TABLE 26: Patient selection for EDOU management—abnormal uterine bleeding.

Exclusion criteria	*EDOU intervention*	*Disposition*
• Hemodynamically unstable • Pregnant • Coagulopathy • Suspected malignancy • Heavy active bleeding • Needs >2 units PRBCs (Hb < 5 g/dL)	• Blood transfusion • Pain control • Gynecology evaluation • Initiation of hormone therapy • Pelvic ultrasound/imaging in new patients to investigate the cause of bleeding	• Home • Stable vital signs • Post-transfusion • Hemoglobin > 8 g/dL • Asymptomatic on exertion • Advise—gynecology follow-up • Hospital • Persistent heavy bleeding • Unstable vital signs • Orthostatic • Requires inpatient procedures

(EDOU: emergency department-based observation unit; PRBCs: packed red blood cells)

TABLE 27: Patient selection for EDOU management—allergic reaction.

Inclusion	*Exclusion*	*EDOU intervention*
• Erythroderma, urticaria, or angioedema not involving the airway • Stable and improved in ED for 2 h after treatment	• Hypotension (systolic blood pressure < 100 mm Hg) • Tachycardia > 110 bpm • SaO_2 < 94% on room air • Suspicion of acute coronary syndrome • Airway involvement—stridor, respiratory distress, hoarseness • Intravenous vasopressors required	• Symptomatic management: Antihistamines, corticosteroids, IV fluids • Periodic assessment for the evolution of rash, airway involvement, wheezing or hemodynamic compromised

Disposition	
Home	**Hospital**
• Improvement or resolution of symptoms • Stable vital signs • Advice—follow-up with allergist	• Progression of symptoms • Persistent/recurrent symptom • Airway involvement • New-onset hypotension • Epinephrine infusion required

TABLE 28: Patient selection for EDOU management—alcohol intoxication.

Alcohol intoxication believed to take 8 h or greater to resolve

Exclusion criteria	*EDOU interventions*	*Disposition*
• Signs/symptoms of alcohol withdrawal • Combative/delirious patients • Requires chemical sedation/restraints • Traumatic brain injury • Metabolic derangements such as alcoholic ketoacidosis • Polyingestion • Active comorbid condition	• IV or oral hydration as needed • Alcohol cessation education • Monitor for signs and symptoms of withdrawal	• Home • Clinically sober: Alert and oriented, able to ambulate unassisted and without difficulty • Stable vital signs • Hospital • Failure to achieve sobriety in 15–18 h • Development of signs and symptoms of withdrawal

SUMMARY

Over the past 50 years the history of observation medicine parallels the rise of emergency medicine to meet the needs of patients, EDs, hospitals, and the healthcare system. Protocol-driven observation units are best managed using basic principles. Observation patients need protocol-driven observation units, as in ED. Just like ED which becomes the safety net of the health system, observation units have become the safety net of ED—preventing inappropriate discharges or admissions while improving healthcare resource utilization. Observation medicine research evolved over the last one decade along with innovations in healthcare. Observation medicine research will continue to refine and improve this well-established

service to the benefit of ED patients and their health care system. Observation units have consistently proved to provide better outcomes than traditional care for selected patients. The growth of observation medicine has been driven by innovations in healthcare, ongoing shift of patients from inpatient to outpatient settings, and changes in health policy. To fully understand observation medicine, it is important to understand observation services payment policy, history, and ramifications.

MULTIPLE CHOICE QUESTIONS

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Triaging

5
CHAPTER

Devendra Richhariya

INTRODUCTION

Triage is derived from the French word "*trier*" which means to sort out or to pick. This process was used in 18th-century Napoleonic wars where injured are removed rapidly from the battlefield to safe places for care. This process has become more refined and is used in the established healthcare setting. In modern medicine, this system is known as the triaging system. Nowadays, triaging area and triage process are important functions in the modern emergency department. The emergency department is a place where many patients may present simultaneously and the available resources become inadequate to provide quality care. Thus, it is both clinically and ethically important to identify those patients who need the most urgent emergency care. Mass casualty incident triaging has also evolved to achieve maximum good for the maximum number of patients.

EMERGENCY DEPARTMENT TRIAGING

With increasing awareness among the public about emergency care, the number of patients visiting the emergency department is increasing day by day. Various triaging strategies are used in the emergency department for clinical service development, patient safety, and clinical risk management. The purpose of the triage system is to deliver quality health services across the population rather than administrative or organizational compulsion.

REQUIREMENT FOR TRIAGING

- The triaging area must be easily approachable, well illuminated, and clearly signposted.
- All patients should enter through a single entry point so that they all go through a similar process.
- A special area for examination of the patient and privacy should be maintained.
- An appropriate communication system between entrance and triage area
- Emergency lifesaving equipment
- Universal protective facilities, e.g., hand washing and gloves
- Strategies to protect staff
- Trauma victim should be prioritized in a specific area.
- Document for recording the triage information
- The level of urgency must be noted at the entry point of the emergency department.
- Triaging should be based on clinical condition only and should not be influenced by any other factors.
- The primary triaging task consists of chief complaints and assessment of urgency.
- The secondary triaging task consists of diagnostic investigations, emergency care, and disposition.
- There should be a well-organized processing system from triage point to disposition.

TRIAGING SCALES

Various triaging scales (**Table 1**) are being used internationally. These include five-tier, four-tier, and three-tier scales. Five-tier triage (**Table 2**) scales are more reliable, valid, and internationally accepted. The valid and reliable scale should have the following characteristics:

- It should be easy to understand and simple to apply by emergency nurses and doctors.
- It should measure clinical urgency.
- The triage scale must be sensitive enough to register clinical urgency with accuracy.

TABLE 1: Types of triage scales.

Five-tier triage scales	*Four-tier triage scales*	*Three-tier scales*
• Australasian triage scale • Manchester triage scale • Canadian triage scale • Emergency severity index • Cape triage score	Hong Kong four-level field triage system	• Simple triaging and rapid treatment (START) • Field triaging, mass casualty triaging

TABLE 2: Five-tier triage scales.

Triage scale	*Level*	*Time to attend by the physician (min)*	*Color coding*
Australasian triage scale	1. Resuscitation 2. Emergency 3. Urgent 4. Semiurgent 5. Nonurgent	0 10 30 60 120	Red Orange Green Blue White
Manchester triage scale	1. Immediate 2. Very urgent 3. Urgent 4. Standard 5. Nonurgent	0 10 60 120 240	1. Red 2. Orange 3. Yellow 4. Green 5. Blue
Canadian triage scale	1. Resuscitation 2. Emergent 3. Urgent 4. Less urgent 5. Nonurgent	0 15 30 60 120	None

TABLE 3: Problems occurring during gestational age.

<20 weeks	*>20 weeks*	*Postnatal problems*
• Vaginal bleeding (common cause of miscarriage) • Abdominal pain (ruptured ectopic pregnancy, torsion, or ruptured cysts) • Domestic violence common in pregnancy	• Antepartum hemorrhage • Preeclampsia • Preterm rupture of membranes and labor	• Postpartum hemorrhage • Puerperal sepsis • Wound infection • Mastitis • Eclampsia • Postpartum cardiomyopathy • Postpartum psychosis

TRIAGING PROCESS

Assessment of Patient

All patients coming to the emergency department should be triaged on arrival by a trained nurse or physician. Diagnosis-making should not be the priority. Vitals measurement should be done to estimate the urgency. Other parameters that should be noted for estimation of urgency are general appearance, chief complaints, and physiological observation. Standing orders should be followed by the treatment nurse and immediate care needs should be fulfilled. As per the hospital protocol, initiate appropriate investigations and treatment.

Triage assessment should be completed within 3–5 minutes. Details that need to be documented in the patient assessment notes are: Patient name, age, sex, date and time of assessment, name of triage nurse and doctor, chief complaints, relevant history, relevant assessment findings (appearance of patient, airway breathing circulation disability), vital signs and random blood sugar, initial triage category, assessment of alertness [Glasgow Coma Scale/alert, verbal, painful, unresponsiveness (GCS/AVPU scale)], assessment of pain (various pain scale implementation), initiation of any treatment measures, care plan and discharge plan if the patient is discharged from emergency. Retriaging should be done if any vital parameter changes. A trauma record sheet should be used in the trauma patient. Other considerations such as pediatric age group, elderly group, and high-risk features (comorbidities, poisoning, severe pain, rashes) history of violence medicolegal cases, should also be considered in triaging.

Triaging in Pediatric Age Group

Children are usually uncooperative during the examination and give poor history, so it is very important to recognize markers of serious illness. Useful signs are drowsiness, hypotonia, respiratory grunt, wheeze, crepitation, stridor tachypnea, pallor, fever, signs of dehydration, abnormal posture, cold periphery, vomit or less urination, convulsion, and tender abdomen.

Assessment of Pain in Triage

Pain is one of the most common symptoms for which people visit to emergency and pain influences the triage category. Pain description and pain assessment should be included in triage assessment as the physiological and behavioral indicators. Description about factors influencing the pain, various pain assessment scales, and pain management strategies should be included in the triage document. Pain assessment should include location, intensity, time of onset, duration of pain, and aggravating and relieving factors. Heart rate, respiratory rate, blood pressure, facial expression, and body language should also be noted during pain assessment. Various pain scales used in triage setting are *verbal pain score, visual analog scale, numerical rating scale, Wong–Baker FACES rating scale, and Abbey pain scale.*

Triaging and Medicolegal Issues

Following documentation are required to fulfill the medico-legal requirements such as patient name, age, sex, address, name of accompanying person, date, time, and place of the event. Name of examining physician, documentation of injuries, details of clinical management are also required. It is the legal responsibility of a doctor to report the incident to relevant authorities and jurisdiction and also to preserve the forensic evidence (in case of poisoning, assault, rape).

Triage and Pregnancy

Pregnant women are at an increased risk of various conditions and may present with a variety of serious situations (**Table 3**). Triage nurses and physicians should be aware of normal physiological and adaptive changes during pregnancy. Pregnant women may present with any disease in the emergency department. Cerebral hemorrhage, cerebral thrombosis, severe pneumonia, venous thrombosis, and embolus pyelonephritis are more common in pregnant women than in nonpregnant women of childbearing age. Triaging should focus on the well-being of the mother and fetus.

BENEFITS OF TRIAGING

Life-threatening, limb-threatening, and time-critical emergencies (such as stroke and myocardial infarction) are treated on a priority basis. Triaging [early warning score (EWS)] is helpful in identifying the patient who is at a greater risk. Triaging improves the patient flow and patient satisfaction and decreases the overall length of hospital stay.

EARLY WARNING SCORE

In many triage systems, various warning scales are used to identify the patients who are at risk of clinical deterioration and who need hospitalization, so these warning scales are beneficial for quality improvement. EWS is based on vital signs: Respiratory rate, heart rate, blood pressure temperature, oxygen saturation, and level of consciousness [alert verbal painful unresponsiveness (AVPU)]. Various warning scores are developed according to the need, e.g., modified early warning score (MEWS), triage early warning score (TEWS), modified pediatric early warning score (MPEWS), and modified early obstetrics warning score (MEOWS). EWSs are an important tool for appropriate risk management and are also helpful in improving the safety and quality of a patient in the emergency department. Measurement of physiologic parameters and early recognition of warning signs and timely action would add value to patient care in the emergency department and can lead to improved quality of care and decreased morbidity and mortality.

Modified Early Warning Score and Triage Early Warning Score

Modified early warning score is based on blood pressure, heart rate, respiration, oxygen saturation, and alertness. In some triage scales, urine output and pain score are also taken into consideration. The patient's clinical deterioration can be anticipated by this score and the requirement of hospitalization can also be assessed. The MEWS score uses basic equipment and simple parameters, so it is easy to use by junior-most staff also. MEWS is useful for triaging of medical emergencies but not for trauma patient triaging. MEWS score >5 is considered as risk of clinical deterioration and need of hospitalization. The components and scoring of MEWS and TWES are described in **Tables 4** and **5**, respectively.

TRIAGE IN MASS CASUALTY INCIDENT

In a mass casualty situation, the number of patients and their severity are much more than the existing capability for management. Triage is the most important part of any disaster

TABLE 4: Modified early warning score (MEWS).

Vital signs	***3***	***2***	***1***	***0***	***1***	***2***	***3***
Systolic BP	<70	71–80	81–100			>200	
Heart rate		<40	41–50	51–100	101–110	111–129	>130
Respiratory rate		<9		9–14	15–20	21–29	>30
Temperature		<35		35–38.4		>38.5	
AVPU				Alert	React to voice	React to pain	No response
In some triaging systems, urine output and pain sore are also added in the early warning score.							

(AVPU: alert, verbal, painful, unresponsiveness)

TABLE 5: Triage early warning score (TEWS).

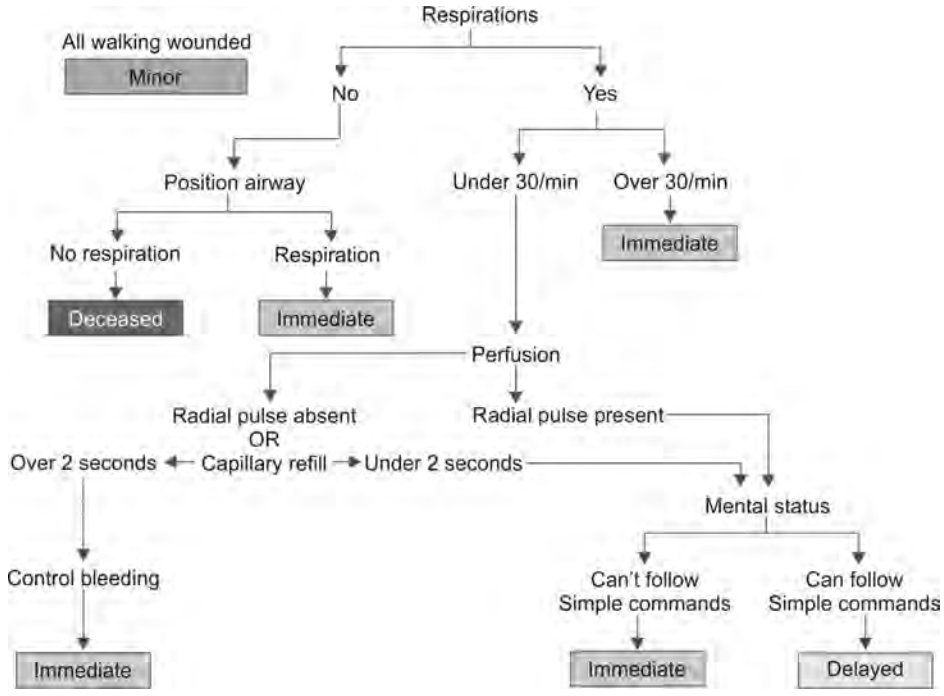
Parameters	***3***	***2***	***1***	***0***	***1***	***2***	***3***
Mobility				Walking	With help	Immobile	
Respiratory rate		<9		9–14	15-–20	21–29	>29
Heart rate		<40	41–50	51–100	101–110	111–129	>129
Systolic BP	<70	71–80	81–100	101–199		>199	
Temperature		<35		35–38.4		>38.5	
AVPU				Alert	React to voice	React to pain	No response
Trauma				No	Yes		
Correlating the triage early warning score with color code triaging							
Color	Red	Orange	Yellow	Green	Blue		
TEWS	7 or more	5–6	3–4	0–2			

(AVPU: alert, verbal, painful, unresponsiveness)

response. The main objective of mass casualty/disaster triage is to do the maximum help to the maximum number of people. Major incidents which cause mass casualties are road traffic accident, building collapse, earthquake, flood, major fire, train derailment, explosion, air crash, terrorist attack, and hazardous material release. The main objectives of triaging in disaster and mass casualty are to decompress the disaster area, to give the best care to the most critical casualty, and to provide special care for burn and crush injuries. In this critical situation, a simple triaging format [simple triaging and rapid treatment (START; **Flowchart 1**) and sort, assess, lifesaving interventions, treatment/transport (SALT; **Flowchart 2**)] should be used.

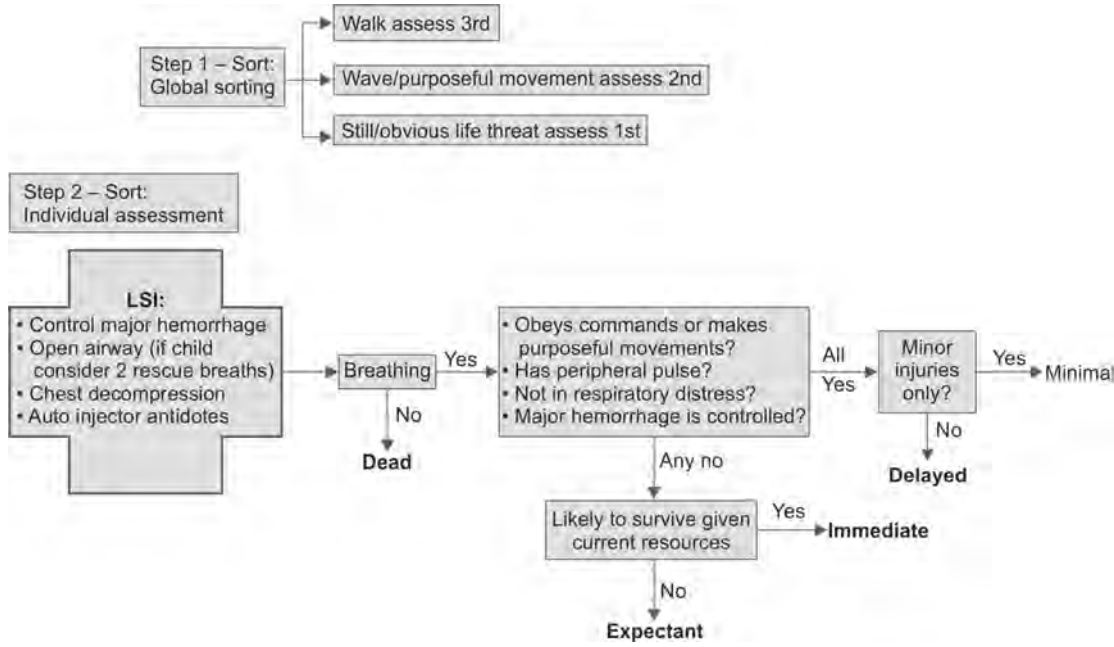
SUMMARY

Triaging is an essential first step in an efficient and effective emergency department. The use of a comprehensive triage tool along with the EWSs will help to save lives and reduce the mortality.



(START: simple triaging and rapid treatment)

FLOWCHART 1: START triaging (based on respiration, perfusion, mental status assessment).



(LSI: lifesaving interventions; SALT: sort, assess, lifesaving interventions, treatment/transport)

FLOWCHART 2: SALT triaging.

MULTIPLE CHOICE QUESTIONS

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Rapid Assessment and Early Treatment

6
CHAPTER

Devendra Richhariya

INTRODUCTION

The emergency department has a challenging working environment; most of the patients present with acute illness, severe pain, and are in great discomfort and often these patients do not get appropriate privacy and empathy that they deserve. The emergency department system is not uniform across the country so different triaging scales are used by various emergency departments for assessing the severity of illness. The patient presents to emergency with a wide variety of complaints such as simple fever pain to severe sepsis shock, polytrauma stroke, exacerbation of asthma, and chronic obstructive lung disease and also as mass casualties. Various assessment tools such as the ABCDE (such as airway, breathing, circulation, disability, exposure) approach, START (simple triaging and rapid treatment for disaster), and various triage methods are based on time, thus making the patient wait according to categories and leading to delay in treatment and increase in errors, and expenditure of unnecessary tests. Since different disease presentations in emergency have different requirements so the superior method should be applied in which care plan (including investigation, treatment chart, admission requirement, and referral) is initiated only by an experienced qualified emergency team and instructions are followed by the rest of the team. Rapid assessment and treatment of a patient by an "experienced and qualified team" in emergency increases the patient safety and satisfaction as well as improves patient flow and also solves the problem of emergency department overcrowding.

BENEFITS OF RAPID ASSESSMENT

- Risk stratification can be done to identify patients for resuscitation.
- Early transfer to high dependency unit or ward; thus clinical risks are minimized
- Patient safety quality and outcome improve.
- Reduces overcrowding
- Provides a learning experience for junior doctors

STEPS FOR RAPID ASSESSMENT AND EARLY TREATMENT

A dedicated team consists of a senior doctor consultant, attending consultant, qualified nurse, social worker, and general duty attendant for this task. The team lead by a senior doctor attends the patient.

All patients are changed into gowns on arrival and given identification bands. A brief history (allergy history) and examination and documentation of management plan are given. Assessment and resuscitation of the patient as soon as he/she arrives in the emergency should be done by a senior doctor and nurse. On the basis of presenting complaints, investigations are decided. Point-of-care testing such as blood sugar, arterial blood gas analysis, and D-dimer is used. Medications are prescribed and delivered as per guidance. Necessary referral should be taken from the specialty if required. On-medical needs should be assessed by a social worker. The patient should be admitted or discharged on the basis of comprehensive assessment. The manager should arrange the bed and manage patient flow. The steps in rapid assessment and early treatment are summarized in **Figure 1**.

Initial Assessment and Resuscitation

Resuscitation should be started within minutes of the arrival of the patient. Assessment should start by acknowledging the patient by his name and by shake hands with the patient. This provides a lot of clinical information such as level of consciousness (LOC), airway patency, and peripheral perfusion of the patient and also provides confidence to the patient and attendant. Focused history and history of examination and investigations from the patient and attendant should be obtained.

Assessment of Airway

Complete airway obstruction leads to death within minutes, but partial airway obstruction is quite common and can be recognized by noisy breathing such as snoring or gurgling

FIG. 1: Summary of steps in rapid assessment and early treatment.

which causes reduced LOC (due to reduced airway muscular tone, loss of protective airway reflexes, principally the gag and cough reflexes, retention of oropharyngeal secretions, and tongue malposition). LOC can be rapidly assessed using the AVPU (i.e., alert, responds to voice, responds to pain, unresponsive) method. If the patient can talk, then it usually implies that the airway is safe. Simple maneuvers, such as jaw thrust or a chin lift, can relieve the partially obstructed airway. Airway adjuncts such as oropharyngeal or nasopharyngeal devices can also be useful.

Assessment of Breathing

Increased respiratory work is commonly associated with the severity of illness as a result of an increased metabolic rate and oxygen consumption. This may lead to respiratory distress, signs of which include: Inability to complete sentences, high respiratory rate, diaphoresis, accessory muscle use, and cyanosis. Focused clinical examination including tracheal palpation, percussion, and auscultation may pinpoint the diagnosis (tracheal deviation—tension pneumothorax, hyper-resonance—tension pneumothorax, dull percussion note—pleural effusion/empyema, wheeze, silent chest—acute severe asthma, left ventricular failure, diminished or bronchial breath sounds—pneumonia). High-flow oxygen should be administered to all acutely ill patients. The effects of therapy should be assessed using pulse oximetry and the target oxygen saturations should be 94–98%. An appropriate oxygen delivery device to use is a mask with a reservoir bag. It is vital that the reservoir be kept inflated at all times. This is usually achieved by setting the flow rate of oxygen to 15 L/min. This mask will usually deliver an inspired oxygen concentration (FiO_2) of 60–85%.

Assessment of Circulation

Assess the radial pulse, rate, rhythm, and character. Attach a cardiac monitor and note the blood pressure. Clinical signs that are common to hypovolemic, obstructive, and cardiogenic shockinclude: Confusion or agitation, cold extremities, reduced capillary refill, tachycardia, absent or small volume peripheral pulses, hypotension, and oliguria. The jugular venous pulse assessment is useful in distinguishing between hypovolemic states (low) and cardiogenic or obstructive shock (elevated). Circulatory features of septic shock include warm peripheries (vasodilatation) and a bounding pulse. Except for cardiogenic shock, complicated by pulmonary edema, the management of shock patients requires the administration of intravenous fluid. The peripheral cannula can usually be inserted into antecubital fossa or external jugular veins and central lines can be inserted into the internal jugular, subclavian, and femoral veins. The sizes of the peripheral cannula are determined by gauge (16 largest to 26 smallest). Two 16-gauge lines are recommended for resuscitation.

Assessment of Disability

Assessment of neurological status and relevant clinical examination would include level of consciousness, focal and localizing neurological signs, pupillary reflexes, and signs of meningism. Rapid assessment is done using the AVPU method.

Pain Management and Assessment of Patient Needs

Pain management is an important aspect in the emergency department and is described in Chapter 53 while assessment of the nonmedical needs of the patient is equally important and involvement of a social worker is helpful.

Investigations and Interventions

Important relevant investigations are carried out once the assessment part is over, e.g., blood tests, X-ray, ultrasound, and computed tomography (CT) scan, while point-of-care testing is helpful in the rapid assessment of a critically ill patient. Other interventions such as specialty reference should be taken on the basis of result of investigations for definitive care.

Diagnosis Definitive Treatment and Disposition

Once a diagnosis is certain or the causes understood, definitive treatment can be started. This may require the transfer of the patient to the operating theater, interventional cardiology laboratory, endoscopy suite, intensive care unit, or high-dependency unit. Proposed management should be carefully communicated to the patient and close relatives of the patient. If the patient is discharged to home medication prescription, the indicating diagnosis, follow-up test, and consultation should be clearly mentioned on the discharge summary.

CLINICAL QUALITY INDICATORS FOR RAPID ASSESSMENT

- Time to analgesia
- Time to delivering urgent medication, including antibiotics and bronchodilators
- Time to starting intravenous fluids
- Time to blood tests
- Time to imaging
- Time to specialty referral and assessment

IMPLEMENTATION OF RAPID ASSESSMENT AND EARLY TREATMENT (SEPSIS, STROKE, AND TRAUMA)

Sepsis

Timely recognition and intervention are important in reducing the morbidity and mortality due to sepsis and shock. Clinical suspicion, thorough physical examination, and laboratory screening using base deficit or lactate can improve outcomes. Rapid assessment and early treatment plan summary is given in **Table 1**.

Stroke

Stroke is time-bound emergency where an ischemic stroke patient needs thrombolysis within the window period. Early assessment of stroke and localization of pathology by stroke syndrome are summarized in **Table 2**. The early treatment plan is summarized in **Figure 2**.

Trauma

Implementation of a trauma system approach is important, which refers to the integration of all aspects of trauma care, to achieve the best outcome. Studies support that implementation of a trauma system approach improved the survival rate by 15–20% among seriously injured patients. **Table 3** summarizes the integrated trauma approach along with rapid assessment and early treatment improves the outcome for polytrauma patients.

SUMMARY

Rapid assessment and formulation of care of plan by a senior doctor ensure the patient's safety. Any important emergency or time-critical interventions are instituted (blood tests, X-rays, ultrasounds, CT scans, etc.). Initial clinical assessment and a clearly documented plan should be communicated with the nursing staff. This system improves the outcome of many critical illnesses such as sepsis trauma stroke.

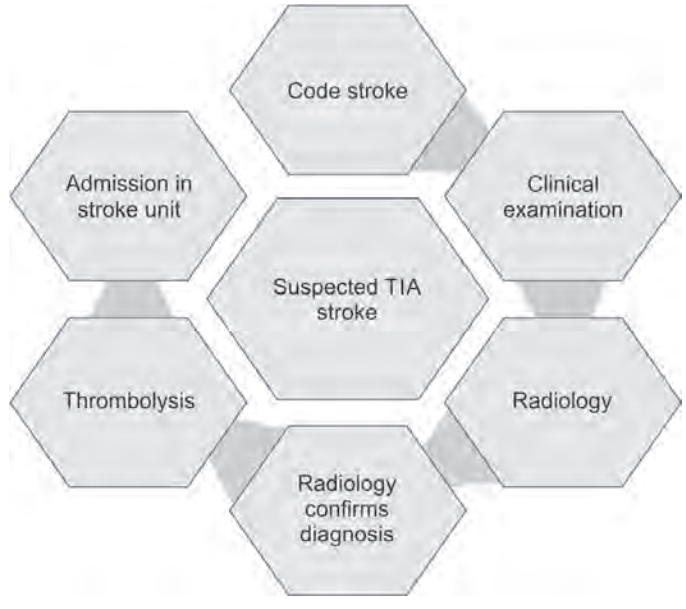
TABLE 1: Sepsis: Improving outcome through rapid assessment and early treatment.

Early recognition of sepsis	WBC high/low, temperature high/low, high heart rate, high respiratory rate, infection
Early recognition of shock	• Tachypnea, tachycardia, weak or bounding peripheral pulses, delayed capillary refill (>2 seconds) • Pale or cool skin, narrowed pulse pressure, oliguria • Lactic acidosis, elevated base deficit
Priorities in severe sepsis	Oxygenation and airway management, fluid resuscitation, hemodynamic stability, blood culture lactate levels, antibiotics, intensive care admission

(WBC: white blood cells)

TABLE 2: Early assessment in stroke patient (stroke syndrome).

• Aphasia (dominant hemisphere) or neglect (nondominant hemisphere) • Contralateral homonymous hemianopsia • Contralateral motor/sensory loss of face, arm, and leg • Conjugate ipsilateral eye deviation	Carotid territory
• Aphasia (dominant hemisphere) or neglect (nondominant hemisphere) • Contralateral homonymous hemianopsia • Contralateral motor/sensory loss face/arm > leg	Middle cerebral artery territory
• Apathy, abulia, disinhibition • Conjugate eye deviation • Contralateral motor/sensory loss leg > arm	Anterior cerebral artery territory
• Ipsilateral palatal weakness, Horner syndrome • Wallenberg syndrome • Ipsilateral limb ataxia • Decreased pain/temperature contralateral body	Posterior inferior cerebellar artery territory
• Ipsilateral deafness • Ipsilateral facial motor/sensory loss • Ipsilateral limb ataxia • Decreased pain/temperature contralateral body	Anterior inferior cerebellar artery territory
• Altered consciousness • Oculomotor difficulties, facial paresis • Ataxia, quadriparesis	Basilar artery territory



(TIA: transient ischemic attack)

FIG. 2: Rapid assessment and early treatment in stroke.

TABLE 3: Rapid assessment and early treatment in a trauma patient.

Trauma team	Emergency team, neurosurgery, orthopedics, surgery/GI surgery, critical care, thoracic surgery, vascular surgery
Criteria for trauma team activation	Blunt trauma, penetrating injury, gunshot wounds, stab wounds with SBP < 90 mm Hg, require endotracheal intubation, mechanically unstable pelvic injury, respiratory compromise, obstruction, or intubation with presumed thoracic, abdominal, or pelvic injury. GCS score < 8. Transfer patients receiving blood from other facilities to maintain vital signs or on the basis of a suspicion that the patient might require urgent operative intervention
Primary survey (ABCDE)	Check patency of airway and clear secretion Oropharyngeal airway, high concentration oxygen. Cervical spine stabilization (c-spine collar), two large-bore cannulas, simultaneously obtain blood for analysis, CBC blood grouping and typing, initial fluid therapy NS/RL, control bleeding, GCS score, pupil size, assess spinal injury, prevention of hypothermia, *Adjuncts*: ABG, cardiac monitoring, insertion of urinary and gastric catheters, consider need for X-ray, chest X-ray, pelvic X-ray, and FAST
Secondary survey	Detail history and examination, obtain history of injury-producing event and mechanism of injury. Reevaluation and detail examination of head, face, cervical spine, chest, abdomen, perineum, rectum, vagina, and musculoskeletal . Reevaluation of neurological status and GCS score
Management of hemorrhagic shock in trauma	Fluid therapy (crystalloid) in a hypotensive trauma patient, target SBP 80–90 mm Hg and urinary output 0.5 mL/kg/h in adult and 1.0 mL/kg/h in children, addition of vasopressors and inotropic agents if not responding to fluid therapy, norepinephrine is preferred, target hemoglobin is 7–9 g/dL, use of blood and blood products, type-specific blood is preferred, but type 0 –ve blood indicated in massive hemorrhage (which is available within 10 minutes in most of the blood bank), early use of RBCs and FFP improves the outcome (initial recommendations 10–15 mL/kg, additional dose depends on coagulation parameters PT or APTT 1.5 times the normal values), platelets transfusion is recommended when platelet counts are <5,000, tranexamic acid 1 g over 10 minutes and then 1 g over 8 hourly, rapid control of bleeding by local hemostatic procedures, packing, direct surgical bleeding control, angiographic embolization

(ABCDE: airway, breathing, circulation, disability, exposure; ABG: arterial blood gas; APTT: activated partial thromboplastin time; CBC: complete blood count; FAST: focused assessment with sonography in trauma; FFP: fresh frozen plasma; GI: gastrointestinal; GCS: Glasgow Coma Scale; NS: normal saline; PT: prothrombin time; RBCs: red blood cells; RL: Ringer's lactate; SBP: systolic blood pressure)

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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7
CHAPTER

Patient Safety and Quality in Emergency Department

Saravana Kumar

INTRODUCTION

The emergency department (ED) of any institution is an entry point for a significant number of patients to any healthcare organization (HCO). The department caters to various trauma and medical emergencies in both adults and children round the clock and is adequately staffed with emergency physicians and nursing to handle such emergencies at all times and days. The department also oversees operations of the prehospital emergency medical services (ambulance) and coordinates their services. The ED is considered particularly high risk for adverse events (AEs): About 60% of ED patients experienced medication error. Various studies suggests that prevalence of AEs related to ED is increasing and most of them are preventable.

Maintaining quality and developing error-free systems have been the focus of engineering over the last few decades. Consider the degree of variability of every individual human being compared to machine and also inputs from the engineering field, for an error-free system that guarantees good quality assistance should be defined a program reasonably simple, locally relevant, easily implementable, not resource intense, and have tangible outcomes which can be measured. The ED of any institution is an entry point for a significant number of patients to any HCO. It has to be conveniently located on the ground floor with direct access to the patients and ambulance. The entrance of the ED is always separate from the outpatient department (OPD) entrance. The department caters to various trauma and medical emergencies in both adults and children round the clock and is adequately staffed with emergency physicians and nursing staff to handle such emergencies at all times and days.

BACKGROUND OF EMERGENCY DEPARTMENT

The common medical emergencies handled in the ED include neurological emergencies such as seizures or stroke, respiratory emergencies such as asthma or any breathing difficulty, cardiac emergencies such as myocardial infarction or cardiac arrest or any acute arrhythmia, varied abdominal and gastrointestinal emergencies, and trauma emergencies that may include head injury, facial and oromaxillary injuries, chest injury, abdominal injury, musculoskeletal injuries, and fractures. Apart from this, the department also caters to patients with poisoning, drowning, hanging, acute allergy, and anaphylaxis and also handles any mass or multiple casualty events and medicolegal cases. During non-outpatient hours, the department also handles outpatient-based complaints and nonemergency cases who generally are triaged out to OPD during OPD hours. Unlike wards or intensive care unit (ICU), the beds in the ED are utilized on a continuous basis for different patients on a given day for initial stabilization and are eventually transferred to appropriate inpatient care areas of the HCO for continuity of care under different specialties (or) discharged from the emergency room (ER) after initial treatment with follow-up advice. There are no recommendations or scope for providing continuity of care in the ED/beds. The department also oversees operations of the prehospital emergency medical services (ambulance) and coordinates their services. More recently, quality issues have received much attention in the medical field and there has been some inputs from the airline industry, replicated to healthcare in error prevention by the introduction of safety checklists. There are, however, some fundamental differences between the medical and engineering field (man and machine).

The first aspect is dealing with uncertainties. One of the primary differences between man and machine is the degree of variability. Unlike machines that can be "cloned," every individual human being is different and each responds and reacts differently to illness and treatment. While there is a general pattern of presentation and response to illness, the uncertainties that one needs to be prepared for and deal with are more in the medical domain than in the engineering domain. In emergency medicine, the uncertainties are particularly enormous as the presenting illness is mostly not well defined by the patients and he/she is not fully coherent or conscious to give his symptoms, signs are not obviously evident, support documents or prior medical history are not available, there is a short therapeutic window, there is a delayed or denied consent, and affordability to emergency medical care is less.

The second aspect is paying attention to detail. Although on the surface there appears to be a similarity between the

medial and the engineering fields, there is a fundamental difference. Domain experts in the engineering field have made a remarkable difference for machines.

However, the domain experts in medicine need to start understanding the key performance metrics and measures for ensuring better outcomes and still need to have a holistic approach and expertise in order to be successful and have a low margin for error. There is also a lack of adequate expertise in emergency medicine available all over the world.

APPROACH TO QUALITY ISSUES IN THE EMERGENCY DEPARTMENT

The prerequisites of a good-quality assurance program are as follows:

- It should be reasonably simple.
- It should be locally relevant.
- It should be easily implementable.
- It should not be resource intense.
- It should have tangible outcomes which can be measured.

ADVERSE EVENTS IN THE EMERGENCY DEPARTMENT

The ED is considered particularly high risk for AEs.

Sixty percent of ED patients experienced medication error. *An AE is defined as "an injury caused by medical management rather than by the underlying disease or condition of the patient."*

It represents a significant threat to patient safety and public health. From a systematic review about AEs related to ED care, it appears that many studies conducted in multiple countries have reported a prevalence of AEs among hospitalized patients ranging from 2.9 to 16.6%, with 36.9–51% of events being considered preventable. Some studies indicate that AEs related to medical conditions such as myocardial infarction, asthma exacerbation, and joint dislocation reach up to 37%. They have also shown that 33% of the near misses were intercepted. About 29% of doctors reported AE or near miss of their ER patients due to poor hand-off. Only 12% of ED revisits within 7 days are due to AEs. Most frequent errors depend on the patient, provider, and system. The reasons behind this are as follows:

First is patient complexity, which depends on many issues such as age, extreme, communication barrier, vague complaints, undifferentiated presentation, mental status changes, cognitive impairment, complex medical condition, delayed presentation, myths and traditional beliefs, and lack of awareness/education or knowledge of a disease.

Second is care workers, who could risk making mistakes due to lack of knowledge and experience on diseases and procedural skills, fatigue (they disrupt sleep cycles for healthcare), prejudice, and risk-taking behavior (not use personal protective equipment during procedures).

Third is the relationship between patient and doctor. Many AEs depend on bad communication: At an average discharge, the verbal exchange between a doctor and patient lasts for 76 seconds. So, the incomplete information during an average discharge is 65%. Only 76% of the ED patients get a written diagnosis at discharge and only 34% of the ED patients get instructions on when and how to return to the hospital.

Fourth is the work environment that is characterized by time constraints, staff inadequacy, staff's lack of experience, team/communication problems, overcrowding, lack of equipment, or failures.

Last, there are *other emerging factors* such as multicultural/multilingual patient, relocation/migration of doctors to various countries and healthcare systems, and multielectronic health recorder (EHR) systems with poor integration for seamless flow.

SAFETY PRACTICE AND IMPLEMENTATION STRATEGY

To guarantee the safety practices and avoid AEs, we have to do an implementation strategy in many settings. The following points need to be addressed:

- Infrastructure requirements
- Basic clinical management process and protocols for quality emergency care
- Establishing a unit of quality department
- Measuring quality of performance (quality indicators)
- Sharing best practices
- Adapting to changing realities

Infrastructure Requirements

The factors which influence the ED size and design include a general scope of clinical services provided in the HCOs, average volume of ER visits, total number of beds in the HCOs, availability of other support services such as radiology and laboratory, total floor space, geographical location, demography of the patients who will be handled in the ER (pediatric, geriatric, trauma, and medical emergencies) or the maximum number of possible users in a given time. The ED design includes the following: *Entrance* which should be directly accessible from the road for ambulance and vehicles, Clearly marked. *Temporary parking space* for cars and other means of patient transport. *Ramp for wheelchair/stretcher*. Stretcher and wheelchair placing area should have a well-lit entrance with wide doors which can open both ways or one way into the ER. The doors should be wide enough to move a patient in an emergency trolley comfortably in and out. The ideal width would be a minimum of 6 feet when both the doors are wide open. The *waiting area* can be of a size that includes seating, telephones, display for literature, public toilets, and circulation space in total. *Triage area* it should be able to accommodate patients in wheelchair/emergency stretcher/walking in. The ideal space would depend on the volume of patients received in the department. There is a close operational relationship between triage and reception where the registration counter is located. *Resuscitation room (priority 1)*: Resuscitation room with at least one Resuscitation bed should be available in ER. Ideally, there should be an individual closed space with provision for an emergency stretcher bed, multiple monitors, defibrillator, crash cart, and ventilator in each room. The room should accommodate four to five staff members, including doctors, comfortably and be able to move around the patient. *Urgent care (priorities 2, 3):* The minimum recommended space between centers of two adjoining beds is 2 m. Each bed can be separated by a screen on all three sides for providing privacy. There should be a *consultation room (priority 4)* for examination and treatment of priority 4 patients. *Emergency short stay unit:* This facility may be provided either within or adjacent to the Emergency Unit for prolonged observation and

ongoing treatment of patients who are planned for subsequent discharge (directly from the ED). It is mostly applicable to high-volume ED. The types of patients planned to be admitted to this unit will determine the number and type of beds provided, and the design of associated monitoring and equipment. However, eight beds, are considered to be the minimum functional size. The configuration of the short stay unit should be a minimum of one bed per 4,000 attendances per year.

Nursing station: A staff room/utility storage room/security room/toilets/pharmacy sub store should also be there.

Patient Flow Management

The ED can have two types of patient: (1) Input-throughput and (2) Output flow based on the volume and space available in the healthcare institution.

For a large-volume department, it is advisable that the entry and exit points of the ED are separate. The triage room and registration can be done at the entry and there is also a facility for registering the patient at the entry point. After triage, the patients are moved to the appropriate preidentified bed space/area for further care. All *priority 1* patients are moved to the resuscitation room. *Priorities 2 and 3* are treated in the urgency care areas which can also be the observation area. *Priority 4* patients are triaged out to OPD or can be handled in ER in a predesignated fast track room or doctor consultation room (especially in non-OPD hours) in the ED and an emergency bed is not necessary for this category of patients. On disposition, the patients are moved into the hospital or discharged through an exit, away from the entry area. Billing counters can be situated at the exit. Bedside billing can also be done.

For low-volume ED*s* and HCOs with limited space, the entry and exit are through the same point and the registration and billing counter is essentially located at the entry/exit point. No separate triage room or space is provided and all the patients visiting ER are allotted a bed straight away and a bedside triaging is done. All *priority 1* patients are either moved to the bed identified for resuscitation purpose or resuscitation can happen in the same bed. *Priorities 2, 3*, and *4* are treated in emergency beds. *Priority 4* can also be treated in the ER doctor consultation room (if available). On disposition, the patients are moved into the hospital or discharged through the same entry/exit point. Billing counters can be situated here and bedside billing can also be done.

Clinical Management Process and Protocols for Quality Care

Each ED is unique as the patient profile varies with the locality of the hospital infrastructure within the same city and the level of acuity that the particular hospital can handle. Also, the disease profiles and healthcare systems vary across the globe.

Clinical management protocols are based on evidence-based recommendations and best practice recommendations, where clinical evidence is not possible.

Clinical protocols have to be region-based applicable to the population demography of the hospital and their health needs.

For example, a trauma center hospital may look into how efficiently it can manage a patient of polytrauma and process to better clinical outcome, such as initiating a massive transfusion versus a peripheral pediatric hospital where the nature of emergencies tends to be more medical in nature than surgical.

Irrespective of the locality: The protocols need to be tested and constantly upgraded based on recent updates.

Appropriate mock assessments conducted periodically and audits are a must to ensure that the policies and processes are implemented at the ground level.

Establishing a Unit of Quality Department

The establishment of a quality department is essential in order to examine the association between the scope of quality improvement (QI) implementation in hospitals and hospital performance on selected indicators of quality. Various key performance indicators (KPI) may be set by an identified champion from the ED, who may be certified through various national or international training programs to conduct an internal audit or program or quality implementation in hospital and with help from external accrediting agencies.

Reviews on various aspects of improving KPI must be taken up as a continuous process in order to reduce errors. Coordinate care among settings and practitioners and ensure that relevant, accurate information is available when needed as critical elements in providing a high level of care.

Achieving Quality Control of the Highest Standard in Medical Equipment

Periodic checks at least once a year are essential in achieving this goal. They can be done for a range of equipment including defibrillators, ventilators, pulse oximeters, infusion pumps, patient monitors, etc. This may be done as part of a set of national and international standards by trained engineers with help of specialized testing and calibrating equipment as per manufacturer recommendations. It should be concluded by documenting test results and issuing a calibration report. Any measuring equipment or device needs to be tested and checked for its accuracy and calibrated whenever the need arises. Testing is done as per domestic standards which imply in accordance with manufacturer specifications for both safety and performance tests. The results need to be formally documented.

Key parameters for testing and calibrating in the ED may include:

- *Defibrillators*: Electrical safety tests, biphasic energy measurements, electrocardiogram (ECG), performance and arrhythmia simulation, waveform simulation
- *Pulse oximeter*: Electrical safety, O_2 saturation, heart rate, pulse amplitude, selectable pigmentation, and ambient light condition
- *Infusion pumps*: Flow rates, occlusion alarm tests, pressure
- *Ventilators*: Modes, lung parameters, etc.

The entire activity must be subjected to appropriate methods of internal control and inspection.

Measuring Quality of Performance (Quality Indicators)

Institutions need to adapt appropriate quality indicators. The following quality indicators (**Tables 1A** and **B**) can represent the quality of EDs: Door to triage time, door to doctor time, door to needle time in stroke thrombolysis, pain score assessment, investigation return time, nurse/patient ratio, patient satisfaction level, time taken for discharge, mortality (adjusted), length of stay, left without been seen by the

TABLE 1A: Measuring quality of performance (quality indicators).

Door to triage time	*Door to doctor time*	*Door to needle time in stroke thrombolysis*	*Mortality parameter*	*Patient satisfaction (effective communication)*	*Patient fall rates*	*Medication errors*
Description: Time interval of patient's arrival to nurse triage *Type of parameter*: Outcome *Formula*: Time from patient arrival to time when triage is completed for a particular category of patients *Benchmark*: Does not exist *Action plan*: Ensure quality in design, conformance	*Description*: In case of emergency, the time shall begin from the time of the patient's arrival at the emergency till the time that the initial assessment is completed *Type of parameter*: Outcome *Formula*: Sum of the time taken for assessment/ total number of patients in emergency *Benchmark*: Does not exist *Action plan*: Ensure quality in design, conformance	*Description*: In case of acute-onset ischemic stroke in the window period *Type of parameter*: Morbidity in stroke *Formula*: Number of stroke patients thrombolysed/ number of eligible stroke patients for thrombolysis *Benchmark*: Does not exist *Action plan*: Ensure quality in design, conformance	*Description*: Standardized mortality rate (SMR) *Type of parameter*: Outcome *Formula*: Number of deaths/number of discharges and deaths × 100 *Benchmark*: None *Action plan*: Ensure quality in design and conformance	*Description*: Efficacy of communication *Type of parameter*: Process *Formula*: Quarterly average score/max score possible × 100 *Benchmark*: Not known *Action plan*: Through patient satisfaction	*Description*: Patient fall rate *Type of parameter*: Safety morbidity *Formula*: Number of falls/numbers of bed days *Benchmark*: 8.46/1,000 bed days *Action plan*: Ensure quality in design (beds) and conformance (sedation)	*Description*: Medication error *Type of parameter*: Safety *Formula*: (Number of errors/numbers of bed days) × 1,000 *Benchmark*: 1.2–9.47/1,000 bed days (reported) *Action plan*: Clinical pharmacists; process (2-people check)

TABLE 1B: Measuring quality of performance (quality indicators).

Compliance to hand-hygiene protocols	*Investigation return time*	*Length of stay in emergency department*	*Nurse–patient ratio in emergency department*	*Pain management in emergency department*	*Time taken for discharge*	*Left against medical advice*
Description: Compliance to hand hygiene *Type of parameter*: Infection, outcome, safety *Formula*: (Number adhered/total number of procedures) × 100 *Benchmark*: 90% adherence *Action plan*: Surveillance; health education	*Description*: Radiology CT investigation report *Type of parameter*: Adherence to protocol *Formula*: Time of order to time of reporting *Benchmark*: 60 minutes *Action plan*: Clinical audit	*Description*: Average length of stay *Type of parameter*: Adherence to protocol, safety *Formula*: Total length of stay of all patients in hours/total number of patients *Benchmark*: 240 minutes *Action plan*: Audit	*Description*: Nurse per bed per shift *Type of parameter*: Safety, mortality, morbidity *Formula*: Number of nurse/number of beds in each shift *Benchmark*: Does not exist *Action plan*: Audit	*Description*: Proportion of patients presenting with pain in whom validated pain score is documented *Type of parameter*: Key performance indicator *Formula*: Patients with pain assessment using validated score/total number of patients presented with pain × 100 *Benchmark*: Does not exist *Action plan*: Audit	*Description*: Discharge is the process by which a patient is shifted out from the ED with all concerned medical summaries after ensuring stability *Type of parameter*: Safety *Formula*: Sum of time taken for discharge/ number of patients discharged *Benchmark*: Does not exist *Action plan*: Audit	*Description*: Percent of patients who leave the ED before the examination *Type of parameter*: Safety *Formula*: Total number of patients who leave ER before seen by doctor/total number presented to ER during the time of study × 100 *Benchmark*: Does not exist *Action plan*: Audit

doctor, pain assessment/reassessment, safety—patient falls, medication error, failed intubation rate incident reporting and hand hygiene compliance.

Nonconformance Control and Management

Any nonconformance observed should be properly reported through the incident reporting system which will be reviewed by a multidisciplinary committee and the quality department of the hospital.

The nonconformances could be:

- Near miss
- Medical error
- Sentinel event

Configuration control and management under the quality of design: Any process changes in the hospital flow system or physical layout or functions related to the assignment pattern of doctors/staff need to be reported and discussed in the leadership team meet of the institution along with the justification of such a change and approval.

Adapting to Change Realities

Digitization

Opportunities for using data to improve the health system are partially driven by technological advances. New analytical methods, more efficient processing, and automation of routine analyses and analytics, for example, make it easier to draw insights from health data and to present the resulting information in an actionable format.

In the clinical setting, secondary use of health data can improve quality initiatives and the effectiveness of frontline care. For health system management, health data can be used to manage and improve the effectiveness and efficiency of the health system by informing program, policy, and funding decisions. For example, costs can be reduced by identifying ineffective interventions, missed opportunities, and duplication of services.

To facilitate health research, health data can be used to support research that gives information on clinical programs, health system management, and population and public health. Such research spans multiple fields.

Measuring Patient Feedback

Patient feedback systems are used to know their experiences when visiting the hospital, understanding of the services the hospitals offer, and opinions on changes you may have recently introduced or plan to make.

With a good feedback system, one can increase one's understanding of what patients think about a hospital, understand areas of concern, and take action to transform the experience for patients. One can make changes and use the system to monitor the patient reaction, gradually improving the practice based on accurate feedback.

Patient Experience Measures

- Should be developed with patient input to ensure that they are representative of their needs, values, and preferences
- Reveal critical information about the extent to which care is truly patient-centered
- Provide a rigorous, validated alternative to the subjective reviews that are posted on a large number of review sites

CLINICAL AUDIT

- The review of clinical performance against agreed standards, and the refining of clinical practice as a result: A cyclical process of QI in clinical care.
- The systematic critical analysis of the quality of healthcare, including the procedures used for diagnosis, treatment, and care; the use of resources; and the resulting outcome and quality of life for patients.
- Monitor the use of particular interventions, or the care received by patients, against agreed standards. Any deviation from "best practices" can then be examined in order to understand and act upon the causes.

There are different modalities with which we can do a clinical audit:

- *Standards-based audit (criteria-based audit)*: This is the recommended process. Current practice is compared against defined criteria, standards, or best practices, through the "audit cycle."
- *Peer review audit*: With the benefit of hindsight, the quality of services provided is assessed by a team, reviewing case notes and seeking ways to improve clinical care. This is especially applicable in "interesting" or "unusual" cases.
- *Significant event audit*: Adverse occurrences, critical incidents, unexpected outcomes, and problematic cases causing concern are reviewed systematically and solutions implemented.
- *Survey*: Opinion or suggestions from patient or special focus groups. Information gathered is then analyzed and change implemented as appropriate.

Stages of an Audit

- Prepare and plan for the project.
- Select an area to audit.
- Defining criteria and setting up standards
- Collection of data
- Analyze results.
- Identify solutions for improvement and implement changes.
- Reaudit to monitor the impact of changes (close audit loop).

This must be led by senior clinicians in the department and must be reported to the audit review boards and discussed with higher stakeholders for implementation and continuous improvement.

FISHBONE ANALYSIS FOR QUALITY IMPROVEMENT IN EMERGENCY DEPARTMENT

The fishbone analysis (diagram) is a visual tool used to explore the factors that influence or cause a given outcome to help to understand the problem more clearly. Quality improvement tool is named by its inventor Kaoru Ishikawa and its resemblance to a fish skeleton. Constructing the fishbone diagram helps to understand the multiple causal factors of the

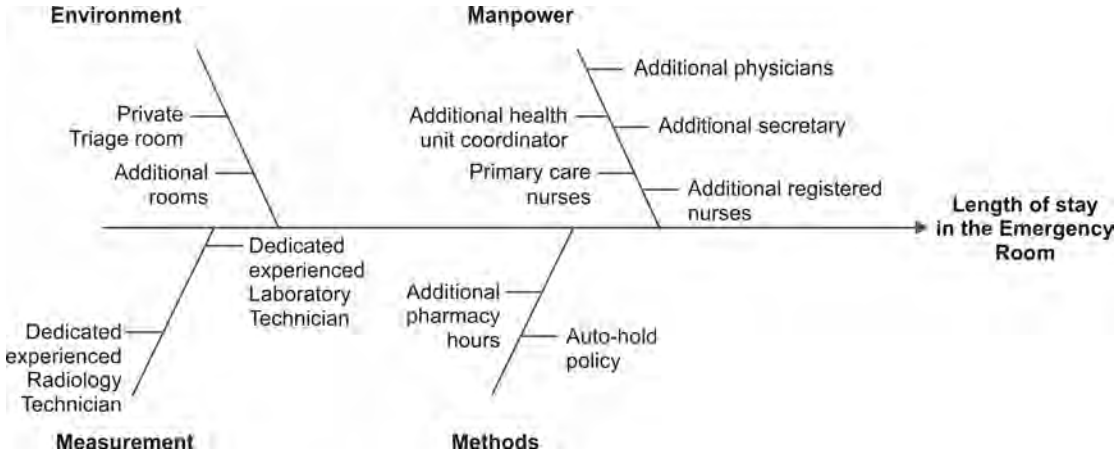

FIG. 1: Fishbone diagram showing the parameter to improve the length of stay in an emergency room.

particular problem and helps us to identify areas of further investigation (**Fig. 1**).

How to draw fishbone diagram/analysis:

- First write single statement in a box that describes the problem.
- Then identify major relevant categories of causes (people, place, policies, and procedures). Draw these main causes (bones) off the large arrow.
- For each main cause (bone) consider factors contribute to it (minor causes). We can use brainstorming for this step.
- Continue analyzing fishbone diagram until every possible contributing cause and influence has been identified.

SUMMARY

All EDs have to ensure that the patients, relatives, and primary physician are well informed about the clinical status of the patient through a structured communication protocol. A communication checklist to ensure that adequate communication has taken before disposition needs to be implemented in all EDs.

Promotion of reporting errors, teamwork, transparency with feedback, learning from errors, and administrative collaboration will be helpful in QI. Identify champions of quality and patient safety in ED.

MULTIPLE CHOICE QUESTIONS

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Hazardous Material (HAZMAT) and Waste

8
CHAPTER

KV Sarma, Devendra Richhariya

INTRODUCTION

Biological, chemical, and radiologic materials that result in adverse effects on the health and safety of exposed individuals are termed hazardous materials (HAZMAT). Are there materials in your workplace that are hazardous? If so, then you must be aware of the following:

- Which ones are hazardous?
- What their hazards are?
- How you can work with them safely.

Hazardous material can be:

- Corrosive
- Explosive
- Flammable
- Radioactive
- Reactive
- Toxic

There are various routes from which they can enter the body. HAZMAT can enter your body by three routes: (1) Skin and eye contact (absorption), (2) inhalation (breathing), and (3) ingestion (eating). This chapter consists of information about the nature of HAZMAT and how they should be labeled, their usefulness in preplanning for HAZMAT emergencies, extinguishing tactics, and environmental protection aspects.

All accidents/spills must be reported to the Safety and Environmental department, and any other departments or persons as the situation requires (i.e., Radiation Safety Officer in case radiation is involved, Lab Safety Officer, Research Centre Chemical Safety Officer, Clinical Engineering, or others). All HAZMAT received in a department shall be handled by appropriate personnel and stored in an appropriate cabinet with proper ventilation, designated for chemical use only.

Hospital Plan

Hospital plan is a written program consistent with local and international regulations/standards to identify, determine control, implementation, and evaluation of all HAZMAT used or generated. The program covers HAZMAT inventory, selection, purchasing, storing, using/handling requirements, spill clean-up measures, and disposal methods.

Department Responsibilities

All HAZMAT received in a department should be handled by appropriate personnel and stored in an appropriate cabinet with proper ventilation, designated for chemical use only. HAZMAT Program is developed, in which departments are responsible for the following: Each department is responsible for identifying and labeling all HAZMAT within its department work area. All departments should inventory their HAZMAT and review them for appropriateness as part of the overall department's inventory program. It is the responsibility of each department to provide training for individual staff who handle HAZMAT; training records must be maintained. Emergency preparedness and spill clean-up procedures must be developed. Purchase of all chemicals including cleaning solutions, laundry chemicals, and chemicals routinely used for facility and grounds maintenance should follow the rules. Are there materials in your workplace that are hazardous? If so, you should know: All accidents/spills must be reported to the Safety and Environmental Section and any other departments or persons as the situation requires (i.e., Radiation Safety Officer in case radiation is involved, Lab Safety Officer, Research Centre Chemical Safety Officer, Clinical Engineering, or others).

CLASSIFICATION OF HAZARDOUS MATERIAL

Hazardous materials can be divided into three groups according to their effects: (1) Substances that affect health, (2) substances that affect fire, and (3) substances that may react violently. HAZMAT may have more than one of these effects, so it is critical to be aware of all the hazards associated with a substance.

Health Hazards

Materials that can affect health include poisons and other toxic substances that may enter the body through breathing (inspiration), swallowing (ingestion), or injecting through the skin (absorption).

Fire Hazards

Fire HAZMAT may be in liquid, solid, or gaseous form. All flammable liquids, by definition, are considered hazardous. A flammable liquid is a substance that has a flashpoint <100°F. The flashpoint of a liquid is the temperature at which the liquid releases vapors in sufficient concentration to support ignition by an external ignition source near the surface of the liquid. Flammable solids are solid materials that are easily ignited and that burn rapidly.

Reactive Hazards

Some materials are classified as hazardous because of the volatile way they react with other substances or with themselves. Explosives are materials that will detonate or will deflagrate. Oxidizing agents (which can be strong corrosives) give off oxygen and support combustion. The reaction of oxidizers with other substances frequently generates heat. Some substances will react violently, even explosively, when water or moisture is added to them. Other substances may react in the same way when they come in contact with air.

Classes of Hazardous Materials

There are nine classes of HAZMAT. Each class has a distinctive symbol for labeling containers. (1) Explosives, (2) gases, (3) flammable liquids, (4) flammable solids and materials that are dangerous when wet, (5) oxidizers and organic peroxides, (6) poisonous and etiologic materials, (7) radioactive materials, (8) corrosive, and (9) miscellaneous HAZMAT.

Combustion Byproducts

Examples: Carbon monoxide, nitrogen oxide, hydrogen sulfide, sulfur dioxide, acrolein, ammonia phosgene, phosphine, hydrogen. Byproducts of combustion are not new to firefighters. However, all of these products are highly toxic by inhalation. Therefore, breathing apparatus (BA) for protection must be worn. Some of these materials will damage the skin. In any event, protective clothing should be worn. Most of these materials are water-soluble, so water fog should be used to dilute and disperse the vapors.

Water-reactive Materials

Examples: Lithium, sodium, potassium, metal hydrides, carbides, organometallic compound. All of these materials will react with water to produce heat and a flammable gas, usually hydrogen. They are also highly corrosive and will react with all common extinguishing agents. Firefighters must wear protective clothing, BA, and evacuate the area. The special dry powder can be used, but this is only effective on small fires. These are highly toxic.

Pressurized and Liquefied Gases

Examples: Acetylene, hydrogen, oxygen, chlorine, carbon dioxide, compressed air, ammonia, butane, propane. Containers containing pressurized and liquefied gases are extremely dangerous under fire conditions. When heated, the excessive internal pressure will build up which is beyond the capability of relieving devices, and the container will rupture. When a rupture does occur, it is impossible to predict the direction of flying fragments. The decision to attack fires involving pressurized containers is a critical one. Containers can rupture in very short periods of time. Ample water must be applied to pressurized containers when exposed to heat. The flow of gas should be shut off and firefighters must wear BA and protective clothing.

Flammable Liquids (Nonpetroleum)

Examples: Alcohols, aldehydes, ketones, esters, ethers, amines. These are toxic and corrosive liquids, which react violently when decomposing under fire conditions. Foam, carbon dioxide, and dry chemical should be used to fight fires on soluble flammable liquids. Firefighters must wear BA and protective clothing.

Flammable Solids

Examples: Naphthalene, camphor, carbon phosphorous, sulfur. These solids present an explosive potential when in dust form and some are pyrophoric, i.e., they will ignite spontaneously in dry or moist air. Most produce highly toxic gases when burning. Large volumes of water should be used to extinguish fires. Protection against toxic gases is required and firefighters should wear BA and protective clothing.

Explosives

Examples: Azides, fulminates, nitro compounds [nitroglycerine, trinitrotoluene (TNT), dynamite, picric acid]. These materials present an extreme hazard due to their sensitivity to heat and shock, and fires should be fought from a distance. When it is not possible to fight the fire from a safe distance and an explosion is imminent, you must evacuate the area.

Poisons

Examples: Cyanides—hydrogen cyanide, sodium cyanide; fumigants—sulfur dioxide; heavy metals—mercury, arsenic, lead; pesticides—dichloro-diphenyl-trichloroethane (DDT), parathion, malathion. Poisons can enter the body in three ways: (1) Inhalation which causes asphyxiation and lung damage, (2) ingestion which causes internal organ damage, (3) skin contact which destroys tissue.

Toxicity is measured by threshold limits, which are assigned to each poison. These limits must be monitored and should not be exceeded. However, you must treat all poisons or chemicals as highly toxic and highly corrosive until reliable information is obtained. When poisons are involved in an emergency, protective clothing and decontamination processes all are required. Evacuation may be considered and required. Protective clothing is another important line of defense against infectious waste. Use every method available to protect yourself from hazardous medical waste.

Corrosives

Examples: Acids—sulfuric, nitric, acetic, carbolic, chlorosulfuric; alkalis—caustic soda, caustic potash, lime; halogens—fluorine, chlorine, promin, iodine. All corrosives destroy human tissue. Many react violently with water such as chlorosulfuric acid. Some are flammable and some react with other materials to start fires. All corrosives are highly toxic. Firefighters must wear BA and protective clothing in emergencies. Be sure that substances are not water-reactive before washing any spills. Tools, equipment, and personnel must be decontaminated any

time corrosives are encountered. Decontamination procedures must be followed.

Cryogenics

Examples: Liquid oxygen, liquid hydrogen, liquid nitrogen, liquid carbon monoxide, liquid natural gas. These substances have a temperature below –150°F (extremely cold) and can be both flammable and toxic. When released into the atmosphere, they expand in a very high vapor. In case of fire exposure, hose streams at sufficient volume and pressure should be employed to reduce the chance of rupture due to over-pressurization.

Oxidizing Agents

Examples: Nitrates, nitrites, chlorates, chlorites. These substances decompose when heated, giving off heat, toxic gases, and oxygen. When involved in fire, intense flame, heat and even explosions can result. Flood the area with deluge quantities of water from a safe distance when oxidizing agents are involved in a fire.

Unstable Materials

Examples: Organic peroxides, inorganic peroxides. These substances are highly flammable and toxic. They are also shock- and friction-sensitive, causing explosions. They decompose to give off heat and oxygen and form highly flammable mixtures and many materials. Evacuate the immediate area and concentrate on protecting exposures if peroxides are burning. You cannot predict what will happen with unstable materials and you must expect the worst possible conditions.

STORAGE AND TRANSPORTATION OF HAZARDOUS MATERIALS

Storage

Chemical storage parameters include temperature control, ventilation, segregation, isolation, ignition control, and regulatory considerations. Departments are responsible for ensuring that chemicals they use or are otherwise under their administrative control are stored safely. Material safety data sheets provide chemical-specific storage requirements. Observing the following general guidelines can minimize risks.

All chemicals shall be properly labeled with a description of the hazard. Materials which are toxic as stored or which can decompose into toxic components from contact with heat, moisture, and acid fumes shall be stored in a cool, well-ventilated place out of the direct rays of the sun. Incompatible toxic materials shall be isolated from each other. All flammable and combustible liquids should be kept in closed containers when they are not in use. Materials which ignite easily under normal conditions (flammable) shall be stored in a cool, dry, well-ventilated storage space. Store according to the hazardous nature of chemical using appropriate security when necessary. Store large bottles of acids on a low shelf or in acid cabinets. Segregate acids from bases and active metals. Segregate acids from chemicals which could generate toxic gases upon contact such as iron and sulfide. Acids and acid fume-sensitive materials shall be stored in cool, dry, well-ventilated areas. Use bottle carriers for transporting acid bottles. Have spill-control pillows and acid/caustic neutralizers available in case of acid or caustic spills. Store solutions of inorganic hydroxides in polyethylene containers. Store pyrophoric substances in a cool and dry place. Store water-reactive chemicals in a cool and dry place. Store oxidizers in a cool and dry place, and do not store close to liquid of low flashpoint. Segregate oxidizing agents from organic acids, flammable, and combustible materials. Keep oxidizers away from reducing agents such as zinc, alkaline, metals, and formic acid. Segregate flammable from oxidizing acids and oxidizers. Store flammable liquids in approved safety cans or cabinets. Keep away any source of ignition, flames, localized heat, or sparks. Corrosives shall be isolated from other materials and shall be stored in a cool, well-ventilated area. Safety cans containing flammable liquids should be grounded and bonded when being used. Firefighting equipment shall be readily available. An automatic firefighting system and smoke detection system shall be provided. Have spill clean-up materials handy. Store highly volatile flammable liquids in a specially equipped refrigerator. In case of fire involving water-reactive chemicals, keep water away. The personal protective equipment (PPE) shall be available for use when handling chemicals. Do routine inspections. Hazardous waste should not be stored outside a building. Compressed gas cylinders shall be handled, stored, and used in a manner that will prevent damage to the valve. Secure them when in an upright position or on hand trucks or lay them flat. Always have cylinder caps securely in place whenever the cylinder, regardless if full or empty, is not in service. Oxygen and oil make an explosive mixture. Never use any petroleum in or near any oxygen system component or equipment. Restrict access to the building where the chemical is being stored. *HAZARDOUS– KEEP AWAY* signs shall be posted in all flammable gas or chemical cabinets. The cabinet shall be operated at negative pressure. It is true that many hazardous chemicals are unpredictable under certain conditions such as when mixed with another chemical. However, even if you are unable to predict exactly what a HAZMAT will do, you must have guidelines to assist you.

Transportation

Chemicals must be transported safely to minimize the potential for spills, releases, or accidental exposures. The following general guidelines should be followed: Chemicals should be transported in sealed and labeled primary containers. Primary containers should be transported in secondary containers. Only manageable quantities of chemicals should be hand-carried. Heavier quantities should be placed on a cart. Only persons knowledgeable about the chemicals' hazards should transport the chemical.

SAFE USE OF HAZARDOUS MATERIAL

To avoid problems, be prepared and read the label which usually tells you the following at a glance:

- What is in the container
- What the hazard could be (health, fire reactivity, etc.)
- Special instructions
- How to protect yourself
- Basic first-aid

Before using HAZMAT:

- Remove things that could burn, explode, or react dangerously with nearby materials.

- Know where emergency showers and eyewashes are located.
- Make sure that the correct type of fire safety equipment is nearby and ready for use.
- Check for adequate ventilation.
- Know what to do in an emergency.
- Assemble PPE that might be required, such as:
  - Safety glasses, goggles, or face shields
  - Gloves
  - Rubber boots or special shoes
  - Respirators

Laboratory Chemicals

Laboratories have a specially written plan to keep the employee safe. The Chemical Hygiene Plan covers the specific operating procedures and safety concerns of the individual laboratory. Always follow the procedures in your laboratory's plan. The Chemical Hygiene Plan is designed to protect from the health hazards associated with hazardous chemicals in the laboratory.

Chemical Hygiene Plan

It outlines the specific work practices and procedures covering: (1) Procedures to follow when working with hazardous chemicals, (2) details on how your chemical exposure will be monitored and limited, (3) ensures that you have the right protective equipment such as a fume hood and that it works properly, (4) specifies that some hazardous tasks be approved in advance by your supervisor, (5) assumes that any unfamiliar chemical is hazardous, (6) considers a mixture to be at least as hazardous as its most hazardous component, (7) do not use any unlabeled substance, (8) strictly follow all chemical safety instructions and procedures, and (9) use common sense and be cautious around all laboratory equipment.

CHEMICAL SPILL AND DECONTAMINATION

Chemical Spills

The range and quantity of hazardous substances require preplanning to safely respond to chemical spills. Only knowledgeable and experienced personnel should clean up a minor chemical spill. Spill response kits or materials with instructions, absorbents, reactants, and protective equipment should be available. A "minor" (few drops) chemical spill is one that staff is capable of handling safely if the following criteria are satisfied: Staff should have access to and wear appropriate PPE. They should have access to and use appropriate spill clean-up equipment. They should have a way to dispose of waste generated from spill clean-up activities. They should be trained. They feel comfortable cleaning up the spill. All other spills are considered "major" (>10 mL) and must be cleaned up by trained Hazmat Chemical Spill Response Team members. The safety department is responsible for investigating significant hazardous chemical spills and unplanned releases. Department heads and other staff are included in the investigation to help identify causative factors and develop strategies to prevent reoccurrence. Spills and exposures are reported by any of the following methods: Physicians report of occupational injury/illness from human resources.

All workers who are likely to discover a HAZMAT spill/release should be trained to notify the proper personnel. All workers at the operation level are trained to contain a spill/release from a safe distance and keep it from spreading and stop the release of HAZMAT. On-site cooperation and knowledge of specific chemicals should be given to government officials. The workers should know how to control an incident scene during an emergency response.

If a chemical spill happens:

- Immediately inform housekeeping.
- Proper protective clothing must be worn. This includes solvent-resistant gloves and respiratory protection.
- In case of a large spill, follow steps set out in the "Chemical Hygiene Plan."
- Small spills can be cleaned up easily by using a chemical spill kit which is available in the laboratory.

Decontamination

Decontamination neutralizes harmful contaminants and removes them from personnel and equipment. It also reduces the chance that contaminants will be carried out of the release area. There are two major methods of decontamination: (1) Physical and (2) chemical. Physical is done by diluting with water or blowing with air jets. Chemical is done by neutralizing HAZMAT with chemicals.

Chemical exposure staff, visitors, and patients can become contaminated with a hazardous substance in a variety of ways, including contact with airborne contaminants, splash walking through a spill on the floor, and contact with contaminated equipment. General guidance regarding decontamination methods and techniques is presented below. The exact procedure is determined after evaluating a number of factors related to the incident and consulting material-specific literature such as the material safety data sheet.

- Eliminate further contact with the material.
- Identify the material.
- Decontaminate with a copious amount of water or other appropriate material.
- Remove contaminated clothes and other material in contact with the victim.
- Assess the amount and concentration.
- Obtain medical assistance.
- Notify supervisor.

HAZARDOUS WASTE AND SEGREGATION

Segregation of Waste System

The waste classification system is effective to sort and handle the various types of waste generated by the hospital and protect our staff and the community from contamination. General objectives regarding the waste classification, with respect to hazardous medical waste including infectious waste and radioactive waste, are to provide technical guidance in hazardous waste segregation, collection, packaging, storage, transporting, treating, and finally proper safe disposal of the waste separation and packaging of different colors that are part of the hospital policies and requirements that everyone must comply with which are actually part of the existing contract. Waste is sorted as follows: *Red bags* for isolation biological/contaminated waste, *yellow bags* for radioactive waste, *orange bags* for toxic waste, *blue bags* for general waste, and *black bags* for regular trash. *General waste*: Not considered infectious;

Infectious waste: Potentially infectious or hazardous, generated in the diagnosis, treatment, or immunization of human beings or animals. The categorization of hospital waste is given in the following text.

General Waste

It consists of all waste materials that are not regulated or defined as hazardous and do not require special handling and disposal. These wastes are sometimes referred to as nonregulated medical waste. General waste is generated by almost every aspect of the hospital including administration, support services, utilities and maintenance, patient rooms, nursing stations, food services (even this type of waste has some special disposal considerations), and many areas throughout the hospital. Although the above waste is not considered hazardous, such waste can pollute the environment. Therefore, in reducing solid waste by establishing recycling programs, all departments should be encouraged to reduce their waste and great effort is requested from all managers to plan for recycling or reusing, and if necessary modify the process in contribution to the reduction in waste.

Medical Waste

It is defined as all waste generated from healthcare facilities. The type of waste classified as medical waste may vary according to the institution in which it is generated. This type of waste is regulated and requires special handling and disposal. The different types of medical waste generated by hospitals are chemical, radioactive, and infectious.

Chemical Waste

Chemical waste includes substances such as:

- Germicides
- Cleaning solvents
- Pharmaceuticals
- Chemicals that have expired or are no longer used.

Chemical waste can create hazardous situations such as fire or explosion. It can harm health. Information on how to handle and store the chemical safely and its specific disposal is important. Always place materials and waste in the right bag and color-coded system. Do not pour chemicals down the drain. If you are not sure about chemical disposal, ask the Laboratory Hygiene Officer, Laboratory Safety Officer, Environmental Officer, or Safety Officer.

Radioactive Waste

Radioactive waste has dramatically increased with the recent advances in nuclear medicine and is found in:

- Iodine 123
- Iodine 131
- Thallium 201

Although radioactive materials and waste are the responsibility of the research center and all radioactive materials are disposed of in accordance with the Nuclear Regulatory Commission. We should mention that radioactive waste is any waste that contains or is contaminated with liquid or solid radioactive material. It is not generated by X-rays or other external beam therapy procedures. It is important to ensure that all disposing wastes are placed with the radiation sign in a yellow bag. Always keep radioactive waste separate from other types of waste.

Infectious Waste

Infectious waste is a very important part of the medical waste disposal because more employees and departments are directly involved with infectious waste than any other type of HAZMAT present in the hospital. Infectious materials are handled every day and include:

- Laboratory cultures
- Blood and blood products from emergency rooms, operating rooms, pathology laboratories, patient rooms, laboratories, clinics, dental clinics, autopsy, and blood bank
- Sharps
- Renal dialysis waste
- Contaminated animal carcasses, body parts, and bedding.

Infectious waste means any waste material that has the potential to carry disease. This includes the following.

Sharp Infectious Waste

Medical items such as scalpel blades and hypodermic needles require careful disposal into rigid, puncture-proof containers called *sharps boxes*. The broken or unbroken glass used in animal or patient care including items such as blood vials are sharps or potential sharps designated for incineration. Other glass and plastic material may be disposed of as solid waste in rigid containers designated for glass disposal. *Never* recap needles. *Do not* bend or break needles. *Always* dispose of used needles in *yellow puncture*-resistant containers. *Change* needle disposal containers when three fourth full. *Submit* an incident report if you are injured by a needle stick/sharp object/instrument. Objects must be labeled in leak-proof, puncture-resistant containers.

- The most effective method of protecting yourself is the implementation of universal precautions.
- Dispose of sharps properly.
- Never bend, shear, recap, or resheath by hand.
- Use a broom and dustpan to pick up broken glass.
- Follow the safety guidelines established for the use of protective clothing and equipment on the job.
- The incineration method is recommended for infectious waste as part of the contract. Incinerators must have the ability to destroy pathogens.

Chemotherapy Waste

It results from the production or use of an antineoplastic agent.

Radioactive Waste

It is related to the use of radioactive supplies, containers, and radioactive iodine.

DEGREE OF HAZARD IDENTIFICATION FOR HAZARDOUS MATERIALS

Below is a system for marking the degree of HAZMAT, which provides a simple and easily understood system. It also provides a general idea of the hazard of the materials and the severity of their hazards (**Table 1**).

HAZARDOUS MATERIAL SAFETY BOOKLET

Also known as material safety data sheet (MSDS), it is the cornerstone of the hazard communication guidelines. They provide information about the chemical substances within a product, safe handling procedures, first-aid measures, and

TABLE 1: Degree of hazard identification.

	Identification of health hazard (type of possible injury) Color code: Blue	*Identification of flammability (susceptibility of materials to burning) Color code: Red*	*Identification of reactivity (susceptibility to release of energy signal) Color code: Yellow*
Signal			
4	Materials that on very short exposure could cause death or major residual injury	Materials which will rapidly or completely vaporize at atmospheric pressure and normal ambient temperature or that are readily dispersed in air and that will burn readily	Materials that in themselves are readily capable of detonation or of explosive decomposition or reaction at normal temperatures and pressures
3	Materials that on short exposure could cause serious temporary or residual injury	Liquids and solids that can be ignited under almost all ambient temperature conditions	Materials that in themselves are capable of detonation or explosive decomposition or reaction but require a strong initiating source or which react explosively with water
2	Materials that on intense or continued but not chronic exposure could cause temporary incapacitation or possible residual injury	Materials that must be moderately heated or exposed to relatively high ambient temperatures before ignition can occur	Materials that readily undergo a violent chemical change at elevated temperatures and pressures or which react violently with water or which may form explosive mixtures with water
1	Materials that on exposure under fire conditions would offer no hazard beyond that of ordinary combustible material	Materials that must be preheated before ignition can occur	Materials that in themselves are normally stable, but which can become unstable at elevated temperatures and pressures
0	Materials that on exposure under fire conditions would offer no hazard beyond that of ordinary combustible material	Materials that will not burn	Materials that in themselves are normally stable, even under fire exposure conditions, and which are not reactive with water

procedures to be taken when a product is accidentally spilt. They must be provided from chemical distributors. All new information regarding certain chemical substances must be provided by the distributor. It is required that all departments using chemicals must maintain copies of the booklet and ensure that they are readily accessible to employees during all work shifts.

PERFORMANCE STANDARDS AND PERFORMANCE IMPROVEMENT

Safety Committee is responsible for monitoring the performance, tracking the events, and monitoring HAZMAT, and waste. Data and significant events, findings, and trends are reported to the committee at least annually to identify potential risk and possible opportunities for improvement. Upon approval, the reports become part of the committee's minutes and are submitted to the administration for review. Other HAZMAT and waste can also be monitors and may be tracked by the safety department. Annual evaluation of the Hazardous Materials and Waste Management Plan is reviewed and evaluated annually by the safety department. The purpose of this evaluation is to determine the degree to which actions taken during the previous year were effective in meeting the goals and objectives of the plan. Plans and policies are also evaluated after events that involve HAZMAT. Plan and policy improvements reflect institutional experiences, regulatory changes, or routine reviews of response protocol. The evaluation also provides a mechanism to determine opportunities for improvement for the next year. This determination forms the basis for setting goals and performance improvement standards for the future. The actions taken to achieve these goals are reviewed to assess their effectiveness. The data for this analysis derives from information supplied to the committee as part of its information collection and evaluation function, along with discussions with staff and record reviews. Opportunities to improve the effectiveness of the plan are identified during the review and evaluation process. Goals are then established for the coming year, along with recommendations for implementing processes necessary to achieve those goals. Performance monitors are reviewed to determine if modifications are necessary in response to the evaluation and established goals.

PERSONAL PROTECTIVE EQUIPMENT IN HAZARDOUS MATERIAL INCIDENTS

Biological, chemical, and radiologic materials that result in adverse effects on the health and safety of exposed individuals are termed HAZMAT. These substances represent significant risks to healthcare workers when hospitals receive patients contaminated with these materials. Therefore, hospitals and their workforce must be prepared to use PPE to protect themselves when these situations arise. There are four key issues, which must be fully understood whenever PPE is required: (1) Various types of PPE, (2) basics of a "hazard assessment," (3) how to select appropriate PPE, and (4) training in the proper use of PPE. It is only after these four key issues

have been adequately addressed that a properly equipped and well-trained healthcare staff facility can provide a safe and effective response.

Types of Personal Protective Equipment

Personal protective equipment are articles worn or equipment used to protect the user from harmful contaminants released into the environment. In this chapter, this means the PPE used by hospital personnel when decontaminating and caring for the patient(s) involved in a HAZMAT incident. The main function of PPE is to provide a barrier between the user and respiratory or skin exposure to the contaminant in the environment or on the skin/clothing of contaminated patients.

Personal protective equipment can be listed in the following categories:

- Respiratory protection
- Eye and face protection
- Hand protection
- Foot protection
- Body protection

A specific combination of PPE from each of these categories is normally needed to properly protect the wearer from each specific contaminant.

There are two primary types of respirators: (1) Air-purifying and (2) supplied air respirators. (1) *Air-purifying respirators (APRs)* have filters, cartridges, or canisters that trap contaminants from the air. APRs are the most common protection method for particulates and vapors and are used in environments where there is no chance of an oxygen-deficient state. Available filters should protect against, at a minimum, organic vapors and also contain a high-efficiency particulate air cartridge for particulates. (2) *Supplied air respirators* are used for oxygen-deficient atmospheres, provide breathable air from a clean source such as an air tank or air compressor located outside the contaminated area, and are suitable for use in an oxygen-deficient environment. Half-face pieces allow workers to wear any appropriate eyewear that does not interfere with the respirator seal, but they provide no eye protection themselves, and contaminated air can enter the mask if the seal is broken. Full-face pieces provide eye protection and a tight-fitting facepiece may be able to pull filtered air into the facepiece if the battery fails on a powered air-purifying respirators (PAPR). Various levels of PPE used in HAZMAT are summarized in **Table 2**.

SUMMARY

Various hazardous materials (HAZMAT), biological, chemical, and radiologic materials are present in and around the workplace that result in adverse effects to the health and safety of exposed individuals. Through the development of policies and procedures the health and safety of staff, patients, and visitors are protected and risks are minimized associated with hazardous materials. Policies and procedures are laid down regarding the selection, handling, storage, use and disposal of hazardous materials, and waste. Hazardous materials and hazardous waste streams include, but are not limited to: Chemical, biological, radioactive, pharmaceutical, chemotherapeutic, hazardous gases and mixed waste. Hazardous materials and waste are identified in and around the workplace, appropriately labeled, evaluated, inventoried, handled, managed, and monitored in compliance with applicable regulations to minimize

TABLE 2: Level of personal protective equipment for HAZMAT.

Level A protection	***Level B protection***	***Level C protection***	***Level D protection***
Highest level of protection for eye skin respiratory system from liquid vapors and gases (**Fig. 1A**)	Level B protection provides adequate skin protection but is not vapor impervious like Level A (**Fig. 1B**)	Level C protection should be used when the atmospheric contaminants, liquid splashes, or other direct contact absorbed through any exposed skin (**Fig. 1C**)	Level D protection is used when the atmosphere contains no known hazard, and hardly any possibilities of splashes, unexpected inhalation of or contact with hazardous levels of any chemicals (**Fig. 1D**)
Components of level A protection	*Components of level B protection*	*Components of level C protection*	*Components of level D protection*
• Positive-pressure, full-face piece, self-contained breathing apparatus (SCBA), or • Positive-pressure supplied-air respirator with escape SCBA • Totally encapsulating chemical-protective suit • Gloves, outer, chemical resistant • Gloves, inner, chemical resistant • Boots, chemical resistant, steel toe, and shank • The disposable protective suit, gloves, and boots	• Positive-pressure, full-face piece SCBA, or positive-pressure supplied-air respirator with escape SCBA • Hooded chemical-resistant clothing (one- or two-piece chemical splash suit; disposable chemical-resistant overalls). Gloves, outer, chemical resistant. Gloves, inner, chemical resistant. • Boots, outer, chemical-resistant steel toe and shank • Boot-covers, outer, chemical-resistant (disposable) • Face shield	• Full-face or half-mask, air-purifying respirators • Hooded chemical-resistant clothing (chemical splash suit) • Gloves, outer, chemical resistant • Gloves, inner, chemical resistant • Boots, outer, chemical-resistant steel toe and shank • Boot covers, outer, chemical-resistant (disposable)	• A work uniform affording minimal protection • Gloves • Boots/Shoes • Chemical-resistant steel toe and shank • Safety glasses or chemical splash goggles • Face shield

(PPE: personal protective equipment)

FIGS. 1A TO D: (A) Level A PPE; (B) Level B PPE; (C) Level C PPE; (D) Level D PPE.

risk to staff, patients and visitors, and their impact on the environment. In response to hazardous materials spills, releases and exposures appropriate protocol should be implemented for reporting and investigating hazardous materials spills, releases, and exposures in order to provide the appropriate and effective response, and to prevent reoccurrences. During the emergency procedures to contain the spills specific precautions, equipment, and protective equipment to be used. Apart from this we need to ensure that employees are oriented to, and educated about the proper procedures to follow in order to protect themselves from exposure to hazardous materials. Environmental air monitoring surveys and work procedure analyses required to confirm the effectiveness of engineering and administrative controls. Administration needs to ensure that mandated licenses and permits are maintained in compliance with applicable law and regulations and the granting regulatory agency requirements. Mechanism needs to be established for the review, development, and dissemination of hazardous materials policies and procedures.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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9 CHAPTER

Infection Prevention in Emergency Department

Josephine Cyrill, Angelika Masih

INTRODUCTION

Emergency departments (EDs) are the frontline providers for all the patients with disease and injuries, including infectious disease conditions. Sometimes, healthcare workers (HCWs) and other patients are often predisposed for the development of secondary infections. HCWs in emergency requires competency not only in the diagnosis and management of disease conditions but also in the control and prevention of the same. Infection control and prevention focus on reducing communicable and infectious disease transmission and preventing healthcare-associated infections.

It is highly recommended to practice measures such as standard infection control precautions (SICPs), transmission-based precautions (TBPs), and the prevention of healthcare-associated infections in the ED.

ADHERENCE TO STANDARD INFECTION CONTROL PRECAUTIONS

Adherences to SICPs, formerly known as "standard precautions," are an important part of the healthcare setting and are designed to offer protection against infections to both HCWs and patients. n SICP includes certain components which are shown in **Figure 1**.

Hand Hygiene

Hand hygiene is the foremost element of SICPs and one of the most effective approaches to prevent transmission of microorganisms. Hand hygiene refers to any action of hand cleansing, such as hand washing or hand rubbing.

The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend hand hygiene before and/or after key actions while dealing with patients and have named it as *"five moments for hand hygiene"*: (1) Before touching the patient, (2) before the aseptic procedure, (3) after body fluid exposure or risk, (4) after touching the patient, and (5) after touching the patient's surroundings.

Personal Protective Equipment

Personal protective equipment (PPE) are wearable equipment that is designed to protect HCWs from exposure to or contact with infectious agents. Common PPE includes gloves, gown, face mask/respirator, goggles/eye shield, shoe cover, and cap.

Respiratory Hygiene/Cough Etiquettes

Respiratory hygiene/cough etiquette is integrated into infection control practices as a new element of standard precautions. This strategy targets all the patients and attendants with

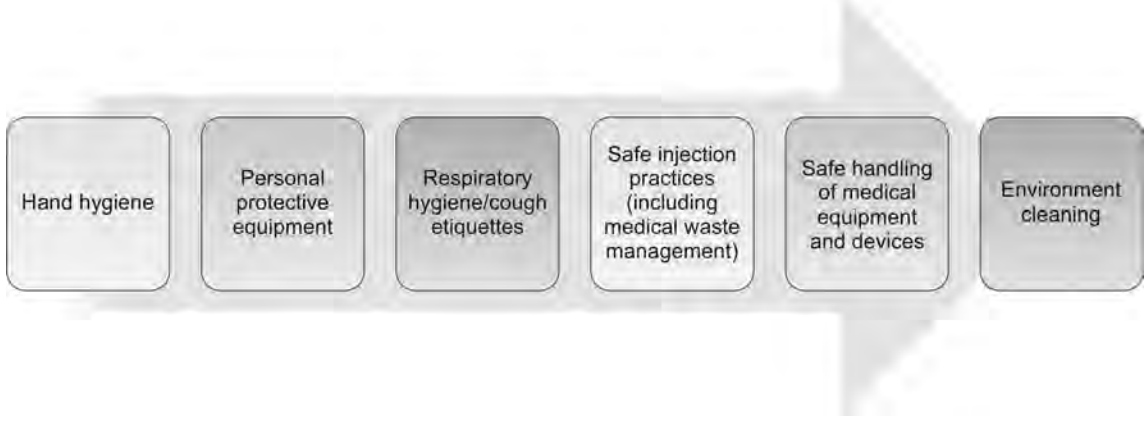

Hand hygiene
Personal protective equipment
Respiratory hygiene/cough etiquettes
Safe injection practices (including medical waste management)
Safe handling of medical equipment and devices
Environment cleaning

FIG. 1: Standard infection control precautions.

Yellow	Red	White	Blue
• Human anatomical waste • Animal anatomical waste • Soiled waste items • Discarded or expired medicine • Chemical waste chemicals • Discarded linen, mattresses, beddings contaminated with blood or body fluid, routine mask and gown	• Wastes generated from disposable items such as tubing, bottles, intravenous tubes and sets, catheters, urine bags, syringes without needles, fixed needle syringes with their needles cut, vaccutainers, and gloves	• Waste Sharps including metals needles, syringes with fixed needles, needles from needle tip cutter or burner, scalpels, blades, or any other contaminated sharp object that may cause puncture and cuts This includes used, discarded and contaminated metal sharps	• Broken or discarded and contaminated glass including medicine vials and ampoules except those contaminated with cytotoxic wastes

FIG. 2: Biomedical waste management.

undiagnosed contagious respiratory infections and applies to any person with signs of illness while arriving to a healthcare facility.

Safety in Injection Practices (Including Medical Waste Management)

Injection safety practices focus on preventing the spread of transmissible infections from one patient to another or between a patient and healthcare worker in the course of preparation and administration of parenteral medications.

Bio Medical Waste Management Rules, 2016, sorts the biomedical waste generated from the healthcare facility into four kinds based on the color code and segregation process (**Fig. 2**).

Safe Handling of Medical Equipment and Devices

Safe handling of medical equipment/devices targets:

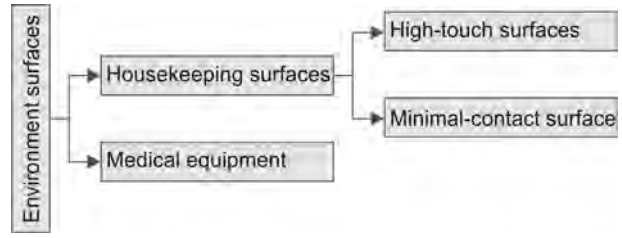
- To prevent the spread of microorganisms to HCWs and patients
- To minimalize inappropriate handling and further damage to medical equipment/devices from extraneous material (e.g., blood, body fluids, saline, and medications)

Environment Cleaning

Environmental cleaning plays a crucial role in the prevention of healthcare-associated infections. The Healthcare Infection Control Practices Advisory Committee (HICPAC) has divided environmental surfaces into two categories (**Flowchart 1**): (1) Medical equipment surfaces and housekeeping surfaces (e.g., floors, walls, tabletops) and (2) housekeeping surfaces which are further divided into "high-touch" surfaces (e.g., door handles, bedside rails, light switches) and minimal-contact surfaces (e.g., floors, ceilings). The cleaning of these surfaces highly depends on the possibility for direct patient contact, the degree and frequency of hand contact, and the risk of contamination with body materials or environmental sources of microorganisms (e.g., soil, dust, water).

PREDETECTION AND TRIAGE MANAGEMENT

Predetection and triage point areas should be equipped with sufficient and appropriate nontouch thermal scanning, hand hygiene products and supplies, PPE and disinfection facilities,



FLOWCHART 1: Categories of environmental surfaces.

etc. ED should have well-developed protocols for early detection and management of potentially infectious patients. HCWs should be well trained and strictly implement SICP protocols whenever necessary.

TRANSMISSION-BASED PRECAUTIONS

Transmission-based precautions are the infection control and prevention approaches which use a combination of PPE and patient isolation. TBPs in ED entirely depend on the patient's clinical presentation and diagnosis of the disease condition.

Transmission-based precautions include specific precautions—airborne, droplet, and contact—and generally require patient isolation (**Table 1**).

Airborne Spread

The particles, in the airborne spread, are smaller (≤5 μm) and remain suspended in the air for long periods. They tend to stay longer in the air and are transported by air during breathing, talking, coughing, and sneezing. Organisms spread via the airborne mode, e.g., measles, varicella, smallpox, highly pathogenic influenza, severe acute respiratory syndrome (SARS), and the Middle East respiratory syndrome (MERS) corona virus.

Droplet Spread

The droplets are usually large particles that are >5 μm. Droplet spread occurs via the upper respiratory tract (nose, nasal passages, and pharynx). Individuals in ED should practice distancing of at least 1 m to prevent the spread of infections from one to another. Droplet infectious agents include mumps, influenza, Neisseria meningitides (meningitis), and COVID-19.

Contact Precautions

Contact spread happens via direct contact with the infected person, the immediate environment, and/or the equipment

TABLE 1: Transmission-based precaution for selected microorganism.

Airborne	*Droplet*	*Contact*
• Tuberculosis • Varicella-zoster virus (chickenpox, disseminated zoster) • Measles • Smallpox	• Meningococcus • Seasonal influenza Rhinovirus, respiratory syncytial virus, German, measles, mumps, pertussis, diphtheria, pneumonic plague • SARS CoV-2, COVID-19	• MRSA • Vancomycin-resistant Enterococcus. Multidrug-resistant gram-negative bacteria (e.g., carbapenem-resistant Enterobacteriaceae, extended-spectrum β-lactamase producing bacteria) • *Clostridium difficile* • Norovirus • Lice, scabies
Highly pathogenic influenza Severe acute respiratory syndrome (SARS) Middle-east respiratory syndrome (MERS)		

(MRSA: Methicillin-resistant *Staphylococcus* aureus)

being used for the patient. It is the most common form of transmission and there are two types: (1) Direct and (2) indirect (**Fig. 3**). Examples of infections and organisms spread by the contact route are COVID-19, MRSA (methicillin-resistant *Staphylococcus aureus*), *Escherichia coli*, and *Clostridium difficile*.

High-consequence Infectious Diseases

High-consequence infectious diseases (HCIDs) may be transmitted by contact, droplet, or an airborne route or by a combination of any of these. HCID is an acute infectious disease which:

- Typically has a high case-fatality rate
- May not have effective prophylaxis or treatment
- Is often difficult to recognize and detect rapidly
- Is able to spread in the community and within healthcare settings
- Requires an enhanced individual, population, and system response to manage effectively, efficiently, and safely

Transmission-based Precautions in Practice

Contact precautions are the most common type of TBPs. Use of N95 masks, single-room isolation with negative pressure (≥12 air exchanges per hour), and airborne precautions by clinicians and other healthcare staff in the ED is mandatory. Continuous audit, training, and adherence to protocols are needed. In case of nonavailability of a negative-pressure room, a well-ventilated single room is required specially to prevent transmission during aerosol-generating procedures (AGPs).

Aerosol-generating procedures:

- Intubation, extubation, and other procedures
- Tracheostomy
- Manual ventilation
- Open suctioning
- Bronchoscopy
- Noninvasive ventilation
- High-frequency oscillating ventilation
- High-flow nasal oxygen

Points to remember:

- Training
- Cleaning and disinfection of high-risk areas such as isolation room
- PPE usage, donning/doffing

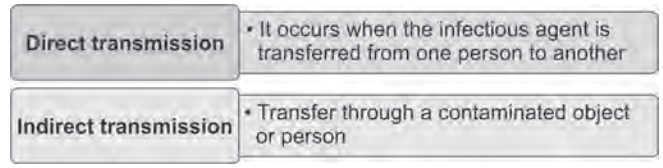

Direct transmission
• It occurs when the infectious agent is transferred from one person to another
Indirect transmission
• Transfer through a contaminated object or person

FIG. 3: Direct and indirect contact transmission.

- Biomedical waste (BMW) practice
- Hand hygiene compliance
- Healthcare personnel vaccinations

The CDC recommends annual influenza vaccination for healthcare teams. Immunization programs ensure immunity to most of the vaccine-preventable diseases.

DISINFECTION AND STERILIZATION OF REUSABLE MEDICAL DEVICES

It is done as per the organization's protocols and policy. In most of the hospitals, cleaning, disinfection, and sterilization are done centrally in central sterile services department (CSSD). The ED has many equipment which are mainly categorized as critical and noncritical devices according to the *Spaulding classification system* (**Fig. 4**).

The following steps have to carefully be monitored:

- Precleaning of surgical instruments before sending them for sterilization
- Use of recommended disinfectants and their dilution
- Training by the infection control team and regular audits
- Awareness on material safety data sheet (MSDS) of chemicals to prevent occupational hazards

Routine cleaning and high- and low-level disinfection ensure patient safety and adherence to infection control recommendations.

DEVICE-ASSOCIATED INFECTIONS

Device-associated infections are one of the largely preventable sources of healthcare-associated infections (HCAIs). Device-related infections can be categorized into catheter-associated urinary tract infections, central line-associated bloodstream infections, and ventilator-associated pneumonia (**Flowchart 2**).

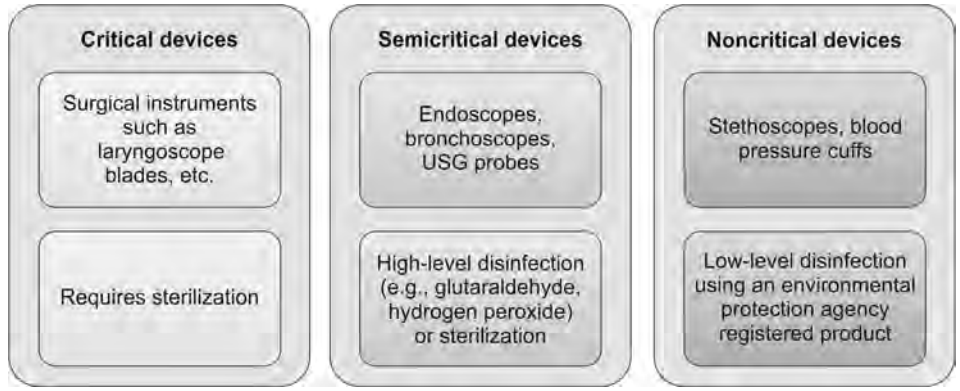
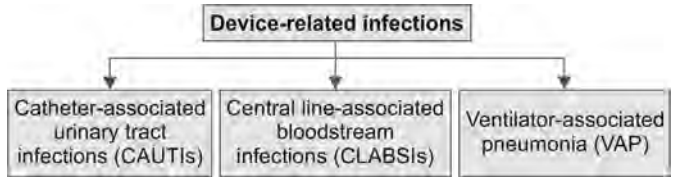

Critical devices
Surgical instruments such as laryngoscope blades, etc.
Requires sterilization
Semicritical devices
Endoscopes, bronchoscopes, USG probes
High-level disinfection (e.g., glutaraldehyde, hydrogen peroxide) or sterilization
Noncritical devices
Stethoscopes, blood pressure cuffs
Low-level disinfection using an environmental protection agency registered product

FIG. 4: Spaulding classification system for medical devices.



FLOWCHART 2: Device-associated infections.

Care bundles have been formulated based on evidence-based research work and best considered practice. Bundles are a powerful weapon against hospital-acquired infections. The EDs require thorough knowledge of the care bundles to prevent HCAI and deliver optimal patient care.

Catheter-associated Urinary Catheter Infections

Although urinary catheter insertion is necessary for emergency care, catheter-associated urinary catheter infections (CAUTIs) are one of the common infections attributing to HCAI. The CDC and the Society for Healthcare Epidemiology of America (SHEA) recommend limited usage of urinary catheterization for managing acute urinary retention and bladder outlet obstruction and accuracy in urine output measurement in critically ill patients, clinical situations, patients who require prolonged immobilization (e.g., pelvic fracture, spine trauma), and selected surgical procedures. The CAUTI maintenance bundle is to enhance the patient care requiring urinary catheterization during acute care and to make certain that urinary catheters are removed as soon as clinically indicated.

Central Line-associated Bloodstream Infections

Central line-associated bloodstream infections (CLABSIs) are a critical infection causing prolongation of hospital stay and increased expense and risk of mortality. CLABSIs are prevented through proper insertion skills and management of the central line catheters. Insertion and maintenance bundles are implemented for reducing the risks for CLABSIs. Multiple organizations in collaboration have given guidelines that comprise education, procedure checklists, a standardized catheter cart or kit, hand hygiene, use of maximal sterile barrier precautions (sterile surgical gown, sterile gloves, mask, cap, and sterile drape), chlorhexidine-alcohol skin antisepsis, and use of ultrasound guidance.

Ventilator-associated Pneumonia

Emergency airway management and resuscitation necessitate endotracheal intubation and mechanical ventilation. Ventilator-associated pneumonia (VAP) is defined as the diagnosis of a new pneumonia after >48 hours of mechanical ventilation, not present at the time of intubation. Endotracheal intubation in the ED and prolonged ED stay have also been related to high VAP rates in comparison with the intensive care unit (ICU). The CDC guidelines provide a basic framework for VAP prevention strategies, including:

- Head elevation of the bed to 30–45°
- Oral care with chlorhexidine
- Daily sedation and vacation
- Subglottic suctioning
- Pressure ulcer prophylaxis
- Deep vein thrombosis (DVT) prophylaxis

Nursing engagement is vital for successful implementation of these bundles.

EDUCATION AND TRAINING

Staff training and education play an essential role in improving compliance with infection control practices measures in the ED. Continuing nursing education help staffs to develop the ability to identify patients with transmissible indications during triage and thereby swiftly implement the required prevention and control methods. Ongoing in-service education and competency-based training of HCWs are necessary to ensure that infection prevention policies and procedures are well understood and followed.

SUMMARY

Healthcare workers should practice infection control and prevention practices as a part of our basic responsibility toward the patients. Hand hygiene remains the vanguard for the prevention of HCAI spread. SICPs, TBPs, environmental cleaning, and care bundles provide additional levels of protection to patients and HCWs. Moreover, staff training and education regarding infection control practices play an essential role. Healthcare facilities are encouraged to refer and further augment their own system and implement in clinical practice.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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10
CHAPTER

Personal Protective Equipment

TV Ramakrishnan, Akilan Elangovan

INTRODUCTION

Healthcare-associated infections (HCAIs) can occur in any healthcare setting. It is the responsibility of every healthcare worker (HCW) to follow the basic principles of infection prevention and control (IPC). The goal is to improve the safety and well-being of health personnel and to avoid transmission of HCAI by following standard precautions.

STANDARD PRECAUTIONS

Standard precautions are a group of IPC practices applied to all patients, at every patient encounter, irrespective of their suspected or confirmed infection status. The basic principle is that all blood, body fluids, secretions, and excretions contain transmissible infectious agents. Hence, the implementation of standard precautions helps to maintain a physical, mechanical, or chemical barrier between microorganisms, the environment, and an individual, thus breaking the disease transmission cycle. These precautions include hand hygiene, use of personal protective equipment (PPE) (gloves, gown, mask, protective eyewear), respiratory hygiene/cough etiquette by patients or HCWs, safe injection practices with proper disposal of sharps, device sterilization, environmental cleaning, and disinfection. Wearing PPE is one such standard precaution, which creates a two-way protective barrier between the HCW and the patient by reducing the risk of transmitting microorganisms, which in turn prevents hospital-acquired infections (HAIs).

PERSONAL PROTECTIVE EQUIPMENT

Personal protective equipment, as defined by the Centers for Disease Control and Prevention (CDC), refers to a variety of protective barriers and respirators used alone or in combination by the HCW to protect the airway, mucous membrane, skin, and clothing from contact with infectious agents. Various PPE used in healthcare include gloves (nonsterile or sterile), mask, respirator, protective eyewear (face shield, goggles, or safety glasses), gown, apron, and other items (headcover, hood, closed-toe shoes, and shoe covers). The most crucial step that one should follow before wearing PPE is hand hygiene. PPE prevent the spread of pathogens (**Table 1**).

HAND HYGIENE

Hand hygiene is the single most crucial method in standard precautions of IPC. It provides the first line of defense in the prevention of transmission of microorganisms in healthcare facilities. The World Health Organization (WHO) recommends *"my five moments for hand hygiene"* which include: (1) Before direct contact or touching the patient; (2) Before performing clean/aseptic procedures on the patient; (3) After contact with blood, body fluids, mucous membranes, nonintact skin, wound dressings, or visibly contaminated; (4) After direct contact or touching the patient; and (5) After touching the patient's surroundings or inanimate objects (including medical equipment) in the immediate vicinity.

To facilitate effective hand hygiene, always perform with sleeves "rolled up" above the elbow, remove any hand or wrist jewelry, keep nails short, use water and liquid soap (if hands are soiled), or an alcohol-based hand rub (ABHR) (if not soiled). ABHR is an effective, inexpensive, and practical alternative to soap and water. ABHR is faster and easier to perform than handwashing with soap and water. It should be performed at every room entry and exit and before any procedure. The use of ABHR has been associated with improved hand hygiene compliance rates and reductions in nosocomial infections. The technique for hand hygiene is summarized by the WHO, which recommends a six-step sequence with liquid soap and ABHR.

TYPES OF PERSONAL PROTECTIVE EQUIPMENT USED IN HEALTHCARE SETTINGS

For PPE to be effective, they must be readily available, provide adequate protection, and be utilized correctly in the appropriate situations and settings. Various types of PPE are used in combination depending on the suspected or known infectious pathogen and its route of transmission.

Gloves

Gloves are the most common and crucial type of PPE used. They serve as a physical barrier, which protects the hands of HCW from contamination with infectious materials and

TABLE 1: Role of personal protective equipment in preventing the spread of pathogens.

Source for pathogen		*Mode of transmission*	*Protective barrier*	*Protection offered*
From healthcare workers	Hands	Touching	Hand hygiene and gloves	Patients, HCW
	Body and skin	Touching	Scrub suit, uniform, gown, apron	
	Nose and mouth	Coughing, talking	Surgical mask, N95 respirator	
	Hair	Shedding scalp hair or facial hair	Headcover, facial hair cover	
From patients	Mucous membranes and nonintact skin	Touching	Hand hygiene and gloves	HCW, patients
	Blood and body fluids	Touching (surface and instruments)	Utility gloves, environmental cleaning, instrument sterilizing and decontaminating reusables	
		Splashing or spraying	Gloves, protective eyewear, mask, gown, apron, head, and shoe cover	HCW
		Infectious waste	Utility gloves, protective eyewear, mask, apron, plastic bags, and appropriate disposal.	HCW, community
	Respiratory secretions	Splashing or spraying	Surgical mask, N95 respirator (for HCW)	HCW, patients, community
Hospital environment		Touching	Hand hygiene and environmental cleaning	HCW, patients

(HCW: healthcare worker)

Sources: 1. Modified from Melanie S. Curless, Bria S. Graham-Glover, Reprolineplus.org, Jhpiego. [online] Available from http://reprolineplus.org/system/files/resources/IPC_M3_PPE.pdf [Last accessed June, 2021].

2. Tietjen LG, Bossemeyer D, McIntosh N. Infection Prevention: Guidelines for Healthcare Facilities with Limited Resources. Baltimore, MD: Jhpiego; 2003.

reduces the likelihood of colonization with microorganisms from the patient. They are worn by HCW when anticipating contact with infectious materials, namely blood, bodily fluids, secretions from mucous membranes, nonintact skin, or potentially contaminated intact skin and when handling equipment that may have been in contact with these. The gloves must be removed correctly and should be followed by complete hand hygiene to prevent the risk of transmission of infections to vulnerable patients.

Selection of Glove

Sterile gloves are worn by surgeons and other healthcare personnel when performing sterile or aseptic procedures, namely surgical, invasive radiological, or vascular procedures. Nonsterile gloves are single-use, disposable ones worn by most HCWs when performing routine patient care activities. They are made of latex, vinyl, or nitrile and their choice should be determined by the degree of risk of exposure to blood or potentially infected body fluids, length of time required for the procedure, and the possibility of allergy (to latex) for HCWs.

Dos and Don'ts for Gloves

Gloves should fit the user's hands correctly to avoid limitations in performing the task. They may be damaged more easily if they are not of the correct size. Gloves should be changed between patient encounters and when they get torn or visibly contaminated, namely between each patient and between different procedures on the same patient to prevent cross-contamination of body sites or contamination of medical equipment. The HCW should not touch their face or environmental surfaces or adjust PPE with contaminated gloves. Gloves are single-use and should never be decontaminated, washed, reused, or shared with another user. They must be discarded into the appropriate waste container immediately after use. They are not an alternative to hand hygiene. Hands should be decontaminated thoroughly with soap and water or ABHR.

Gown/Apron

Gown provides a fluid-resistant barrier that protects the HCW's skin from splashes and spills. It avoids soiling or contamination of clothing during procedures and patient-care activities, when there may be possible contact with blood, body fluids, secretions, excretions, or objects. There are three types of protective gowns used in healthcare facilities: (1) Isolation gowns, (2) Surgical gowns, and (3) Coverall suits with hood. The gown should fully cover the torso, fit comfortably over the body, and have long sleeves that fit snuggly at the wrist, thus providing 360° protection. They are of single-use and preferably disposable. Plastic aprons provide a waterproof barrier along the front of the body (i.e., front torso), protecting the skin of the HCW from contamination with blood and other body fluids during patient care or handling soiled items.

Selection of Gown

Selecting the appropriate gown is based on the type of patient interaction, including the anticipated degree of contact with infective material, the potential for blood and body fluid penetration of the barrier, and the kind of task or procedure to be performed by the HCWs.

Plastic aprons are the preferred PPE for standard precautions. Sterile gowns are necessary for a sterile procedure such as central line insertion or a surgical procedure in an operating room to protect the sterile field. During standard precautions, an isolation gown is worn if blood or body fluid contact, spills, or splashes onto clothing is anticipated.

During contact and droplet precautions, an isolation gown is used to prevent transmission of an infectious agent that cannot be prevented by standard precautions alone. Isolation gowns should be worn in combination with gloves and other PPE depending on the various routes of transmission of the pathogen, as recommended.

Dos and Don'ts for Gown

Gowns should be changed routinely during shifts and between patients or between different procedures on the same patient when visibly soiled. Remove the gowns carefully using ties and be careful not to touch the outer surface and always decontaminate hands thoroughly after removal of gown and gloves.

Protective Eyewear

The mucous membrane of the eyes is a susceptible portal of entry for infectious agents (e.g., respiratory tract and bloodborne pathogens) from exposure to respiratory or aerosolized droplets and splashes of blood, body fluids, secretions, or excretions. Hence, protective eyewear is used to shield eyes and the surrounding skin from potential risks of transmission, while performing procedures of close proximity (e.g., aerosol-generating procedures or invasive vascular procedures). Goggles, safety glasses, masks with an attached shield, and full-face shields are used according to the need anticipated during procedures and patient-care activity.

Selection of Protective Eyewear

Eyes can be protected either by wearing goggles or by a visor, but these do not protect from splashes or sprays to other parts of the face. Face shields can be used as an alternative to goggles, as they extend from the chin to the crown of the head and wrap around the sides and hence provide better face and eye protection from splashes and sprays. The choice of eyewear for a specific work situation depends upon the type of exposure, other PPEs used, and the HCW's vision needs.

- As part of standard precautions (if the risk of spraying or splashing is anticipated)
- As part of droplet precautions to protect from respiratory secretions
- As part of contact precautions during procedures that involve spraying or splashing of blood and body fluids
- During specimen collection or aerosol-generating procedures in patients with specific respiratory tract pathogens

Dos and Don'ts for Protective Eyewear

Personal eyeglasses and contact lenses are not an alternative to eyewear. The eyewear should fit comfortably over and around the eyes and allow sufficient peripheral vision. It should fit over personal prescription lenses and provide antifog features to help maintain clarity of vision. It is of single-use and preferably disposable. If reusable, it should be placed separately after use and decontaminated. Hand hygiene should be performed after removing the eyewear.

Masks and Respirators

Masks cover the mouth and nose to protect the respiratory tract from inhalation of respiratory droplets, transmitted by coughs or sneezes from patients with infected or suspected respiratory tract pathogens via droplet or airborne transmission.

The choice of particulate respirators is selected based on the natural fit and the protective factor expected. The filtering efficiency of the N95/ FFP2 respirator is at least 95% and that of N99/FFP3 respirator is at least 99% of tiny test particles (0.3 μm).

Powered air-purifying respirators (PAPRs) are an alternative to particulate respirators that use high-efficiency particulate air filters (HEPA) and a battery-powered blower to provide filtered air to a hood. PAPRs are more expensive than particulate respirators and require electricity to charge the battery. A comparison of surgical mask and respirator is given in **Table 2**.

Headcover/Hood

Headcovers or hoods are most often worn during surgery and in procedure areas where a sterile field is required. They are not necessary for most other regions of the healthcare facility. Headcovers are not part of routine PPE for contact, droplet, or airborne precautions unless used during pandemic outbreaks. These are used to protect the HCW's hair and scalp from the spread of infectious pathogens by droplet or airborne transmission.

Footwear/Shoe Cover

Sturdy shoes with closed toes are recommended for all clinical areas, as these decrease the risk of exposure to blood, body fluids, or other potentially infectious materials and avoids injuries by sharps. Open-toe slippers and flip flops are not appropriate footwear for safety concerns in healthcare settings. Shoe covers are not part of routine PPE for contact, droplet, or airborne precautions unless used during pandemic outbreaks. This is because they do not prevent transmission of the pathogen from the floor but rather prevent contamination of shoes with blood and body fluids. If shoe covers are used, dispose them properly and perform hand hygiene immediately after removing them.

DONNING AND DOFFING PERSONAL PROTECTIVE EQUIPMENT

Personal protective equipment are used as a part of standard precautions, transmission-based precautions in an operating room, isolation rooms, and during disease outbreaks (e.g., novel respiratory disease). The sequence of donning and doffing PPE depends upon the purpose for which the PPE is being used. Failure to properly don and doff PPE in the correct sequence could lead to exposure to infectious agents.

Key Points About How to Safely Use Personal Protective Equipment

Carefully wear them before you have any contact with the patient, generally before entering the room. Once you have PPE on, check for proper fit and use them carefully. Avoid touching the face and unwanted surfaces to prevent contamination. Change, when torn or heavily contaminated. After completing your tasks, remove the PPE carefully and discard it in the containers provided. Perform hand hygiene either by hand rub or by handwash before moving on to the next patient.

TABLE 2: Comparison of surgical mask and respirator.

	Surgical mask	*Respirator*
Testing and approval	• Approved by the US Food and Drug Administration (FDA)	• Evaluated, tested, and approved by the US National Institute for Occupational Safety and Health (NIOSH)
Intended use and purpose	• Fluid resistant and protects from inhalation of large droplets of >5 µm in size transmitted by splashes or sprays of bodily or other hazardous fluids. Also, it protects the patient from the wearer's respiratory emissions • Do not filter or block tiny particles in the air that may be transmitted by coughs, sneezes, or specific aerosol-generating procedures	• Protects from inhalation of tiny droplet particles <5 µm or less in size transmitted by cough, sneeze, talk, or undergo aerosol-generating procedures (nebulization, suctioning, intubation, and resuscitation)
Indication for usage at work	• Patients with respiratory secretions, to protect healthcare workers from patients' infectious material (such as aerosols containing blood or body fluids) • Patients undergoing sterile procedures (including central line insertion, invasive spinal procedures), to protect patients from respiratory aerosols generated by healthcare personnel performing the procedure • Besides, masks should be worn by patients with respiratory secretions who are coughing to limit the spread of infectious secretions to other patients and healthcare workers	• As part of droplet precautions to protect from respiratory secretions during invasive respiratory procedures of close proximity (sputum collection, endotracheal suctioning, intubation) • As a part of airborne precautions to protect from infectious pathogens transmitted by airborne particles • During aerosol-generating procedures (nebulization, intubation, and resuscitation) on patients with specific respiratory tract pathogens (TB, SARS-CoV-2, novel respiratory viruses) that can spread via droplet or airborne route
Face seal fit	• Loose-fitting mask as they are not designed to form a tight seal around the nose and mouth	• Tight-fitting, hence usually challenging to breathe through. One must undergo medical evaluation to determine that it is safe to wear a respirator, fit test for the appropriate respirator size and type, and training on how and when to use a respirator. Facial hair interferes with the proper fit of masks
Fit testing requirement	• Not required as they are loose-fitting by design	• Required every time the respirator is donned and with any change in physical characteristics affecting the fit
Seal check requirement		
Filtration	• Does not provide the wearer with a reliable level of protection from inhaling smaller airborne particles and is not considered respiratory protection	• Filters out at least 95% of airborne particles, including large and small particles
Leakage	• Leakage occurs around the edge of the mask when the user inhales, hence does not provide complete protection from contaminants	• When properly fitted and donned, minimal leakage occurs around the edges of the respirator when the user inhales
Use limitations	• Single-use, disposable. Not to be shared or reused. Discard after each patient encounter	• Ideally should be discarded after each patient encounter and after aerosol-generating procedures. It should also be discarded when it becomes damaged or deformed, no longer forms an effective seal to the face becomes wet or visibly dirty, breathing becomes difficult, or becomes contaminated with blood, respiratory or nasal secretions, or other bodily fluids from patients

(SARS-CoV-2: severe acute respiratory syndrome coronavirus disease-2; TB: tuberculosis)

Source: Modified from Centers for Disease Control and Prevention National Institute for Occupational Safety and Health. Difference between the surgical mask and N95 respirator. [online] Available from https://www.cdc.gov/niosh/npptl/pdfs/UnderstandDifferenceInfographic-508.pdf [Last accessed June, 2021].

How to Don a Gown

Perform hand hygiene. Select the gown of the right size and appropriate type for the task. Unfold the gown and insert both hands in the sleeves of the gown, one after the other. Completely cover the torso from neck to knees, arms to the end of the wrists, and wrap around the back. Ensure that the opening of the gown is in the back. Secure both sides using the tie at the neck and the waist (seek help if needed). Make sure that you tie the waist knot on the side so that it is easy to untie at the time of removal (**Fig. 1**).

How to Don a Mask

Masks are fastened either with ties or with an elastic band. If the mask has ties, place the mask over your mouth, nose, and chin. Fit the flexible nosepiece to the form of your nose bridge; tie the upper set at the back of your head and the lower set at the base of your neck. If a mask has elastic bands, pull and place behind the ears and secure them comfortably. Adjust the mask to ensure that it is secure and fit snuggly around your face, so there are no gaps (**Fig. 2**).

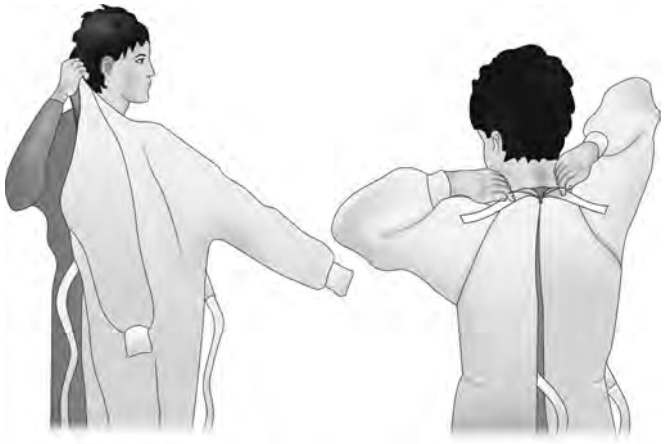


FIG. 1: Donning a gown.

FIG. 2: Donning a mask.

How to Don a Particulate Respirator

Donning a particulate respirator is similar to a mask with elastic bands. Cup the respirator in one hand and the nosepiece at the fingertips, allowing the headbands to hang freely below your hand. Position the respirator under the chin first with the nosepiece up. Pull off the top strap over your head, resting it high at the top back of your head. Pull off the bottom strap over your head and position it around the base of the neck, below the ears. Perform "fit test" to verify that the respirator is both comfortable and its size fits correctly. Now place two fingertips from both hands at the top of the metal nose clip. Slide fingertips down both sides of the metal strip to mold the nose area to the shape of your nose. Perform "seal check test" to verify that the particulate respirator is properly sealed without leakage. A successful negative pressure check is when while inhaling the respirator collapses slightly under the negative pressure that is created, and a positive pressure check is when while exhaling the respirator is somewhat pressurized before increased pressure causes outward leakage (**Figs. 3A** to **C**).

How to Don Goggles or Face Shield

Put on protective eyewear after putting on the gown and mask. Either goggles or a face shield must be worn over the face and eyes and secured to the head using the attached earpieces or headband. Adjust to fit comfortably and assess the field of vision. Goggles should feel snug but not tight (**Figs. 4A** to **C**).

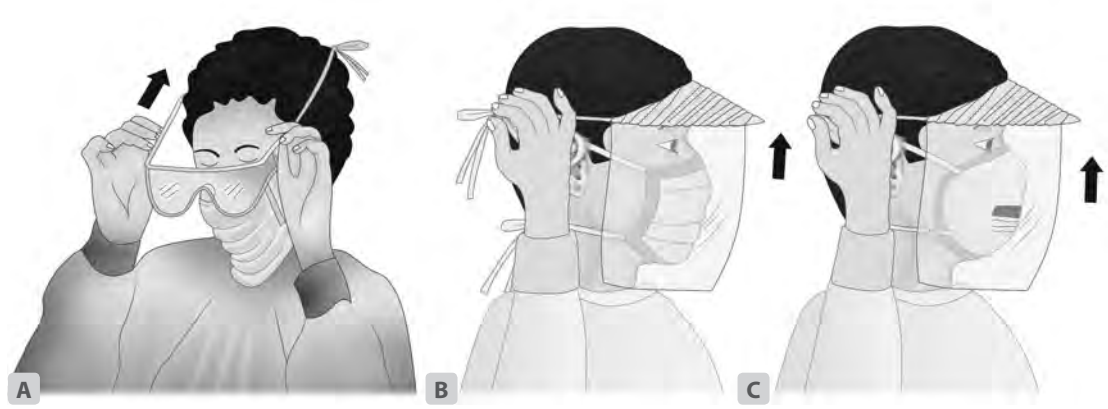
How to Don Gloves

The last PPE to be donned is the gloves. Select the appropriate type of glove needed for the task, in the size that best fits you. Insert each hand into the suitable glove and adjust as needed for comfort and fit. If you are wearing an isolation gown, secure the end of the gloves over the gown cuffs. This offers continuous barrier protection for your skin. Once gloved, hands should not touch anything else that is not defined by indication for glove use (**Fig. 5**). Check for complete coverage and proper fit of the PPE before approaching the patient (**Fig. 6**).

Key Points About How to Safely Doff Personal Protective Equipment

Personal protective equipment should be removed promptly and disposed of properly. To remove PPE safely, first, identify the sides which are considered clean or contaminated.

FIGS. 3A TO C: Donning particulate respirator. (A) Wearing; (B) Fit test; (C) Seal check.



FIGS. 4A TO C: Donning eye and face. (A) Goggles with mask; (B) Face shield with mask; (C) Face shield with N95.

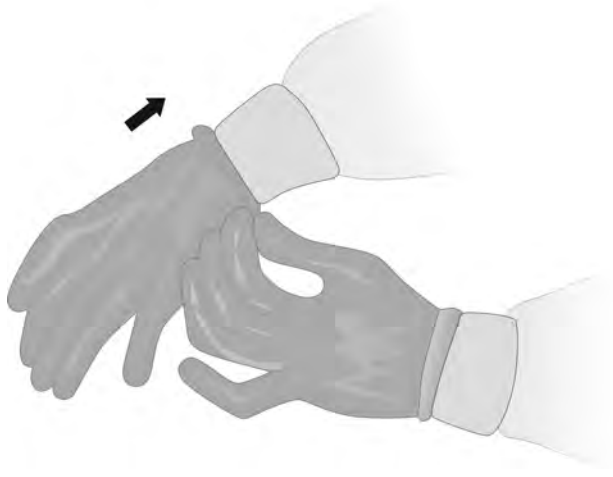


FIG. 5: Donning gloves.

(PPE: personal protective equipment)

FIG. 6: Full PPE.
Courtesy: Srinath Senthil.

Generally, the outside front and sleeves of the gown and the outer aspect of the goggles, gloves, mask, and face shield are considered contaminated, regardless of whether it is visibly soiled. The sites that are considered clean are the parts that will be touched when removing PPE, namely inside the gloves, inside and back of the gown, including its ties, and the ties or elastic bands of the mask, goggles, and face shield. The sequence for removing PPE is gloves, face shield or goggles, gown, and mask or respirator.

How to Doff Gloves

Using one gloved hand, carefully hold the outer part of the opposite glove near the wrist. Pull and peel off the glove away from the hand. The glove must now be turned inside-out, with the contaminated side on the inside. Remain to hold the removed glove in the opposite gloved hand; now slide one or two fingers of the ungloved hand beneath the wrist of the remaining glove. Peel gloves off from the inside, making a bag for both gloves. Discard in the appropriate container (**Fig. 7**).

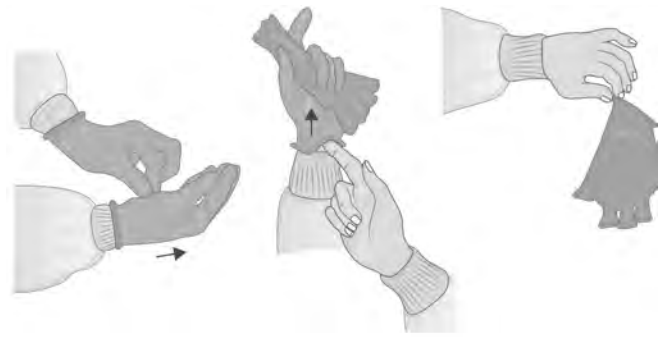


FIG. 7: Doffing gloves.

How to Doff Goggles or Face Shield

Do not grab the front of goggles or face shields as they are contaminated. Using ungloved hands, grasp the clean earpiece or headpiece and lift away from the face. If the goggle or face shield is reusable, place it in a designated container for subsequent reprocessing. Otherwise, discard it in the appropriate container (**Figs. 8A** to **C**).

How to Doff a Gown

The front and sleeves of the gown are contaminated. Unfasten the gown ties by first releasing the neck knot, being sure not to

FIGS. 8A TO C: Doff goggles or face shield. (A) Goggles with mask; (B) Face shield with mask; (C) Face shield with N95.

contaminate the neck, followed by the side knot. Slip hands beneath the gown at the neck and shoulder and peel away from the shoulders. Slip the fingers of one hand beneath the cuff of the opposite arm. Now pull the hand into the sleeve, grasping the gown from inside. Then reach across and push the sleeve of the opposite arm. Fold the gown inside out and roll into a bundle, ensuring that you avoid touching the gown's outer surface. Dispose of the gown in a contaminated-waste container (**Fig. 9**).

How to Doff a Mask

The respirator or mask should be removed last and outside the patient room or in an anteroom after removing all other PPE, including gloves. Do not touch the front of the mask, as it is considered most contaminated. Remove by handling the bottom ties or elastic bands first, followed by the top tie or band. Move the mask away from the face and discard it into the designated waste container (**Fig. 10**).

How to Doff a Respirator

Pull off the bottom elastic strap around the neck first and then pull off the top strap over your head. This must be performed slowly to prevent the respirator from snapping off the face. Remove it without touching the front of the respirator, which may be contaminated. Discard the respirator immediately.

Perform Hand Hygiene

Hand hygiene is a crucial infection control practice to protect patients, healthcare personnel, and visitors and is required for both standard and transmission-based precautions. Hand hygiene must be performed immediately before and after removing PPE, even during PPE changes, and between patient contacts. Wash your hands methodically with soap and warm water or, if hands are not visibly soiled, use an ABHR (**Fig. 11**).

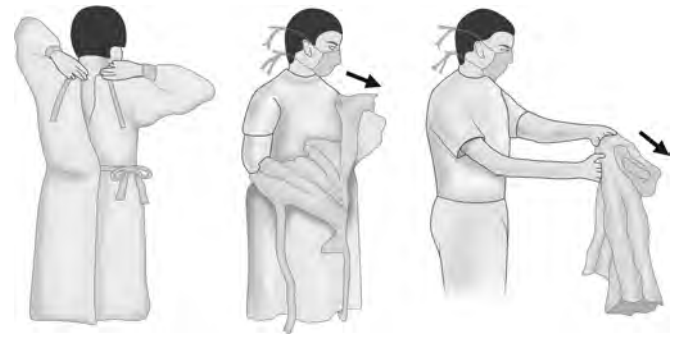


FIG. 9: Doff isolation gown.

FIG. 10: Doff a mask and respirator.
Courtesy: Srinath Senthil.

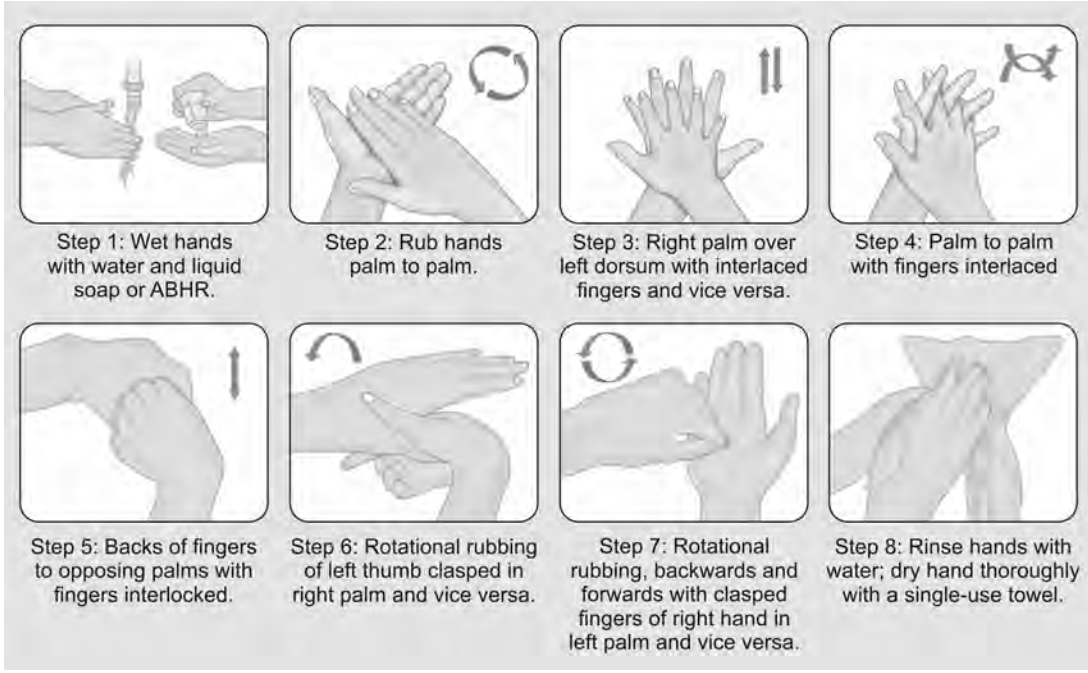
SELECTING THE APPROPRIATE PERSONAL PROTECTIVE EQUIPMENT FOR HEALTHCARE WORKERS

The decision made regarding the selection of PPE is determined by CDC recommendations for standard precautions and transmission-based precautions (i.e., exposure to blood, body fluids, infectious agents, and the likely mode of transmission).

The HCW must select appropriate PPE according to the risk assessment done, which is not based on the clinical presentation or diagnosis of the patient but rather on the potential of the HCW coming into contact with infectious materials, namely blood, body fluids, mucous membranes, or respiratory droplets, during each task and procedures undertaken. Decisions should be based on the suspected or identified infectious agent, transmission route of the infectious agent, patient care setting, and tasks or procedures performed.

TRANSMISSION-BASED PRECAUTIONS

Transmission-based precautions are used additionally for patients who are known or suspected to be infected or colonized with those infectious agents that require additional control measures to prevent transmission of infection in


Step 1: Wet hands with water and liquid soap or ABHR.
Step 2: Rub hands palm to palm.
Step 3: Right palm over left dorsum with interlaced fingers and vice versa.
Step 4: Palm to palm with fingers interlaced
Step 5: Backs of fingers to opposing palms with fingers interlocked.
Step 6: Rotational rubbing of left thumb clasped in right palm and vice versa.
Step 7: Rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa.
Step 8: Rinse hands with water; dry hand thoroughly with a single-use towel.

(ABHR: alcohol-based hand rub)

FIG. 11: Steps of hand hygiene.

Courtesy: Srinath Senthil.

health care facilities effectively. They are intended to decrease the risk of contact, droplet, and airborne transmission among hospitalized patients and the HCWs, when the disease transmission cycle is not entirely interrupted using standard precautions. They are used empirically, according to the clinical syndrome and the likely etiologic agents at the time of admission, and then modified when the pathogen is identified or a transmissible infectious etiology is ruled out. They are categorized according to the route of transmission of the infectious agent, namely contact precautions, droplet precautions, and airborne precautions.

LEVELS OF PERSONAL PROTECTIVE EQUIPMENT AND TYPES OF PRECAUTIONS FOR INFECTION CONTROL

Table 3 outlines the recommended PPE to minimize the risk of cross-transmission of infection to self and others when providing patient care.

OPTIMIZING PERSONAL PROTECTIVE EQUIPMENT USAGE DURING CRISIS

The CDC offers guidance on optimizing PPE supply during a crisis, when sudden increases in patient volume affect the existing infrastructure and resource capacity. These strategies include:

- Cancelling nonurgent surgical procedures
- Implementing standard precautions at all healthcare facilities for all patients at all times
- Using appropriate PPE based on the suspected route of transmission
- Prioritizing the use of specific PPE for only the highest risk of interventions on patients
- Minimizing face-to-face encounters with the patient by designating entire units within a facility, to care for infected or suspected patients in isolation (i.e., cohorting), limiting the number of people who examine the patient, using medications with extended intervals to reduce nursing encounters, and allowing patients to convey needs to providers using tablets or other electronic interfaces.
- Limiting visitors and nonessential staff contact with patients
- Limiting patient's movements outside of the designated areas
- Disinfecting patient care environments and reusable equipment between each patient
- Cautious extended use or decontamination of PPE for reuse may be reasonable.

DECONTAMINATION OF PERSONAL PROTECTIVE EQUIPMENT FOR REUSE

In general, most PPE are single-use, disposable, and designed to be used only one time and by one person; it cannot be washed, or reused, or shared. Washing PPE changes its protective barrier capabilities, and it may no longer be effective, if reused. Sharing PPE that is proposed for single use may expose another person to infectious materials. Disposable PPE should be removed promptly, using proper removal and disposal procedures. The CDC and WHO have highlighted few exceptions for some types of respirators such as elastomeric respirator masks, N95 respirators, and protective wear such as goggles, visor, face shield for reuse with appropriate decontamination when supplies are critically low. Decontamination with ultraviolet

light, hydrogen peroxide vapor, moist heat, and ethylene oxide has been shown to reduce the viability of single-stranded ribonucleic acid (RNA) viruses, such as H1N1 influenza and novel coronavirus (SARS-CoV-2), on N95 respirator and other environmental surfaces.

LIMITATIONS OF PERSONAL PROTECTIVE EQUIPMENT

Personal protective equipment will protect HCWs only from exposure to infectious agents or penetration of substances such as solid, liquid, or airborne particles but will not protect them from a specific disease. The other limitations are:

- Restricted movement due to its weight
- Decreased vision due to visual field limitations
- Difficulty in communication due to face protection
- Psychological stress resulting from the confining nature of full suits
- Heat stress and the risk of dehydration

REGULATIONS AND EFFICIENCY OF PERSONAL PROTECTIVE EQUIPMENT USAGE

The Occupational Safety and Health Administration (OSHA) focuses on workplace health and safety, which require effective use of PPE in healthcare settings to protect HCWs from exposure to bloodborne and airborne pathogens. Employers must provide the appropriate PPE to protect employees and provide training sessions on the proper use of PPE and their

TABLE 3: Levels of PPE and types of precautions for infection control.

Level of protection and types of precaution	*Recommended PPE*	*Suspected or known infectious agent*	*Major specifications*
Level 1 • Standard infection control precautions (SICPs)	• Disposable gloves • If the risk of spraying or splashing of blood/body fluids is anticipated: ○ Disposable surgical mask ○ Goggles or a full-face visor ○ Disposable apron	• No suspected or known infectious agent • Use as standard for all patients at all times	• Perform hand hygiene before and after every patient contact* • Anticipate exposure to blood and other body fluids • Safe disposal or cleaning of instruments and linen • Cough etiquette: Patients and visitors should cover their nose or mouth when coughing, promptly dispose of used tissues, and practice hand hygiene after contact with respiratory secretions
Level 2 • Contact precaution • Patients are placed on contact precautions when they have a known or suspected infection transmitted directly or indirectly from an infected or colonized individual by touch or contact with the patient or the patient's environment (surfaces and equipment). Contact is a common way that germs spread in healthcare facilities	• Disposable gloves • Disposable apron, consider fluid-resistant disposable gown if apron provides inadequate cover for the procedure or task being performed. • If the risk of spraying or splashing of blood/body fluids is anticipated: ○ Disposable surgical mask ○ Goggles or full-face visor ○ Disposable headcover/hood ○ Disposable shoe covers over surgical boots or closed shoes	• Colonization of any bodily site with multidrug-resistant bacteria (MRSA, VRE, drug-resistant gram-negative organisms) • Enteric infections (Norovirus, *Clostridium difficile**, *Escherichia coli*) • Viral infections [HSV, VZV, RSV†, parainfluenza, enterovirus, Rhinovirus‡, certain coronaviruses (SARS-CoV-2, MERS-CoV)], scabies, impetigo, noncontained abscesses or decubitus ulcers (especially for *Staphylococcus aureus* and group A *Streptococcus*)§	In addition to standard precautions: • Place the patient in a single room; cohorting is allowed if necessary • Gloves required upon entering the room • Change gloves after contact with contaminated secretions • Clean, nonsterile gown required if clothing may come into contact with the patient or environmental surfaces or if the patient has diarrhea • Discard PPE before exiting the room. Perform hand hygiene immediately after removing PPE • Do not wear the same PPE for the care of more than one patient • Use new PPE before coming in contact with another patient or patient environment • Noncritical items must be dedicated to use for a single patient if possible • Use disposable or dedicated patient care equipment (e.g., blood pressure cuffs) • Clean and disinfect reusable equipment before use on another person • Minimize the risk of environmental contamination during patient transport (e.g., the patient can be placed in a gown)

Continued

Continued

Level of protection and types of precaution	*Recommended PPE*	*Suspected or known infectious agent*	*Major specifications*
Level 2 • Droplet precaution • Patients are placed on droplet Precautions when they have known or suspected infections transmitted by large respiratory droplets (>5 µm in size) generated by coughing, sneezing, talking, or during the performance of aerosol-generating procedures. Droplet transmission requires close proximity or contact between the source and the susceptible host. These remain in the air briefly and can travel about 1 m (3 feet) or less. These may also land on surfaces later and be transferred by contact transmission	• Disposable gloves • Disposable apron, consider fluid-resistant disposable gown if apron provides inadequate cover for the procedure or task being performed • Disposable surgical mask with goggles or full-face visor • If high risk of direct physical or close contact is anticipated: ○ N95 respirator with goggles or full-face visor ○ Disposable headcover/ hood ○ Disposable shoe covers over surgical boots or closed shoes	• *Neisseria meningitidis, Haemophilus influenzae* type B, *Mycoplasma pneumoniae, Bordetella pertussis* • Group A *Streptococcus*[§], Diphtheria, Pneumonic plague, Influenza, Rubella, Mumps, Adenovirus, Parvovirus B19 • Rhinovirus[‡], Certain coronaviruses (SARS-CoV-2, MERS-CoV, and SARS)	In addition to standard precautions: • Place the patient in a single room • Cohorting is allowed if necessary, provided a distance of at least 1 m (3 feet) is maintained between patients along with a physical barrier such as a curtain or divider • Make sure eyes, nose, and mouth are fully covered before entering the room • Discard PPE before exiting the room • Perform hand hygiene immediately after removing PPE. (If PPE is to be reused, it must be cleaned and disinfected before each reuse) • Always wear a mask when within 1 m (3 feet) of the patient • Patients should wear a mask in the room and during transport in order to minimize the risk of environmental contamination. • Cough etiquette: Patients and visitors should cover their nose or mouth when coughing, promptly dispose of used tissues, and practice hand hygiene after contact with respiratory secretions
Level 2 • Airborne precaution • Patients are placed on airborne precautions when they have known or suspected infection transmitted by tiny droplet nuclei (<5 µm in size). Due to their tiny size, these particles can be suspended in the air for extended hours and can spread widely within a room or over longer distances on air currents	• N99/FFP3 respirator or PAPR • Goggles or full-face visor. • If high risk of exposure during a task or close contact is anticipated: ○ Disposable gloves ○ Disposable apron, consider fluid-resistant disposable gown if apron provides inadequate cover for the procedure or task being performed ○ Disposable headcover/ hood ○ Disposable shoe covers over surgical boots or closed shoes	• Tuberculosis, varicella, measles, smallpox, certain coronaviruses (SARS-CoV-2, MERS-CoV, and SARS), Ebola	In addition to standard precautions: • Place the patient in an AIIR— Monitored negative-pressure room with at least 6–12 air exchanges per hour • Room exhaust must be appropriately discharged outdoors or passed through a HEPA filter before recirculation within the hospital • A fit-tested certified N99/FFP3 respirator or PAPR must be worn before entering the room • Discard all PPEs except the respirator before exiting the room • Remove respirator always after exiting the room • Perform hand hygiene immediately after removing PPE • Restrict susceptible HCWs or individuals visiting or entering the room • Doors must always remain closed and avoid frequent movements of HCWs caring for the patient • Transport of the patient should be minimized; the patient should wear a mask, if transport within the hospital is unavoidable • Cough etiquette: Patients and visitors should cover their nose or mouth when coughing, promptly dispose of used tissues, and practice hand hygiene after contact with respiratory secretions

Continued

Continued

Level of protection and types of precaution	*Recommended PPE*	*Suspected or known infectious agent*	*Major specifications*
Level 3 • Enhanced precaution • Suspected or confirmed infectious agent spread by multiple modes of transmission and more than one transmission-based precautions category may be used	• Disposable gloves (two sets) • Reinforced fluid-resistant long-sleeved surgical gown (or) full-length disposable plastic apron additionally over the gown (or) 360° fluid-resistant coverall-suit with the hood • N99/FFP3 respirator or PAPR • Disposable goggles or full-face visor additionally over the goggles • Disposable fluid-resistant hood (if wearing a gown without an attached hood) • Disposable shoe covers over surgical boots or closed shoes (if wearing a gown)	• For suspected or confirmed infectious diseases of high consequence (IDHC) which spread by direct/indirect contact, droplet, airborne route	• Along with standard precautions to consider precautions required for multiple routes of transmission anticipated • All PPE except gloves need not be changed in between confirmed patients or cohorting unless they are visibly soiled or contaminated. Gloves should always be changed in between patients irrespectively • Ideally, all PPE including gloves should be changed in between suspected patients irrespective to being visibly soiled or contaminated. If not possible, at least gloves and plastic apron worn in addition to gown or coverall should be changed between patients
For all aerosol-generating procedures (AGP) use Level 3 PPE at any circumstances. (Nebulization, tracheal intubation, noninvasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy)	• Fluid-resistant coverall-suit with the hood plus: ○ N99/FFP3 respirator or PAPR ○ Disposable goggles ○ Disposable gloves (two sets) • Fluid-resistant long-sleeved surgical gown plus: ○ N99/FFP3 respirator or PAPR ○ Full-length disposable plastic apron additionally over the gown ○ Full-face visor additionally over the goggles ○ Disposable hood/headcover ○ Disposable shoe covers over surgical boots or closed shoes ○ Disposable gloves (two sets)		• Place the patient in an AIIR (airborne infection isolation room) – Monitored negative-pressure room with at least 6–12 air exchanges per hour • Room exhaust must be appropriately discharged outdoors or passed through a HEPA filter before recirculation within the hospital • All PPE should be changed after an aerosol-generating procedure irrespective to being visibly soiled or contaminated • Remove respirator always after exiting the room • Reusable PPE should be placed separately for decontamination

* Alcohol-based hand disinfectant is an acceptable alternative to soap and water in all situations except in the setting of norovirus and *Clostridium difficile* infection, for which soap and water should be used.

† RSV may be transmitted by the droplet route but is primarily spread by direct contact with infectious respiratory secretions. Droplet precautions are not routinely warranted but are appropriate if the infecting agent is not known, if the patient may be coinfected with other pathogens that require droplet precautions, and if there is a chance of exposure to aerosols of infectious respiratory secretions.

‡ The most important route of transmission for rhinovirus is via droplets; contact precautions should be added if copious moist secretions and close contact are likely to occur (e.g., young infants).

§ Patients with invasive group A streptococcal infection associated with soft-tissue involvement warrant both droplet precautions and contact precautions. Droplet precautions alone are warranted for patients with streptococcal toxic shock or streptococcal pneumonia as well as for infants and young children in the setting of pharyngitis or scarlet fever. Droplet and contact precautions may be discontinued after the first 24 hours of antimicrobial therapy.

Note: NHS Sheffield – NIPCM – HPS are aware of the high consequence infectious diseases (HCID) consensus PPE model drafted by Public Health England's HCID Programme (article in press) and will review this aide-memoire following an evidence appraisal. Adapted from original work produced by Public Health England and NHS Sheffield. https://hpspubsrepo.blob.core.windows.net/hps-website/nss/3037/documents/1_nipcm-appendix-16.pdf

(AGP: aerosol-generating procedures; AIIR: airborne infection isolation room; FFP3: filtering facepiece 3; HSV: Herpes simplex virus; HEPA: high-efficiency particulate aerator; MERS-CoV: Middle East respiratory syndrome coronavirus; MRSA: methicillin-resistant *Staphylococcus aureus*; PAPR: powered air purifying respirator; PPE: personal protective equipment; RSV: respiratory syncytial virus; SARS: severe acute respiratory syndrome; SARS-CoV-2: severe acute respiratory syndrome coronavirus disease-2; VRE: vancomycin-resistant enterococci; VZV: varicella-zoster virus)

Sources: Siegel JD, Rhinehart E, Jackson M, et al. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control. 2007;35:S65.

competency should be assessed. Employers should have a management program that ensures effective use of PPE by HCWs. Employees must ensure that they wear the appropriate PPE to protect themselves from possible exposure to infectious agents. Employees should attend mandatory IPC training to perform all tasks related to wearing PPE which include how to select appropriate PPE, properly check for fit, don and doff in the correct sequence and safe disposal of PPE, know the limitations of PPE, and proper care and maintenance of PPE.

SUMMARY

- The goal must be to improve the safety of health personnel and to avoid transmission of HCAI by following standard precautions.
- Hand hygiene is the single most crucial method to reduce the incidence of HCAI.
- PPE is a two-way protective barrier between the HCW and the patient and reduces the risk of transmission, thus preventing HAI.
- For PPE to be effective, they must be readily available, provide adequate protection, and utilized correctly.
- Gloves should be changed between patient encounters and when they get torn or visibly contaminated.
- Gowns provide a fluid-resistant barrier that protects the HCW from soiling or contamination. Plastic aprons are the preferred PPE for standard precautions. Sterile gowns are necessary for a sterile procedure such as central line insertion or a surgical procedure in an operating room.
- Protective eyewear is used to shield eyes from potential risks of transmission while performing procedures of close proximity.
- Masks offer protection from inhalation of respiratory droplets. For all aerosol-generating procedures, use an N95 respirator. Always perform "fit test" and "seal check test" to verify that the N95 respirator fits comfortably and is properly sealed without leakage. Masks should be discarded when they become damaged, no longer form an effective seal to the face, or become wet or contaminated with blood, respiratory, or nasal secretions from the patient and after aerosol-generating procedures.
- Failure to properly don and doff PPE in the correct sequence could lead to exposure to infectious agents.
- Appropriate PPE is selected according to the risk assessment done, which is not based on the clinical presentation or diagnosis of the patient but rather on the suspected or identified infectious agent, transmission route of the infectious agent, patient care setting, and tasks or procedures undertaken.
- Transmission-based precautions are used additionally for patients who are known or suspected to be infected or colonized with those infectious agents that require additional control measures to prevent transmission of infection in healthcare facilities effectively.
- Employees should attend mandatory IPC training to perform all tasks related to wearing PPE.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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ONLINE REFERENCES

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Section 2: Recent Concepts in Emergency Medicine

11 CHAPTER

Research Methodology

Padam Singh, Pooja Sharma, Manish K Singh

INTRODUCTION

This chapter provides all the systems and tools used for dissertation and also gives a broad overview of the research methodology, empirical methods of the approach, and particular techniques to approach objectives of the research. Research in emergency medicine aims at generating evidence for new therapeutic interventions to provide appropriate health care in emergency settings. Research requires sound planning and systematic implementation through a sequence of steps. *The sequence of steps in research are as follows*:

- Rationale for the study—identification of research problem through extensive research review
- Objectives, research hypothesis, and statistical hypothesis
- Study design
- Sample size
- Sample selection—inclusion/exclusion criteria
- Method of data collection and study tools
- Data management and analysis including use of software
- Summarization of data and statistical inference
- Interpretation

LITERATURE REVIEW

The literature review is the first step in undertaking any research as it is through this only that the gap in knowledge is identified which would justify and provide the rationale for carrying out the research. There are different search engines that might be used to locate relevant material which are summarized in **Table 1**.

FORMULATING A RESEARCH QUESTION

Based on the literature review, the next step in any research study is to clearly define the research question. An ideal research question is one that is relevant and doable within the specific time frame. A well-built research question should include four elements, referred to as patient, intervention, comparison, and outcomes (PICO) concept.

1. *P*: Patient or characteristics. The first step in the PICO process is to describe characteristics patients of under study such as age, gender, disease status, or any other patient's related characteristic.
2. *I*: Intervention. The second step in the PICO process is to identify the intervention or the exposure intended to be studies in the research. This may include the use of a specific diagnostic test, treatment, adjunctive therapy, medication, etc.
3. *C*: Comparison. It is the alternative exposure or control to which the intervention will be compared, which might be the standard of care or a placebo. The comparison component is the only optional one in the PICO question, since the researcher might study the intervention alone either due to no interest in comparison or due to lack of a comparable group.
4. *O*: Outcome. It is for the evaluation of the interventions effect. This may include cure or level of control of a disease, efficacy of a diagnostic test, etc.

Examples of research questions are given in **Box 1**.

ESSENTIALS OF BIOSTATISTICS

While undertaking any research, an understanding of the basics of statistics is necessary for scientific planning, appropriate analysis, and valid interpretation of findings. Importantly, statistics deals with variables which are broadly categorized as quantitative and qualitative variables. The parameter of interest in a research study could be either a proportion (for a categorical response) or an average (for a quantitative outcome). Quantitative variables are those which are measurable and are always a number which can be either continuous or discrete. On the other hand, qualitative variables are nonnumerical which can be either ordinal or nominal. Qualitative variables, also called "categorical variables," classify or divide individuals into classes/groups, so that quantitative variables may be compared among the classes. All research hypotheses are related to claim for the improved outcome and superior drug/diagnostics. This claim

TABLE 1: Search engine for literature review.

Search engine	*Website/Characteristics*
PubMed	www.pubmedcentral.nih.gov. The National Library of Medicine's free search service. Available through the World Wide Web
MEDLINE	www.nlm.nih.gov. Contains abstracts and references from 1966 to the present. Combines more than 3,900 medical and nursing journals into a single database
Ovid	Ovid is a comparable search engine to PubMed. Its advantage over PubMed is that it searches more databases in addition to MEDLINE, including EMBASE and the Cochrane Database of Systematic Reviews (CDSR). This means that your search will expand to include more results giving you more evidence to use for your research/writing
Web of Science	Web of Science uses a large database of 8,700 international scientific journals from Thomson Reuters. The database includes a large number of international publications from Asia and requires a subscription to access the articles. Web of Science has a useful database to search for scholarly research data on emerging trends. It is useful for writing protocols or guidelines. It covers over 250 disciplines in science, social science, arts, and humanities
Science Direct	• Science Direct is a very familiar search engine for researchers. It is a full-text scientific database • The search engine allows to find articles in over 3,800 science, technology, and medicine journals owned by the academic publisher Elsevier. Another similar portal is Springer Link that has access to over five million articles in journals operated by the publisher Springer
Scopus	Scopus is a large database of over 60 million peer-reviewed literature also owned by Elsevier. Scopus interfaces with the EMBASE and MEDLINE databases to search records for journal articles. It gives access to the full-text articles from >4,200 full-text journals
Cochrane Library	For systematic reviews or meta-analyses, the Cochrane Library is the best source. In addition to results obtained from the Cochrane Database of Systematic Reviews (CDSR), Cochrane library search results can also include control trials in MEDLINE and EMBASE, Cochrane protocols, and editorials. Cochrane Library is a subscription-based search platform. However, some open-access articles may be retrieved, depending on when the article is published
Google Scholar	Google Scholar is a free medical journal search engine indexing journal; however, login may be required via a subscription for some full-text journal articles

BOX 1: Example of a research question.

1. Does smoking among men older than 35 years increase the risk of asthma compared to nonsmokers?
   - *Broad topic of interest*: Men's health
   - *Narrowed topic*: Men and asthma
   - *Focused topic*: Men smokers and asthma

   PICO: P = men (age > 35 years); I = bidi/cigarette smoking; C = no smoking; O = asthma
2. Serum enzymes and CT severity score for assessing the severity of pancreatitis in the patient presenting to the emergency:
   - *Broad topic of interest*: Emergency patients
   - *Narrowed topic*: Pancreatitis in patients presenting to emergency
   - *Focused topic*: Severity of pancreatitis in patients

   PICO: P = emergency patient; I = serum enzymes; C = CT severity score; O = comparison of serum enzymes and CT severity score for assessing the severity of pancreatitis
3. Predictive values of mREMS and RAPS in determining the outcome (mortality and morbidity) in trauma patients reaching the emergency and trauma care, assessing the morbidity score by Glasgow outcome scale:
   - *Broad topic of interest*: Trauma patients
   - *Narrowed topic*: Mortality and morbidity among trauma patients
   - *Focused topic*: Glasgow outcome scale for assessing morbidity

   PICO: P = trauma patients; I = Glasgow outcome scale; C = mREMS and RAPS; O = predictive value of mREMS and RAPS
4. Glasgow Coma Scale (GCS) versus Full Outline of Unresponsiveness (FOUR) score as predictors of mortality in traumatic brain injury patients:
   - *Broad topic of interest*: Trauma patients
   - *Narrowed topic*: Traumatic brain injury patients
   - *Focused topic*: Predictors of mortality in traumatic brain injury patients

   PICO: P = brain injury patient; I = full outline of unresponsiveness score; C = Glasgow Coma Scale; O = predictive value of GCS

(CT: computed tomography; mREMS: modified rapid emergency medicine score; RAPS: rapid acute physiology score)

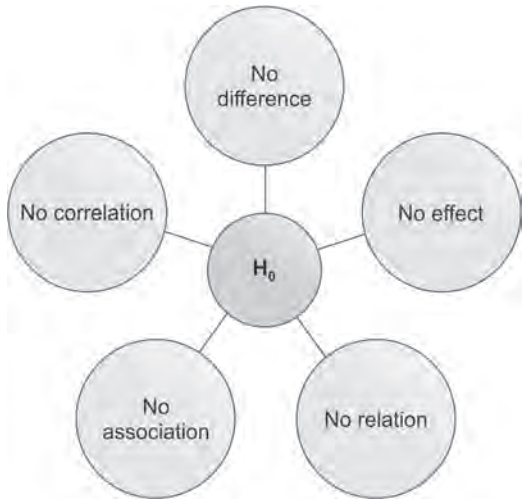


FIG. 1: Commonly used null hypothesis.

is required to be tested against a null hypothesis negating the claim by indicating that the effect of interest is zero. In most of the situations, the statistical null hypothesis is the negation of the research hypothesis. The commonly used null hypothesis is shown in **Figure 1**. The null hypothesis is evaluated against a competing hypothesis (alternative hypothesis) in which the effect of interest is considered as nonzero. Hypotheses are always stated in terms of a population parameter, such as the mean "μ" or proportion "*P.*" An alternative hypothesis may be one sided or two sided. A one-sided hypothesis claims that the parameter under the alternative hypothesis is either larger or smaller than the value given by the null hypothesis. A two-sided hypothesis claims that the parameter is not equal to the value given by the null hypothesis—the direction does not matter and could be either side.

Errors in Testing of Hypothesis

In the testing of hypothesis, there are probabilities of committing two kinds of errors: (1) False rejection (type I error); and (2) False acceptance (type II error) of the null hypothesis (**Table 2**).

In order to explain these concepts, let us consider the possible errors in clinical practice as follows:

- Diagnosing a person wrongly as suffering from the disease when he/she is not
- Missing the diagnosis and declaring the person as free from the disease when he/she is actually suffering from the disease

The null hypothesis in the present case is "person is not suffering from the disease" (**Table 3**).

The probabilities of type I error and type II error are denoted by α and β, respectively.

There are two terms: (1) Confidence level; and (2) Power, which are complement to these errors as follows:

Confidence level = Probability of accepting the null hypothesis when it is true
= 1 – Probability of type I error
= 1 – α

Power = Probability of rejecting the null hypothesis when it is false
= 1 – Probability of type II error
= 1 – β

TABLE 2: Type of errors in null hypothesis.

Type I error	False rejection	Reject H_0 when H_0 is true
Type II error	False acceptance	Accept H_0 when H_0 is false

TABLE 3: Null hypothesis—person is not suffering from the disease.

Type I error	Diagnosing a person who is not suffering from the disease as suffering from the disease would imply rejecting null hypothesis when it is true
Type II error	Declaring a person free from the disease when he/she is actually suffering from the disease would imply accepting the null hypothesis when it is false

TABLE 4: *p*-value and related inferences.

Values of p	***Inferences***
$p > 0.10$	No evidence against the null hypothesis
$0.05 < p < 0.10$	Weak evidence against the null hypothesis
$0.01 < p < 0.05$	Good evidence against null hypothesis
$0.05 < p < 0.001$	Strong evidence against the null hypothesis
$p < 0.001$	Very strong evidence against the null hypothesis
Notes: Conventionally, $p < 0.05$ is referred to as statistically significant and $p < 0.001$ as statistically highly significant. When presenting *p* values, it is a common practice to use the asterisk rating system.	

Importantly, α is commonly referred to as the level of significance. The implication of type I error in the context of a clinical research is that the new regimen, although not effective, is adopted and prescribed, i.e., an ineffective drug is allowed to be marketed. In a trial on a new regimen, type II error would imply that the new regimen is not approved when it is actually effective. Thus, the medical profession and the society are deprived of the benefits of this new regimen.

p-value: The *p*-value is calculated based on the null distribution, which is a distribution of the test statistic when the null hypothesis is true. The *p*-value indicates how probable the results are due to chance. Statistical inferences indicating the strength of the evidence corresponding to different values of *p* are given in **Table 4**.

RESEARCH DESIGNS

The research designs are broadly categorized as observational or interventional. The commonly used situations of observational and interventional studies specific to emergency medicine are given in the following text.

Observational Studies

In an observational study, the natural history of treatments (standard of care) is studied, i.e., there is no intervention. Some examples are as follows:

- Profiling of patients attending an emergency clinic for different conditions such as stroke and accidents

- The pattern of antibiotic use for patients admitted in an intensive care unit (ICU) with sepsis
- The birth outcome of pregnant women in advanced shock from uncontrolled postpartum hemorrhage (PPH)

In observational studies, the study design could be cross-sectional, cohort, or longitudinal, which are discussed in brief in the following text.

Cross-sectional Design

In cross-sectional studies, data are collected only at one point in time. Such studies are better suited for estimating the prevalence of an outcome of interest. As a cross-sectional study assesses both the exposure and the outcome concurrently, it cannot be utilized to establish cause and effect relationships.

Longitudinal Design

A longitudinal study follows the same sample over time and makes repeated observations. Longitudinal research designs describe patterns of change. Measurements are taken on each variable over two or more distinct time periods. *Example*: Study of growth of children from birth till 5 years.

Cohort Design

A cohort study generally refers to a study in which a defined group of people (the cohort) is followed over time. In this, subjects under study have some commonality or similarity. Examples are victims of calamities such as methyl isocyanate (MIC) gas leak, earthquake, and fire.

Interventional/Experimental Studies

In these studies, there is an active intervention (drug, diagnostic, procedure, etc.) for a desirable change in the outcome. Examples are as follows:

- Clinical studies evaluating the response of specific treatment to patients of a disease, i.e., pre versus post
- Clinical trials comparing the outcome of an intervention (experimental) with that of control (standard of care)

Experimental designs comparing two groups relate to (1) an experimental group (that receives the new intervention) and (2) a control group (placebo or standard of care). Both groups are measured on the same dependent/outcome variable. Observations are made before and after the implementation of the intervention.

In such situations, *randomized control trials (RCTs)* are conducted. The common study designs employed in RCTs include parallel-group design, matched pairs, and cross-over designs. In parallel-group design, the patients are enrolled, followed, and observed for outcomes on a parallel basis. In matched pairs, patients are matched for different variables and those matching the required variables are then randomized to various treatment groups. This type of study design overcomes the influence of variables on outcomes. Cross-over design is particularly used when the effect of a drug is reversible and transient. In a cross-over design, the patients are given more than one treatment but in sequence, i.e., one after another when the effect of the previous treatment is washed out. Cross-over design, thus, requires less number of patients. *Randomization* is a prerequisite for such studies and *blinding* is desirable. These are discussed in the following text.

Randomization

Randomization is a scientific method of allocation of subjects between the treatment and the control groups. This method ensures that there is no bias or preference in selecting specific treatment for any subjects. Further, randomization provides equal chance/probability to subjects for allocation into different groups. Importantly a prerequisite, all statistical tests of significance assume that the sample drawn is random, which is met through randomization.

Randomization techniques used in RCTs are simple randomization or stratified randomization. In simple randomization, subjects are allocated to different groups without any matching. On the other hand, in the stratified randomization technique, subjects are classified into groups, i.e., strata, and then within a group, they are randomized to various treatment groups. This ensures matching of subjects for confounding factors that might influence the outcome and thus helps in drawing valid conclusions netting out the effects of confounders. For allocation of subjects in different groups, the random numbers are generated through the computer using appropriate mathematical algorithms. In the case of two groups generally, odd numbers correspond to group I and even numbers to group II.

As an example, in the case of two groups with a sample size of 30 each, a sequence of 60 two-digit random numbers are generated of which 30 are odd and 30 even. The sequence of random numbers will be kept in opaque-sealed envelopes. In this, the serial numbers will be written on the envelopes and the group to which the subject at that serial number has been allocated will be kept inside the envelope. After recruitment of the subjects and taking their consents, the allocation of the subjects to two groups will be based on the sequence of random numbers kept in opaque envelopes. The envelopes will be kept with a biostatistician and will be opened after recruitment of the subjects and obtaining the consent.

Blinding

To avoid any bias in the study, blinding is resorted which means concealing or masking of the subject's assignment to a study group (control or treatment) from those participating in the study."

The blinding could be single-blinded, double-blinded, or triple-blinded as given in **Table 5**:

- *Single-blinded*: The study subjects will not know whether they would receive the treatment (test intervention) or control (placebo).
- *Double-blinded*: Neither the study subjects nor the experimenter will know which of the subjects are in the treatment (test intervention) or control (placebo) group.

TABLE 5: Type of blinding studies.

	Concealment about the allocation of subjects to a group (√: Yes; X: No)		
Type of blinding	***Subjects***	***Experimenter***	***Observer***
Single	√	X	X
Double	√	√	X
Triple	√	√	√

- *Triple-blinded*: Neither of the study subjects, experimenter, and observer will know which of the subjects are in the treatment (test intervention) or control (placebo) group.

The non-blinded study is referred to as an open-label study. In this type of study, all three—subjects, experimenter, and researcher, are aware of the treatment allocation.

SAMPLE SIZE

Background

"How big a sample do I require to get a reliable estimate and valid inference in my research study?" is one of the most frequently asked questions by researchers. For answering this question, the sample size should be determined on the basis of scientific statistical criteria, which take into account the objective of the study, outcome parameter, and study design along with certain assumptions. The criteria will vary according to whether the study design is observational or interventional/experimental and also whether the parameter is "a proportion" or an average. The determination of sample size in different situations is discussed as in the following text.

Situation A: Observational studies for proportions: In this situation, the formula to be used for computation of sample size is as follows:

$$n = \frac{Z_\alpha^2 PQ}{d^2}$$

where P = Likely value of the parameter
Q = 1 – P
d = Permissible margin of error—a measure of precision
Z_α = Value of standard normal deviate corresponding to the desired confidence level

In view of this, the information needed in determining the sample size is as follows:

- *Likely value of the parameter*: Speculating about the parameter may be tricky. The investigator may get some idea about this from the review of literature, from the studies with similar study designs, and from the reference population. From the reviews, one may get an idea about the parameter in terms of range, say for instance, 60–65%, 40–50%, 20–35%, etc. In such situations, the value of P in the range which gives a higher sample size may be considered.
- *Confidence level*: In most studies, a 95% confidence level is considered. However, in some situations, it can be relaxed to 90% and there could be situations where it should be as high as 99%. The values of Z_α, the standard normal variate corresponding to the desired confidence level α, are given in **Table 6**.
- *Level of precision:* The permissible margin of error, a measure of precision (d), is often expressed in percentage points, ±5%, ±10%, etc. The thumb rule in deciding the appropriate precision in prevalence studies is as follows:
  - If the likely prevalence is around 50%, d may be taken as 10%.
  - If the likely prevalence is <20% or >80%, d may be taken as 5%.
  - Alternatively, d can be taken as a fixed percentage of P, i.e., $d = e \times P$. In such cases, e is relative precision.

TABLE 6: Z_α and confidence level.

Confidence level	Z_α
99%	2.576
95%	1.960
90%	1.645
80%	1.282

Example: Consider an example for a study of compliance of a clinical care pathway for patients undergoing gastrectomy, where the likely/anticipated value of parameter P to be estimated is 90%. What would be the sample size if this parameter is desired to be estimated with precision of ±5% and confidence level of 95%. In this case, P = 0.9, Q = 0.1, d = 0.05, and Z_α = 1.96.

Substituting these in the formula, the sample size is computed as:

$$n = \frac{Z_\alpha^2 PQ}{d^2} = \frac{(1.96)^2 \times 0.90 \times 0.10}{0.05 \times 0.05} = 138$$

Thus, a sample of 138 patients undergoing gastrectomy will be required to be followed to find out the proportion of compliance of the clinical care pathway.

Example: Consider another example for estimation of complications among patients following pancreaticoduodenectomy, where the likely/anticipated value of parameter P is 20%. What would be the appropriate sample size if this is to be estimated with a precision of ±5% and the confidence level of 95%. In this example, P = 0.20, Q = 0.80, d = 0.05, and Z_α = 1.96. Substituting the value in the formula, the sample size is determined as:

$$n = \frac{Z_\alpha^2 PQ}{d^2} = \frac{(1.96)^2 \times 0.20 \times 0.80}{0.05 \times 0.05} = 245$$

A sample of 245 patients of pancreaticoduodenectomy will be required for this study.

Alternative formula for determination of sample size: Considering "d" in terms of relative precision $d = e \times P$, the formula for sample size reduces to the form as:

$$n = \frac{Z_\alpha^2 Q}{Pe^2}$$

where e = relative precision.

Following are the implications of P, d, and α on sample size:

- "n" is inversely proportional to "P". A small sample size may suffice for high prevalence, but we need a large sample size for lower values of P. This is the case with rare diseases.
- "n" is inversely proportional to e^2. Thus, for higher precision (i.e., lower relative margin of error), a larger sample size will be required.
- "n" is directly proportional to the confidence level. Thus, a larger sample size will be needed for a higher confidence level.

Sample sizes for some typical values of "P" are given in **Table 7** for α = 0.05 and 10% relative margin of error.

TABLE 7: Sample size in relation to prevalence.	
Likely value of "P"	***Sample size "n"***
0.50	400
0.10	3,600
0.05	7,600
0.005	80,000
0.0005	8,00,000

It is seen that sample sizes increase rapidly with the decline in prevalence rates, i.e., rare situations/diseases. The commonly encountered rare situations are the prevalence of cancer, infant mortality rate, maternal mortality rate, serious adverse effects, etc.

Situation B: Observational studies for average: In dealing with averages, the formula for estimating sample size is given by

$$n = \frac{Z_\alpha^2 \sigma^2}{d^2}$$

where σ = Likely value of standard deviation.

Importantly, though the average does not feature in the formula, *d* is taken as some fraction of the likely value of average.

Example: Consider an example of estimation of the average hemoglobin level among adolescents with

d = ±0.5 g/dL and 95% confidence level, where the likely value of standard deviation σ = 5 g/dL.

Here, σ = 5, *d* = 0.5, and Z_α = 1.96. Substituting these values, the sample size is calculated as:

$$n = \frac{Z_\alpha^2 \sigma^2}{d^2} = \frac{1.96^2 \times 1.96 \times 5 \times 5}{0.05 \times 0.05} = 400$$

Thus, a sample of 400 subjects will be needed for this study.

Situation C: Sample size for paired comparison (pre vs. post): In many studies, the impact of a medical intervention may be desired to be evaluated. An example of an intervention is when a metformin drug leads to a change in the glycated hemoglobin (HbA1c) level for type 2 diabetic patients. In such situations, the estimates of baseline (pre) and end line (post) are compared for statistical significance of a change of the desired magnitude. In planning such studies proper sample size needs to be considered. The formula for calculation of sample size in such situation is given by:

$$n = [(Z\alpha + Z\beta)^2 \times \sigma_\Delta^2]/\Delta^2$$

where Δ = Change in value of the parameter
σ_Δ = Standard deviation of the change
Z_β = Value of standard normal variate for the desired power

Example: Consider an example of metformin drug administered to patients where intervention for 3 months is expected to reduce the HbA1c level by 1 g/dL. What will be the sample size for this study under the assumptions of σ_Δ = 7.5 with 95% confidence level and 80% power?
Here, σ_Δ = 7.5, Δ = 1.0, Z_α = 1.96 and Z_β = 0.84

$$n = [(1.96 + 0.84)\, 2 \times\ 7.5 \times 7.5]/(1.0)2 = 441$$

Thus, a sample of 441 patients is required to be covered in this study.

Situation D: Sample size for comparative studies: Interest may be to compare complications in patients undergoing colorectal surgery with c-reactive protein (CRP) level at the baseline. Here again, the outcome parameter is a proportion which is a complication rate. The calculation of sample size is discussed in the following studies:

Situation D: Comparative studies for proportions: The formula for calculation of sample size in this situation is:

$$n = 2\,PQ\,[\frac{Z_\alpha + Z_\beta}{d}]\,2$$

where P_1 = Parameter for group 1
P_2 = Parameter for group 2
P = $(P_1 + P_2)/2$
Q = 1 – P
d = $P_1 - P_2$

Thus, the information required for the calculation of sample size is as follows:

- Approximate value of *P* for the control group (say group 1)
- Approximate value of *P* for the interventional group (say group 2)
- Confidence level (usually 95%)
- Power of detecting the difference as significant (usually 80%)

Example: Suppose the cure rate on a standard treatment is 60%. A new treatment is claimed to have a cure rate of 80%. What is the minimum number of patients required to verify the claim at 95% confidence level and 80% power?

In this case, P_1 = 0.80, P_2 = 0.60, and thus
$P = (P_1 + P_2)/2 = 0.70$ and $Q = 0.30$.
Further, $d = P_1 - P_2 = 0.20$, Z_α = 1.96, and Z_β = 0.84.

Substituting these in the formula, the sample size works out as 82. Thus, 82 patients will be required to be administered the newer drug and control drug after proper randomization.

Situation E: Comparative studies for averages: In other situations, the parameter of interest could be average. The formula for calculation of sample size in this situation is:

$$n = (\sigma_1^2 + \sigma_2^2)\,[\frac{Z_\alpha + Z_\beta}{d}]\,2$$

where σ_1 and σ_2 are standard deviations and *d* is the difference in the mean values for two groups.

Example: A trial is proposed to be conducted with two arms, say new treatment protocol and existing standard of care, with the claim that the duration of hospital stay will be reduced by 2 days with the new treatment protocol as compared to the existing standard of care. The standard deviation for these two arms is 3.9 and 2.6 days, respectively. What will be the minimum sample size for testing the claim with 95% confidence level and 80% power?

In this case, σ_1 = 3.9, σ_2 = 2.6 and thus *d* = 2 days.
Further, Z_α = 1.96 and Z_β = 0.84.

Substituting these in the formula, the sample size works out as 43. Thus, 43 patients each will be required to be treated by the new treatment protocol and existing standard of care.

STATISTICAL ANALYSIS

For continuous variables, while undertaking the statistical analysis the assumption of normality is required to be tested. For data satisfying normal distribution, the mean and median should be approximately equal and the standard deviation generally <30% of the mean, else the data will not satisfy the normality assumption. The exact test for testing the normality of data is the Shapiro–Wilk/Kolmogorov–Smirnov test. The desirable pathway for deciding about the method of statistical analysis to be used in a given situation is depicted in **Flowchart 1**. The details of the exact test to be used in different situations are outlined in **Table 8**.

TEST OF SIGNIFICANCE FOR POPULATION MEAN (μ)

Situation A: *One sample test when standard deviation (σ) is known*: In this situation, the null hypothesis is H_0: $\mu = \mu_0$, i.e., the population mean μ is equal to a given value μ_0. The alternative hypothesis could be $\mu \neq \mu_0$ or $\mu < \mu_0$ or $\mu > \mu_0$.

For such situations, the appropriate significance test is "*Z* test" which is defined as:

$$z = \frac{\bar{x} - \mu_0}{\sigma/\sqrt{n}}$$

Here, "*n*" denotes sample size and $\bar{x}$ is the sample mean. The test statistic follows the standard normal distribution.

Example: The normal value of the pulse rate is 72, with standard deviation 10. It is assumed that the pulse rate follows the normal distribution. In a sample of 16 persons doing physical exercise, the mean pulse rate observed was 78. Does this experiment provide evidence that the mean pulse rate among the persons doing exercise is higher than the normal? The null hypothesis H_0 in this situation will be that the mean pulse rate for persons doing physical exercise is not different from the normal pulse rate. The alternative hypothesis would be that the mean pulse rate for persons doing the physical exercise is higher than the normal pulse rate.

In this case, $n = 16$, $\sigma = 10$, $\bar{x} = 78$, and $\mu_0 = 72$. Substituting the values in the formula, the *Z* statistic is computed as:

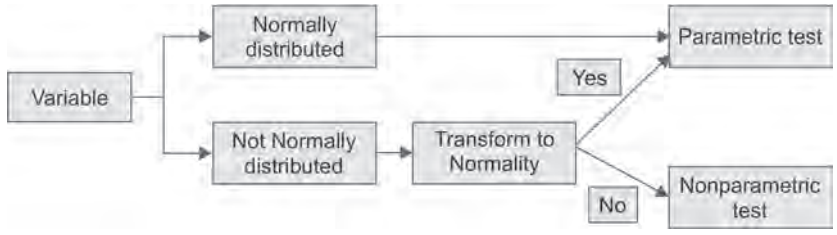
$$Z = (78–72)/(10/\sqrt{16}) = 6/2.5 = 2.4$$

Since this is a one-tailed test, the *P*-value is calculated as:

$$P\,(Z > 2.4) = 1–P\,(Z \leq 2.4) = 1 – 0.9918 = 0.0082$$

As the computed *P*-value is < 0.01, one can confidently reject H_0 given this result. Thus, the average pulse rate for persons doing physical exercise is higher than the normal pulse rate.

Situation B: One sample test when standard deviation is unknown – In most practical situations, the standard deviation for the population will not be known. In such situations, the



FLOWCHART 1: Pathway for statistical analysis.

TABLE 8: Summary of the statistical tests to be used at different situations.

	Type of data		
	Continuous variable		
Situations	***Parametric test***	***Nonparametric test***	***Categorical variable***
One sample	*Z* test (for large samples) One-sample *t*-test (for small samples)	Sign test	*Z* test (for large samples) Fisher exact test (for small samples)
One sample: Pre–post comparison	Paired *t*-test	Wilcoxon Sign Rank test	McNemar or *k* test
Two independent samples	Two independent sample *t*-test	Wilcoxon Rank Sum test	Chi-square test
More than two groups	One-way ANOVA	Kruskal–Wallis test	Chi-square test
Two or more groups repeat observations	Repeated measure ANOVA	Friedman test	Cochran's Q
Association/correlation	Pearson correlation	Spearman correlation	Contingency coefficients
Prediction of outcome from predictor values	Univariate linear/nonlinear regression	–	Univariate logistic regression
Prediction of outcome from several predictor values	Multivariate linear/nonlinear regression	–	Multivariate logistic regression

(ANOVA: analysis of variance)

standard deviation s in the formula is replaced by the estimated standard deviation (s). The distribution of the sample mean $\bar{x}$ is no longer normal. Instead, the sample mean follows a "*t*" distribution.

The test statistic "*t*" is defined as:

$$t = \frac{\bar{x} - \mu_0}{S/\sqrt{n}}$$

The *t* distribution is described by its degrees of freedom. For a sample of size *n*, the *t* distribution will have (*n* – 1) degrees of freedom. As the sample size *n* increases, the *t* distribution approaches the normal distribution. *Example*: Persons working in tea garden are reported to have higher blood pressure (BP). In order to examine this, a sample of nine tea garden workers were selected and their BP was measured. **Table 9** summarizes the results on systolic blood pressure.

The normal systolic BP is known to be 120 mm Hg. In order to test whether tea garden workers have high BP, the null and alternative hypothesis are given by:

H_0: μ = 120.0

H_0: μ > 120.0, it being a one-tailed test

The test statistic "*t*" is computed as:

$$t = (126 - 120.0)/\{7.2/\sqrt{9}\} = 6/2.4 = 2.5$$

Degrees of freedom = 9 – 1 = 8

The table value of "*t*" for 8 degrees of freedom with 5% level of significance (one-tailed) is 2.306. Since the calculated value of "*t*" is more than the table value of "*t*" there is sufficient evidence to reject the null hypothesis. Hence, the average systolic BP of tea garden workers is more than the normal BP.

Situation C: Matched pairs: In many experiments, one is interested in comparing the measurements for the same set of individuals in the "before" and "after" situations. Such studies have *a* matched pair design, where the difference between the two measurements in each pair is the variable of interest. Analysis of data from a matched pairs experiment compares the two measurements by subtracting one from the other and basing the test hypothesis upon the differences. Usually, the null hypothesis H_0 assumes that the mean of these differences is equal to 0, while the alternative hypothesis H_1 would be that the mean of the differences is not equal to zero (the alternative hypothesis may be one or two sided, depending on the experiment). In this situation, using the differences between the paired measurements as a single observation, the standard *t*-test for one sample is followed. The difference for each pair of values is denoted by "*d*". Once this is obtained, the situation reduces to one sample "*t*" test given by:

$$t = \bar{d}/\{sd/\sqrt{n}\}$$

where $\bar{d}$ is the sample mean and s_d the sample standard deviation of the differences.

TABLE 9: Sample test when standard deviation is unknown.

Variable	*Value*
Sample size (*n*)	9
Sample mean ($\bar{x}$)	126 mm Hg
Sample standard deviation (s)	7.2 mm Hg

Example: For eight patients undergoing treatment for liver disease in a hospital, the albumin levels were measured before and after the treatment. The results are given in **Table 10**.

Test whether there is a change in albumin levels with the treatment.

Here,

Null hypothesis H_0 = There is no change in the albumin level

Alternate hypothesis H_1 = There is change in the albumin level

For the above example, "*n*" = 8, $\bar{d}$ = 0.075, and s_d = 0.17

Substituting these in the formula, the "*t*" value is computed as:

$t = 0.075/\{0.17/\sqrt{8}\} = 1.25$ and degrees of freedom = 8 – 1 = 7

The critical value of *t* for 7 degrees of freedom and 5% level of significance (two-tailed) is 2.365.

Since the calculated value of "*t*" is less than the critical value of "*t*," the null hypothesis of no change cannot be rejected. Thus, there is no change in the albumin levels of liver patients with the treatment.

Situation D: Two-sample test: In situations dealing with comparison of the mean of two populations, i.e., averages of one group with that of another group to test whether they are equal or not, a two-sample student's *t*-test is used. In this, independent samples are drawn from two populations. Based on the sample values, the formula for the two-sample "*t*" test is given by:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s\sqrt{\{(1/n_1) + (1/n_2)\}}}$$

where n_1 and n_2 = Sample sizes

$\bar{x}_1$ and $\bar{x}_2$ = Sample means

s = Pooled sample standard deviation

Subscripts 1 and 2 referred to groups 1 and 2, respectively.

Here, the degrees of freedom will be $n_1 + n_2 - 2$

Example: Two independent samples of 15 males and 15 females were examined for 24-hour creatinine excretion in urine samples. Apply a suitable test of significance to examine if a difference exists in results by gender. The results are given in **Table 11**.

The null hypothesis for this example is that there is no difference in average 24-creatinine excretion between males and females. Since it is not known a priory that a male would have higher creatinine excretion or a female, the alternate hypothesis is two-tailed. In this case, the computations are as given in **Table 12**.

TABLE 10: Albumin level (g/dL).

Patients	*Before treatment*	*After treatment*	*Difference*
1	5.2	4.9	0.3
2	3.9	3.8	0.1
3	4.1	3.9	0.2
4	4.8	4.8	0.0
5	4.6	4.7	–0.1
6	4.9	5.1	–0.2
7	4.2	4.1	0.1
8	3.7	3.5	0.2

TABLE 11: 24-hour creatinine excretion (mg/dL).

Patients	*Male*	*Female*
1	16.8	23.4
2	20	22.2
3	17.3	22.1
4	17.2	16.9
5	15.8	14.4
6	20.5	23.4
7	24.9	25
8	18.7	25.7
9	17.8	28.3
10	22.2	22
11	25.1	21.1
12	18.6	18.2
13	17.1	19.7
14	21.3	20.8
15	23.5	17.5

TABLE 12: Alternate hypothesis.

	Male	*Female*
Sample size	15	15
Sample mean	19.79	21.38
Sample SD	3.03	3.65
Pooled SD	3.39	

(SD: standard deviation)

Substituting these in the formula, the value of "*t*" is 1.30 with 28 degrees of freedom. The critical value of *t* for 28 degrees of freedom at 5% level of significance (two-tailed) is 2.048. Since the calculated value of *t* is less than the critical value of *t*, the null hypothesis of equality cannot be rejected. Thus, the samples do not provide sufficient evidence that the average level of creatinine excretion in men is any different than in women.

TEST FOR PROPORTIONS

Similar to the test for averages, the *Z* test (based on the Gaussian distribution) is also employed in testing for proportions.

Situation A: One-sample test: In case of a one-sample test, the test statistic "Z" is given by:

$$Z = \frac{p - P}{\sqrt{P(1-P)/n}}$$

Here, p = Sample proportion
P = Proportion under null hypothesis
n = Sample size

Example: In a hospital, out of 400 consecutive patients of diabetes, the males were 216. Does the data suggest that the prevalence of diabetes among males or females is equally likely? In this situation, the null hypothesis is that the proportion of either gender is 50%, as against the alternative hypothesis that it is not 50%. In this example, n = 400, p = 216/400 = 0.54, and P = 0.50.

Substituting these values in the formula the calculated value of *Z* is 1.6 which is less than the critical value of 1.96 at 5% level of significance. Hence, the null hypothesis that the gender of the diabetic patients is equally likely cannot be rejected.

Situation B: Two-sample test for proportions: Many times, proportions (cure rate, prevalence of a condition, etc.) for two groups are required to be compared and in such situations a two-sample Z test is used, which is given by

$$Z = \frac{p_1 - p_2}{\sqrt{\{p_1(1-p_1)/n_1\} + \{p_2(1-p_2)/n_2\}}}$$

Here, p_1, p_2 = Proportions for samples 1 and 2
n_1, n_2 = Sizes for samples 1 and 2

Example: In samples of 60 men and 40 women of age 50–55 years, the proportion of cataract cases was 62% and 75%, respectively. It is of interest to know whether the prevalence of cataract is higher among women as compared to men. Here, n_1 = 60, n_2 = 40, p_1 = 0.62, and p_2 = 0.75.

Substituting these in the formula, the computed value of *Z* is 1.4. The critical value of *Z*, one-tailed with 5% level of significance, is 1.64. Since the calculated value of *Z* is less than the critical value, the null hypothesis cannot be rejected.

TABLE 13: Test of significance.

Situation	*Statistical test of significance*
Association of attributes	Chi-Square test
Comparing the averages for more than two groups	F-test, analysis of variance (ANOVA)
Follow-up observations over time: Comparison of proportions between groups	Repeat measure analysis

OTHER COMMONLY USED TESTS

Some of the other commonly used statistical tests of significance are chi-square test, *F*-test, etc. **Table 13** summarizes the situations where these tests are employed. The data used in the test of significance are collected through surveys or experiments (**Table 13**). The next section describes the details on sampling techniques for gathering of data.

STATISTICAL SOFTWARE

Various software (Microsoft Excel) are used in undertaking statistical analysis of data on health (**Table 14**). Other software such as SPSS, SAS STATA, and R are used.

HOW TO READ A SCIENTIFIC PAPER

Reading and understanding research papers is a skill that every single doctor and scientist has had to learn during graduate school and to be able to distinguish between good and bad interpretations of research. Scientific paper reading is a completely different process from reading an article. Not only we have to read the sections in a different order than they're written, but necessary to take notes, reading paper

TABLE 14: Software used in undertaking statistical analysis of data on health.	
Microsoft Excel	
Background	This is part of the Microsoft Office suite of programs. Excel version 1.0 was first released in 1985, with the latest version Excel 2016
Application features	• Extremely easy to use and interchanges nicely with other Microsoft products • Excel spreadsheets can be read by many other statistical packages • Add-on module which is part of Excel for undertaking basic statistical analyses • Can produce very nice graphs
Limitations	• Excel is designed for financial calculations, although it is possible to use it for many other things • Cannot undertake more sophisticated statistical analyses without the purchase of expensive commercial add-ons
Source	Most computers come with Microsoft software already installed. For blue-plated (UniSA) computers, contact the IT helpdesk to install the latest Microsoft Office software. For your own computer, you can always purchase Microsoft Office from a retail store

multiple times, go through the other papers too in order to understand some other details. Reading a first paper may take very long-time, but process will go much faster as reader gain experience.

Benefits of reading the scientific paper: Journal papers are latest and reflection of latest development in the field. In today's word journals are the most approachable means of obtaining the information. To learn how a certain research is conducted, and explain the data every physician must learn to do research, because one day most of the clinician could be writing papers too. Student can develop critical thinking about quality of research papers. It is important to learn scientific paper quickly and insightfully.

Reading a scientific article is a complex task. The incorrect way to read the scientific paper is to read it like a textbook (reading from title to literature cited, digesting every word without any insight or criticism). The best way to start the reading is the "skimming the article" to identify its structure and features. Look for the author's main points as you proceed further. Generate questions before, during, and after reading. Draw conclusion based on your own experiences and knowledge, take notes as you read to improve understanding and recall.

Scientific papers are broadly categorized in to two types; Review articles: Which is a summary and conclusion of many studies and give an overview of the scientific field. Primary research articles: Contain the original data and conclusions of the researchers who himself involved in the experiments. Review and Primary research paper can be distinguished by the following ways:

- Many reviews will be labeled as "review" on the first page of the article.
- Reviews don't have a "methods" section.
- In a review article, graphs, tables, or figures containing actual data will contain citations in the figure legend to the primary research papers that originally reported the findings.

The Typical "Anatomy" of a Paper

Most articles are divided into the various sections: Before start reading the scientific paper, we should know the components of a scientific paper these are enumerated as:

- Title and authors
- Abstract/Summary
- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgements
- References
- Figures/Tables
- *Title and authors*: Title is very descriptive (often states the main finding) and is not about being creative. Order of authors is important.
- *Abstract/Summary*: Gives the brief description of subject, purpose for the study, major findings of the study, relationship between these findings and the field.
- *Introduction*: Presents the background information for a fellow scientist (possibly in another field) to understand why the findings of this paper are significant. Introduction mainly consists of accepted state of knowledge in the field, focuses on a particular aspect of the field, data related to particular field. It is important for the clinician to approach the introduction systematically: Grab a blank piece of paper: Take notes, Draw mini figures, Define vocabulary Answer these questions: What is the accepted state of knowledge? What are the available data prompted the work on this paper? What is the hypothesis being tested? What are the basic conclusions? Making notes gives us benefits to take a break (hours to days), then resume the reading of paper and you won't have to re-read the part you have completed.
- *Material and Methods*: Should be detailed enough for another scientist to replicate the work (volumes, times, company material was purchased from etc.). In reality, often compressed and you may need to look up another paper that is referenced for more detail. Should you read the materials and methods? Skim the paper before the result, then switch back to article to clarify the experiment methods. Whether sample number is taken appropriate?
- *Results*: While the introduction poses the questions being asked, the results describe the outcome of the experiments that were done to answer the questions. Figures and tables are used for interpretation of the results. How to read the results: Read the text straight through, examine the figure. Figure should be able to explain: (1) The basic procedure, (2) The question it sought to answer, (3) The results, (4) The conclusion; and (5) Criticisms.
- *Discussion*: Data is analyzed to show what the authors believe but readers not necessarily have to agree with their interpretations. How to read Discussion; Take notes and answer these questions: What conclusions do the authors draw? Be sure to separate fact from their opinion/

interpretation? Describe for yourself why these data significant whether it contribute to knowledge or helpful in correction of the errors.
- *Acknowledgements*: Thank people who contributed materials, clinical nonclinical or technical people. (May not be authors).
- *References*: Papers cited in the text; what parts of the paper cite other papers?

How Should We Read a Scientific Paper?

It is not necessarily that we should read scientific paper in same order. A four-step method should be adopted based on: *Ann McNeal, School of Natural Science, Hampshire College, Amherst MA—*
- *Step 1*: Skim the entire paper: Look at the major headings (whether they follow the "anatomy" just described) How many figures are there, what kinds of figures are they (tables, graphs, microscopic images) What is the conclusion of the paper? (It may not give you any clue to you at the moment, but note for a moment.)
- *Step 2*: Vocabulary: Go through the paper as a whole simply underlining words and phrases you do not understand. At this moment we are not reading the paper for comprehension of the whole paper, but try to understand the words and then comprehend it.
- *Step 3*: Read for comprehension, section by section; Introduction-what is the accepted state of knowledge in the field (take notes and even draw your own figures). What is the previous data prompted to do this work? What question are they answering? (Is there a clear hypothesis?) What are their conclusions? Materials, Methods and Results: Go through the methods first or read them as you read the results. Figure should be able to explain: (1) The basic procedure, (2) The question it sought to answer, (3) The results; and (4) the conclusion. After reading one should be able to explain all of these to another colleague. Discussion; try to understand what conclusions do the authors draw? Categorize and differentiate fact from their opinion/interpretation? Try to understand significance of the data, whether it enhancing your knowledge or helpful in correcting the errors.
- *Step 4*: Reflection and criticism: Write down your thoughts whether you agree with the authors' rationale for conducting this research, and if they perform the experiments properly? Do you agree with the authors' conclusions from these data? Have they neglected any factors that could have accounted for their research? What further questions do you have? What might you suggest they do next?

Tips for Successful Reading

- Spend a lot of time on each paper now look up every detail that you are unsure of. (Time you invest now will pay off in the long run). The best ways to learn and to retain the information is discovering the answers for yourself.
- Imagine yourself teaching the paper or figures to colleagues—teaching something to others is also another great way to learn.
- Start making a database of procedures that you take the time to look up and teach to yourself (e.g., western, immunoblots, RT-PCR, Neutralizing antibodies assay, apoptosis assays, etc.).
- The more you understand the research methodology, the more critical you can be of data analysis and interpretation.
- Read papers when you are tuned and interested in reading.
- If you are already in the field you plan to stay in, consider starting a database on papers that relate to your lab/project/responsibilities. You will be able to impress your seniors/colleagues with your quick analysis and summary of a monumental paper.

SUMMARY

Researchers need to understand the features of different study designs, with their advantages and limitations so that the most appropriate design can be chosen for a particular research question. Evidence-based medicine offers a useful tool to determine the type of research design used in a particular study.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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Transforming Emergency Department with Digital Technology

12 CHAPTER

Rajesh Kumar Gupta

INTRODUCTION

Emergency department (ED) in any hospital is usually where patients present with no prior appointment, seeking immediate attention for an acute condition. In such a scenario, urgent care can be provided only if a patient's medical record is available real time, accessible easily on the move, with information shown in a way that is suited for emergency room (ER) clinicians, nurses, and technicians.

Digital technology plays an extremely important role in defining such care pathways. It has revolutionized the way doctors and nurses retrieve and view a medical record, initiate diagnostic and procedure orders, get real-time alerts and notifications, and adjust treatment plans on various devices at the point of care or on the move.

For a better understanding of the ER digital transformation, let us break the urgent care delivery process in the following steps:

1. Ambulance management
2. Check-in at ER
3. Triage
4. Initiating a care protocol
5. Clinical documentation
6. Discharge home or transfer to inpatient department (IPD)

Each step is described further in detail with the possible digital transformation solutions one can take to improve the urgent care delivery process.

AMBULANCE MANAGEMENT

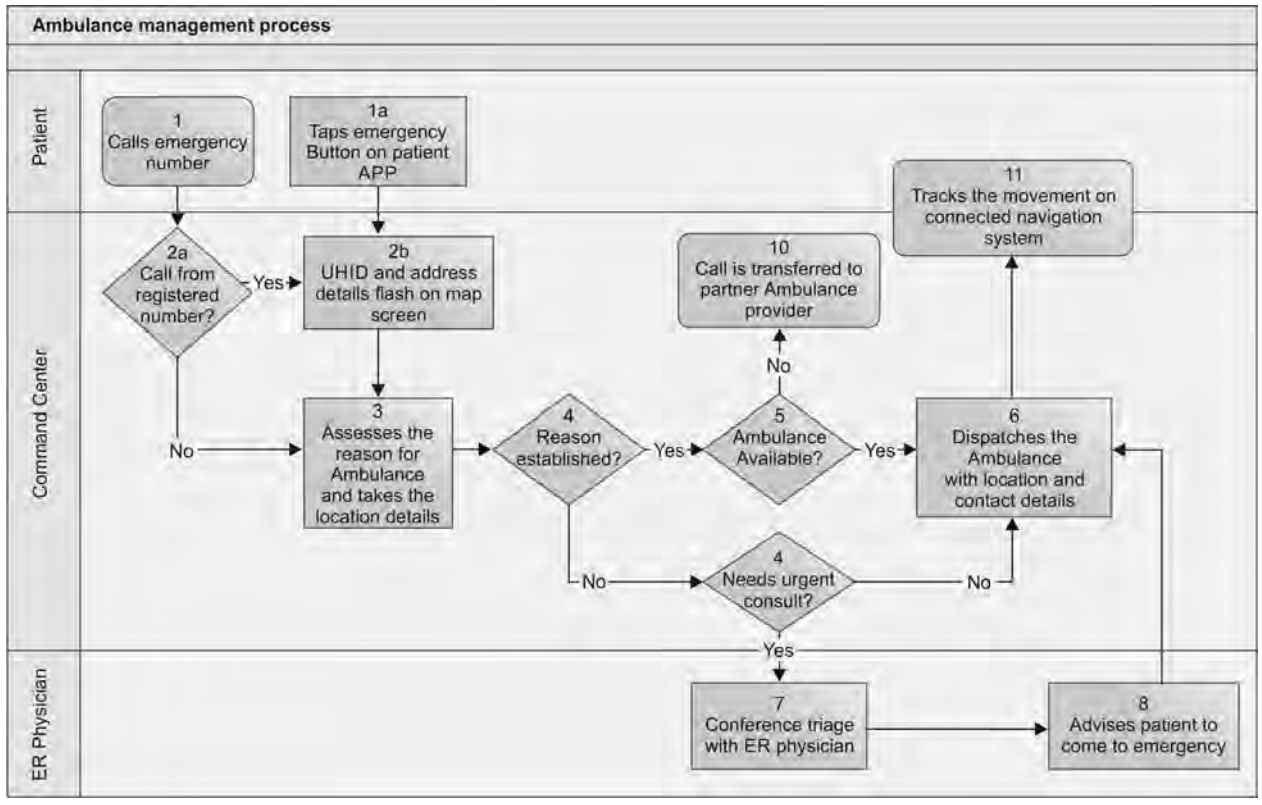
The ambulance management process can vary a little from hospital to hospital; however, the core remains the same. (**Flowchart 1**). As a best practice, before proposing a process automation, we must document the process flow. Each step in the process should be measurable for further analysis in terms of effectiveness and efficiency, especially when data can be represented in a dashboard format, as described in the admin dashboard section later.

Request for Ambulance

Digital technology enables initiation of the care delivery process even before a patient physically arrives at ED. Today, patients can request for an ambulance at the touch of a button, using digital platforms such as a patient app or patient portal. This automatically initiates a call to the emergency number of the hospital, with the exact geolocation fetched from the calling device, and patient demographic details getting populated automatically for an already registered patient. A set of configurable questions to derive at the criticality of a patient's condition can be defined as displayed in the screen in **Figure 1**. A single-screen command center view automatically retrieves key medical information of the patient and helps in quick decision-making according to the patient's current acute condition and past medical history. Appropriate category of the ambulance is dispatched by a single click and tracked via Global Positioning System (GPS).

Patient Care in Ambulance

The process flow depicted in **Flowchart 2** describes the patient care process in the ambulance. While care initiation in an ambulance is always expected to be prompt, retrieving a patient's past medical record from the paramedic app enables the health workers to take an informed decision quickly. If no previous record exists, the app provides the functionality to register the patient and generate a unique hospital identification (ID) within a single click and push the patient details automatically to ER reception where the team can be ready proactively, to receive the patient, generate a barcoded wristband for patient ID with unique hospital identification (UHID), maintaining immediate care continuum. Referral to other specialty experts can be initiated from the ambulance itself, thereby saving critical time in getting help once the patient arrives in ER. Integration between patient monitoring systems and electronic medical record (EMR) via mobile devices allows real-time monitoring by both clinicians in the ambulance and senior doctors at the ER department through real-time data transmission (**Fig. 2**). Equipping ER command center with video conferencing equipment and high-speed internet enables the opportunity for teleconsultation with specialists at the hospital. Ability to view and analyze medical records helps not only in concluding a diagnosis, initiating appropriate treatment, but also in completing the triage in the ambulance itself. On arrival, the patient can then be taken to the appropriate area



(ER: emergency room; UHID: unique hospital identification)

FLOWCHART 1: Ambulance management process.

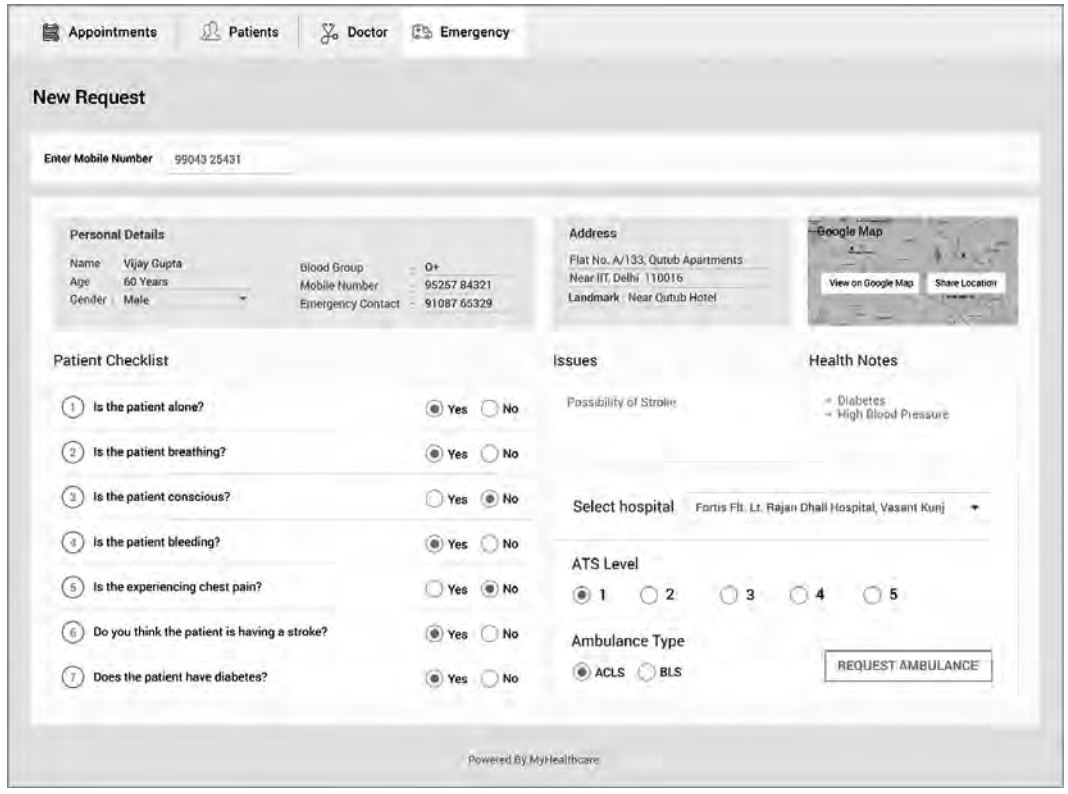
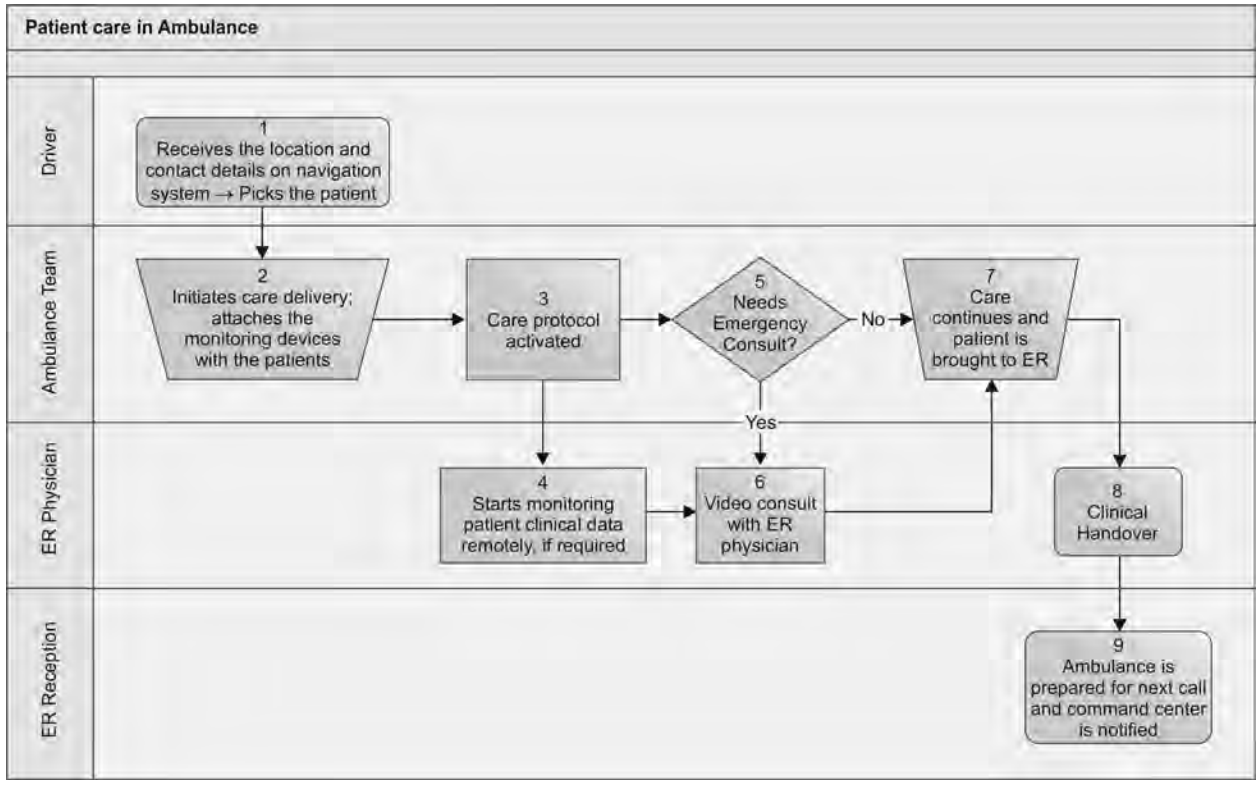


FIG. 1: Ambulance request.

Courtesy: My Healthcare Connected Care Ecosystem.



(ER: emergency room)

FLOWCHART 2: Patient care in ambulance.

in ER, intensive care unit (ICU), or operation theater (OT) immediately.

CHECK-IN AT EMERGENCY ROOM

Check-in of the patient coming by ambulance can easily be a one-click activity with process automation (described earlier) which transfers entire billing data to the hospital information system (HIS) for further processing while the ambulance is made available to cater to the next patient immediately. If a patient is arriving in his/her own transport, the attendant can be allowed to check-in online via a mobile device. This reduces the documentation burden on already stressed triage and reception staff and expedites the check-in process for patients.

TRIAGE

The biggest challenge in digital transformation in an emergency setting is the inability of EMR systems to provide a single view for ER clinicians to find all the information required in real time. It is practically impossible for them to navigate through multiple menus and screens of EMR software to retrieve the details required or to perform an action as close to near real time as possible, considering how critical time is in an ER setting. The ER clinical dashboard is a one-screen view that attempts to overcome this challenge and help ER clinicians to manage a patient as described further, as shown in **Figure 3**.

Emergency room dashboard provides a holistic view and at the same time allows clinicians to act quickly with the following functions in real time:

- Color-coded bed and triage category management with easy bed shifting within ER and real-time LOS
- Critical alerts and notifications
- *Triage*: Entering the vitals, triage documentation and initiating a treatment protocol
- Nursing and physician assessments, specialists' referrals—with color-coded status as due, overdue, and completed
- Order tracking of laboratory, radiology, other diagnostics, and medication administration with adverse drug reactions
- Short cuts to place a new order
- Status update on transfer request to IPD or discharge
- Quick response (QR) code-based quick actions

The triage process should be configurable to adopt a set of guidelines (Australasian, Canadian, etc.), followed by ED. Alternatively, the system should allow defining custom guidelines for ED. The ability to view test results with a quick turnaround time enables speedy treatment for patients, referral with the right specialist, and faster clinical decisions, thereby improving patient outcomes and increasing patient satisfaction.

CLINICAL DOCUMENTATION

The EMR module can integrate a wide variety of clinical records and documents into a patient's medical record. The system allows a quick generation of patient history, systemic review, and physical examination information by allowing configuration of the clinical notes as per a structured format. The clinical note can be designed in such a way that it requires minimum typing effort and more touch-based documentation such as selections from a dropdown, radio buttons and checkboxes, to save time. Voice to text feature can also be provided in case detailed notes need to be recorded by clinicians. The discharge summary format can autopopulate already captured relevant information from the patient record, making it easier and faster with the elimination of transcription errors. Provision to

FIG. 2: Teleconsult in ambulance.

Courtesy: My Healthcare Connected Care Ecosystem.

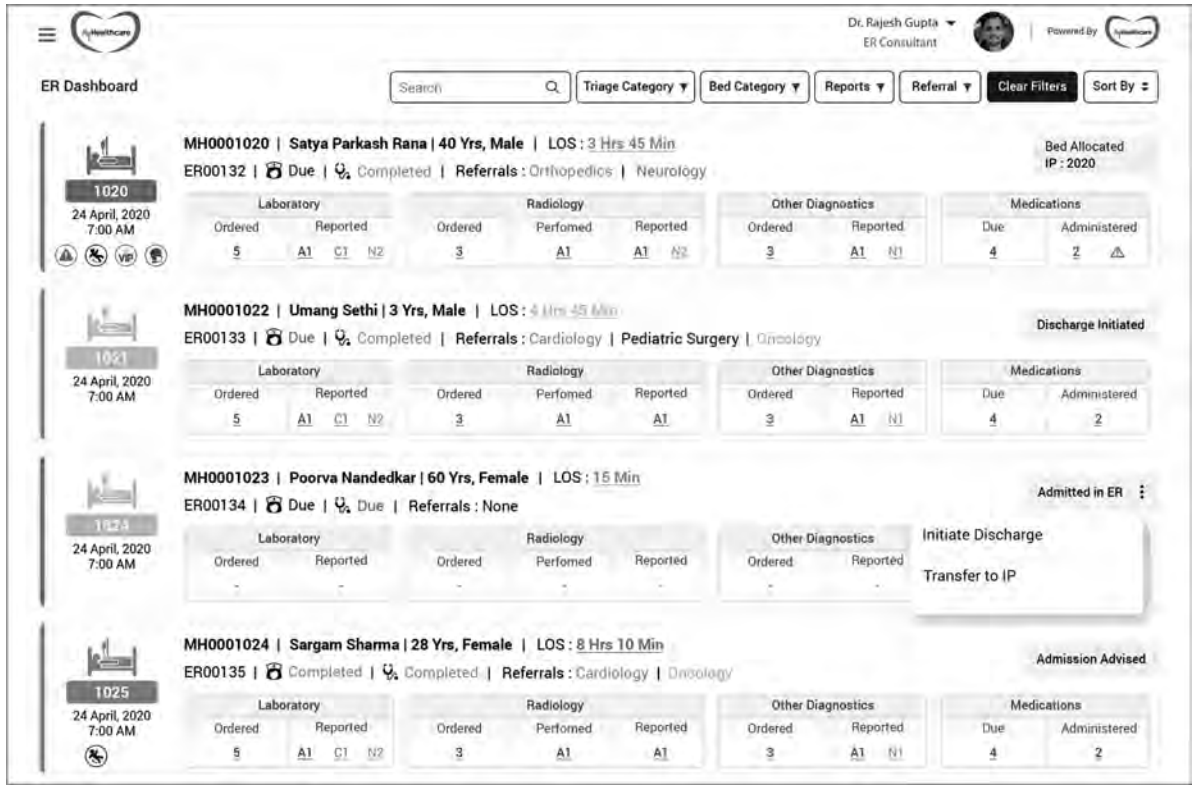


FIG. 3: Emergency room clinical dashboard.

Courtesy: My Healthcare Connected Care Ecosystem.

manage the images in addition to creating the various clinical notes for the patient care makes the document more evidence-based. Documentation features may include:

- Recording clinical notes in prespecified templates with data prepopulated as much as possible
- Dynamic validation rules—age, gender, encounter type, specialty, etc.
- Two-step documentation—draft notes entry by one person and review/finalization by another as per predefined setup and rules
- Audit trail maintained for the amendments and addendums made for traceability and accountability
- Sharing the notes amongst clinicians for review/second opinion

INITIATING A CARE PROTOCOL

Despite the success of process standardization in multiple other industries, its adoption in health care has always been challenging. Having said so, hospital managers, clinicians, and nurses are beginning to realize the potential of coordinated interdisciplinary care to improve the quality of care and reduce revenue leakage at the same time. While individual care is essential, standardizing evidence-based best practices is a significant part of delivering effective, safe, and affordable care. There are numerous benefits to standardized care:

- Improved patient safety by reducing errors
- Improved quality of care
- Reduced redundancy of work
- Better compliance to documentation
- Reduced process waste
- Improved productivity and efficiency
- Reduced costs
- Consistent outcomes
- Higher patient satisfaction

Standardized clinical protocols offer specific instructions on best practices to treat a given condition with the use of evidence-based medicine. They help in making care delivery more consistent and efficient and bridge the gap between what clinicians practice and what evidence-based medicine recommends (**Fig. 4**).

An example of an automated care protocol is shown in **Figure 4**. This allows to make certain steps and actions mandatory (pre-ticked when the protocol is initiated) while providing the flexibility to change it real time depending on the patient's conditions, availability of past reports, drug allergy profile, etc. The right use of devices (computer, tablet, or mobile) enhances the adoption of clinical protocols to a great extent by providing a single view of clinical protocols from initiation to completion. Technology adds value by highlighting and measuring any deviation from the clinical protocols with clinical justification.

FIG. 4: Clinical protocol.

Courtesy: My Healthcare Connected Care Ecosystem.

DISCHARGE HOME OR TRANSFER TO INPATIENT DEPARTMENT

It is extremely important to discharge the patients from the ER or transfer them to IPD if their clinical condition is not favorable to discharge. This is to ensure that the department has the adequate number of beds ready to receive new patients should there be an influx of patients from a nearby accident or disaster. Discharge initiation or transfer request to IPD from the ER clinical dashboard itself makes it easier for ER clinicians to track the process described in **Flowchart 3**.

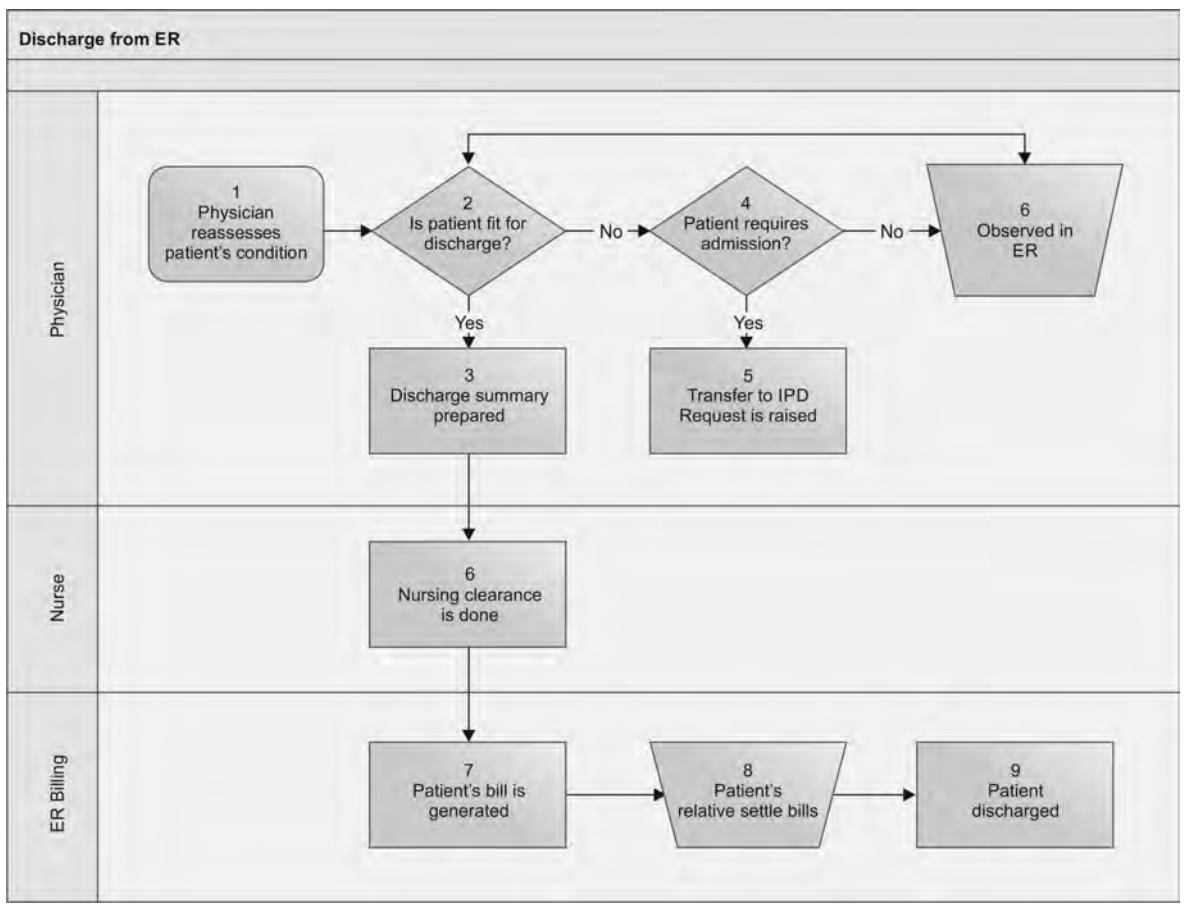
The discharge status is updated on the ER clinician dashboard when the request is acknowledged, the bed is allocated, and so on, thus avoiding time wastage in multiple follow ups. This also results in increased overall patient satisfaction. Automated discharge and transfer to the IPD process also allow measuring the turnaround time of each step. Details of such key performance indicators (KPIs) are described further in the ER admin dashboard section.

EMERGENCY ROOM ADMIN DASHBOARD

Dashboards provide a consolidated view for ER operation managers to access, interact, and analyze real-time and meaningful information to be able to make smarter, data-driven decisions (**Fig. 5**). A good dashboard for the ED enables the head of the department or his/her designated administrator to monitor and measure performance and metrics on the go. They can visualize and analyze data and focus on KPIs across ER processes that have been laid out in consultation with the medical administration and quality departments of a hospital on a single-screen dashboard, helping with valuable insights to drive quick and accurate decision-making.

For instance, it can be anywhere from few minutes to many hours from when a patient arrives in ER and a physician or nursing assessment is done or when a patient's emergency medical treatment is complete and he/she leaves the ED to either go home (discharged patients) or to a hospital bed (transferred to IPD). Knowing the total length of stay in ER is important for understanding the patients' overall experience. The longer a patient stays in the ED, the longer a new patient must wait to see an emergency doctor. The patients' total length of stay is dependent on several factors. For instance, while patients are being treated in the ED, they may also be waiting for things such as laboratory results, referrals by other specialists, results from an imaging, or observing how they respond to treatment. If ER patients remain in the ED waiting for an IPD/intensive care unit (ICU) bed in the hospital to become vacant, it increases their length of stay. An ER admin dashboard with drill-down view till a single transaction level really helps the administrator to find a root cause for delay and its impact on care delivery and thus to initiate an immediate corrective action. An effectively implemented ER admin dashboard can provide the following benefits:

- Total visibility into ER department
- Compliance to processes and defined turnaround time (TAT)
- Improved outcome



(ER: emergency room; IPD: inpatient department)

FLOWCHART 3: Discharge process.

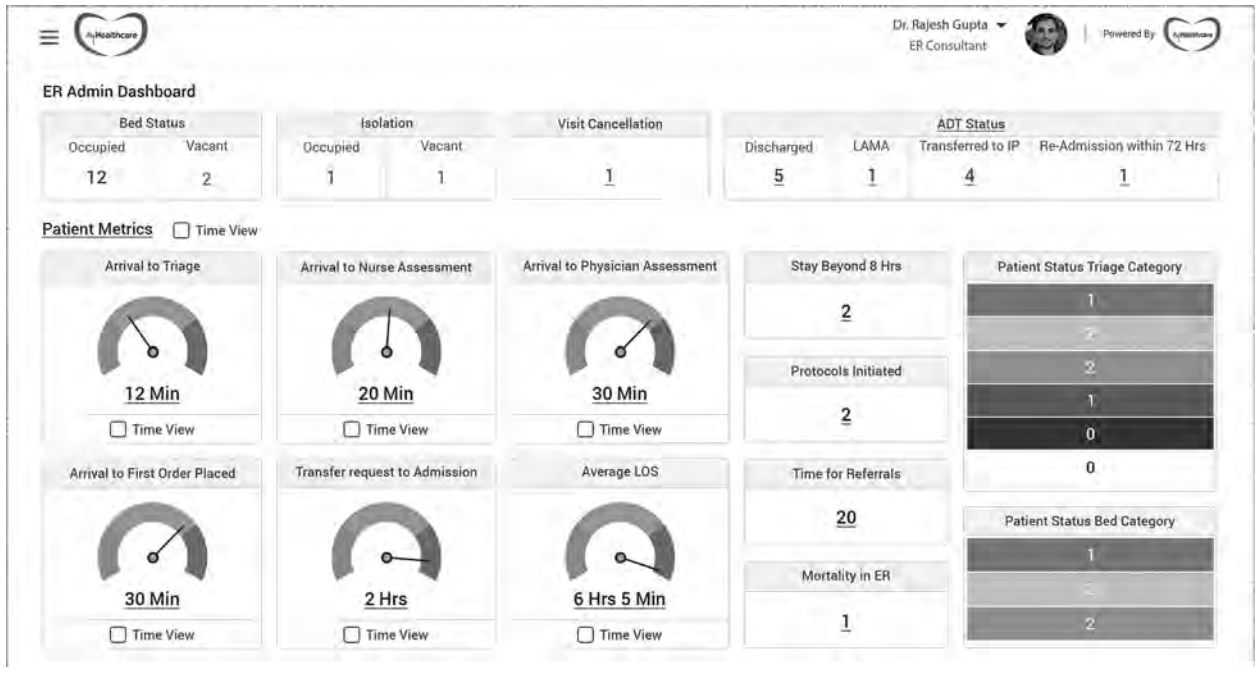


FIG. 5: Emergency room admin dashboard.
Courtesy: My Healthcare Connected Care Ecosystem.

- Increased productivity
- Reduce costs

Dashboards allow us to measure performance objectively with data as proof. For example, we could see metrics such as average time taken to complete a specialty referral, the average time taken to acknowledge a referral request, etc. This metric can be compared between different specialties in a leadership dashboard, which would eventually lead to an overall improvement in the performance and results. However, for any dashboard to provide accurate information and any process automation to work effectively, it is necessary to have a robust and stable process. Only a stable process can give rise to meaningful data which can then be processed and converted into information to taking smart decisions. Recent advancements in technology in the form of QR codes in mobile devices and interoperability with medical devices have made technology hand in hand with ER making it much easier to implement digital technology in making a process more robust and stable.

TECHNOLOGY HAND IN HAND WITH EMERGENCY ROOM

Quick Response Code Technology

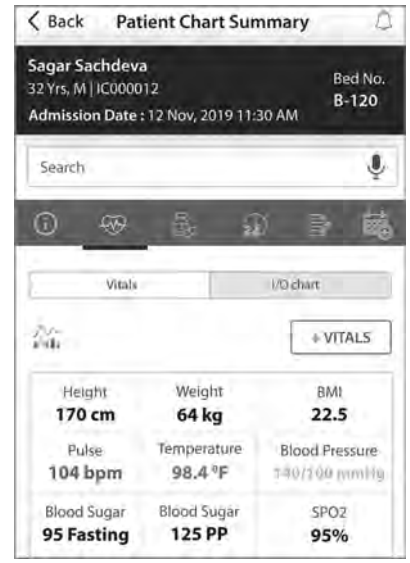
Barcode technology has been in use in health care for decades, especially in sample tracking and laboratory process automation. The success of barcode technology in a laboratory process prompted wider use in health care across various departments. A barcoded wristband to identify the right patient has enabled faster completion of clinical transactions. The QR scanner (available in a smartphone camera module) reads the patient's UHID and his/her bed details from the patient's wristband and ties it to any new order, documentation, and point-of-care test. It also helps nurses to administer medication by following five rights: (1) Right patient, (2) Right drug, (3) Right time, (4) Right dose, and (5) Right personnel. Scanning technology can also prevent blood transfusion mishaps, such as giving the wrong blood to the wrong patient. After scanning the patient's wristband and blood bag, the computer system alerts the nurse if the wrong blood unit is being transfused or if it is for the wrong patient. With the use of barcode technology in ER, it ends up optimizing many of the existing processes, which ultimately changes the way hospitals practice emergency medicine, and reducing the manual errors drastically.

Mobility Devices

The ED by its nature of work requires a lot of actions to be done on the move; hence, handheld devices have started playing a big role in enabling the clinicians to perform their tasks on mobile devices (**Figs. 6** and **7**). With high-speed data connectivity being available easily across the globe at a much lesser cost, and with Wi-Fi being an integral part of hospital infrastructure planning, the use of the mobile device has reached a greater acceptability. Camera modules of mobile devices help in capturing images and sharing them in real time across the care team by saving it in EMR as part of clinical documentation. It also acts as a barcode scanner, thereby eliminating the need of a bulky computer on wheels which is much more costly to procure and maintain. Additionally, with people getting so used to using a variety of apps on their smart devices, the training effort required to increase EMR adoption has gone down to a great extent. Patients are also increasingly demanding for platforms where they can contribute and engage in their own health management. Therefore, tablets and smartphones are increasingly brought into daily use by clinicians and patients alike as they are finding it much easier to receive results, alerts, decision support, and charting on these devices. As part of the overall infrastructure planning, hospitals are now looking to implement touch screen tablets

FIG. 6: Doctor's worklist.

Courtesy: My Healthcare Connected Care Ecosystem.



(BMI: body mass index)

FIG. 7: Vitals view.

Courtesy: My Healthcare Connected Care Ecosystem.

with every bed similar to having a paper chart mounted next to the bed but much more secure with the capability of generating additional information, which can be used for data analytics.

Interoperability

The adoption of digital health technology is largely dependent on systems' integration to leverage data and insights from various diagnostics, monitoring, and treatment devices used in silos currently. Data lying in individual systems do not provide a holistic view. For instance, a laboratory result in conjunction with medication administration provides more meaningful insights into what is the impact on laboratory values when a medicine is administered. Since episode-based EMR is the primary interface most clinicians are adopting today, the path to improved data-driven outcomes is likely to be through the EMR only. However, unless EMR is tightly integrated with next-gen internet of medical things (IoMT) devices and other clinical applications using integration standards [such as health level 7 (HL7), fast health interoperability resource (FHIR), etc.] and coding standards (such as ICD-10, SNOMED CT, NANDA, and LOINC), meaningful clinical data analytics and predictive analytics will not be possible. As a transaction-based system, the EMR is fundamentally not designed to facilitate real-time, point-of-care clinical decision support especially when large data is lying in silos. Hence, it is extremely important to choose software solutions which comply with the latest integration standards and all efforts should be made to interface these systems as *one* clinical system for the hospital.

SUMMARY

It is an exciting time to be in a digital healthcare transformation space. Digital innovation and its implementation into the ER department process design has improved both the patient experience and care delivery with better outcomes. The future lies in relentless innovation to facilitate continuous adoption of digital technology for improved care delivery, increased patient engagement in care, and increased process efficiency in ER.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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ONLINE REFERENCES

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Advanced and Future Technology in the Emergency Department

13 CHAPTER

Devendra Richhariya

INTRODUCTION

Technology has revolutionized the way medical professionals work, communicate, and process information. Nowhere is this more apparent than in the emergency department (ED). Digital communication tools allow nurses and clinicians to uncover and track data in real time and adjust the course of treatment. As healthcare architects, we strive to incorporate creative and cost-effective technologies into ED spaces to help improve patient outcomes and the delivery of care. The emergence of medical technology and new equipment helps healthcare in maintaining the quality and moving forward, and medical technology advancements will not slow down anytime soon.

The ED is particularly focused as this is the face of any healthcare system, about 40–60% of the inpatient and observation patients being admitted through the ED. Emergency medicine is the field of practice based on knowledge and skills which is used to prevent diagnose and manage the acute and urgent aspect of the illness. The goals of the emergency care are to improve the patient care, lessen the patient care stress on staff, limit the financial cost to the hospital, and allow more available time for teaching.

Today, our emergency care system has multiple roles, not only to attend and manage urgent and lifesaving emergencies but also to maintain quality and safety standards, disaster preparedness, and public safety net care and provide care even with increasing patient volume with limited resources. The newer technology has an acceptable wide range of role and impact on the ED within the larger hospital and healthcare system and can address a wide range of issues which include:

- Patient flow and overcrowding by information technology
- Workforce issues across multiple disciplines
- Tracking patient safety and the quality and efficiency of emergency care services
- Emergency care-related clinical research
- Use of newer technology for setting up emergency care in rural settings

The a list of innovations that are transforming the way emergency care is provided is given in the following text.

ONLINE CHECK-IN

Recent advances in telemedicine also enable the patient to virtually check-in with healthcare staff in the ED before arrival. Several EDs allow for patients to check-in online via a mobile device, Entering personal information such as insurance and point of contact data. Registration can occur at home, in the car, in the waiting room, or bedside in a treatment room. This elevates the paperwork burden on already stressed triage and reception staff and expedites the check-in process for patients. Implementation of algorithms and artificial intelligence will help the triaging patients to get medical care at the right time and right location.

PATIENT FLOW SOFTWARE

Gone are the days of nurses walking up and down hallways documenting empty beds. Today, patient flow software manages where patients are (and are not) within the hospital. It can identify available beds by specialty, thereby streamlining the registration and decreasing wait times. These systems have been said to improve communication across departments and expedite both admissions and discharge procedures.

REAL-TIME LOCATING SYSTEM

Similar to patient flow software, real-time locating systems digitize information regarding where a patient is, or is not, during his/her course of treatment. This technology can also be adapted to track all movements in the hospital by applying location transmission tags to patients, beds, staff, and equipment alike. With this information, practitioners are able to more accurately track movements to efficiently manage time and care. Additionally, hospital administrators may utilize movement data to analyze workflow, standardize care, identify best practices, and eliminate waste.

MINIATURIZATION OF IMAGING AND DIAGNOSTIC EQUIPMENT

Point-of-care ultrasound machines allow emergency doctors to make diagnosis easier by identifying injuries and

illnesses such as bleeding in the abdomen, gallstones, kidney obstructions, or acute heart failure. While medical imaging is required to perform comprehensive scans, point-of-care ultrasound (POCUS) allows emergency physicians to answer binary questions that may influence the course of care and dramatically improve outcomes. Physicians are able to travel with a dedicated imaging machine, eliminating the waste of learning how to operate a different machine or having machines sit idle. Miniaturization is also starting to extend into the fields of endoscopy and laryngoscopy, where a handheld device is replacing a bedside cart.

Noninvasive bedside laboratory testing is also changing the delivery of care model. The i-STAT blood testing system delivers laboratory-quality test results through a handheld device and then wirelessly transmits results to a patient's electronic medical record (EMR). This bedside technology eliminates the waste of transporting samples to and from a laboratory and frees up highly coveted ED real estate.

Research has shown that immediate access to imaging is vital to the diagnosis and outcome of stroke and head trauma patients. However, because CT scanners have traditionally been large and expensive, they are not always immediately accessible to the ED. New miniaturized CT scanners are portable and wireless, able to be brought directly to a patient's bedside. These portable CT scanners are revolutionizing the standard of care by eliminating the dangers associated with both the transportation and wait times traditionally required to move a critical patient to a medical imaging suite.

Handheld Devices: Portable Ultrasound, ECG, and Other Point-of-care Devices

As with the rest of society, over the past several years EDs have become more computerized. Tablet, computers, and smartphones are increasingly common in daily use by practitioners and patients alike. Physicians can now review EMR data (such as glucometer readings or stethoscope sounds) from anywhere on their smartphones. Given the prevalence of handheld devices, it is inevitable that more decision support, charting, and patient record management will be performed on these devices. Moving forward, all horizontal surfaces in an ED should be adaptable into a touch-down workstation with data connectivity and power (including the incorporation of wireless inductive charging surfaces to eliminate unnecessary wires).

The bigger machines of ultrasound ECG are a thing of the past which require one manpower to move. The portable diagnostic devices, which are almost pocket-size and user friendly, are easier to operate and are helpful in treating the patient quickly and thus diagnostics are carried out on the spot.

A few years ago, only a radiologist had the privilege to carry out the ultrasound and only in the radiology department which was sometimes not feasible since it was difficult to move critically ill trauma patients to the radiology department. Now more and more emergency physicians are getting trained and using POCUS for the immediate answer (yes/no) about intra-abdominal bleeding (**Fig. 1**). Handheld devices allow any doctor to use them easily while working on a code or a critically ill patient (**Fig. 2**).

Long back ago ECG can be interpreted on the smartphone with one lead but many situations can be missed easily, and interpreting 12-lead ECG is required for detailed assessment. Now the available device allows the end-users to get 12-lead ECG wirelessly on their smartphones/tablets, which is as accurate as a similar standard bedside exam (**Fig. 3**).

FIG. 1: Handheld ultrasound.

FIG. 2: Handheld echocardiography.

FIG. 3: Wireless 12-lead electrocardiograph.

With handheld devices, long waiting hours for laboratory results are also gone. Handheld, lightweight point-of-care testing (POCT) devices and accurate blood analyzers equipment allow doctors to evaluate the patient's blood sample on the spot and wirelessly transmit the results or the data to colleagues, thus saving invaluable time during emergency situations and enabling the emergency physician in timely decision-making.

TELEMEDICINE

Equipping ED treatment rooms with cameras, monitors, and high-speed internet invites new opportunities for remote consultation with specialists around the world. This technology empowers small rural hospitals to partner with sophisticated centers of excellence, no matter how far from the facility, to provide patients with a higher standard of care. Some EDs incorporate smart TVs in the exam rooms connected to the facility picture archiving and communication system so that imaging data can be pulled up in a patient room as an aid for discussions. In the future, touchscreen tablets outside every exam room door will function as both a room sign and a tool for medical staff to bring up patient data prior to entering the room, similar to having a paper chart mounted next to the door but more secure and capable of generating additional information.

Additionally, Wi-Fi-connected equipment, both in and outside of the hospital, allows for patient data to be securely collected and transmitted to physicians for evaluation and tracking (**Fig. 4**). For example, systems currently exist in which a patient may upload glucometer readings or stethoscope sounds directly to their EMR for physicians to review.

BARCODE SCANNER

Barcode scanner is another relatively new advancement in technology implementation in the ED (**Fig. 5**). More and more healthcare organizations are integrating barcode technology into their facilities; many of their processes ultimately change the emergency medicine practice. On arrival to ED, a patient receives a wristband with a unique code and the scanner captures the code from the patient's wristband and matches it to any test, lab result, or procedure. The bar code technology is helpful in the speedy delivery of accurate results. The bar code technology reduces the labeling errors and manual errors which take a lot of time to rectify. It has been reported that barcode technology increases the patient satisfaction and positive health outcomes, and there is a huge potential for expanded use of the technology. The bar code technology, also known as radio-frequency identification (RFID), allows improving turnaround time on laboratory test results which are helpful in initiating the definitive treatment early and early referral to the right physician which ultimately increases the patient satisfaction.

Each time patients provide blood or urine samples, the nurse scans the patient's wristband and then scans the specimen; it updates the patient's EMR and his/her specimen identification code is connected to his/her ID number, which increases efficiencies and decreases the incidence of error.

Barcode technology creates a tracking process that helps decrease medical errors because a nurse scans a patient's wrist band each time a process is done. Scanning technology can also prevent prescription mishaps, such as giving the wrong medications. After scanning the patient and his/her medication, the computer system alerts the nurse if the wrong medication is being administered or if it is for the wrong patient.

The barcode technology reads the barcode through the skins and also helps the surgical team to track surgical tools and sponges during surgery with accuracy rates between 98 and 100%.

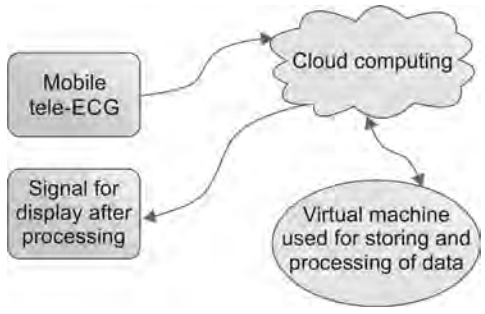
Mobile tele-ECG
Cloud computing
Signal for display after processing
Virtual machine used for storing and processing of data

FIG. 4: Secure data transfer to the physician for analysis.

FIG. 5: Barcode technology.

COMPUTERS ON WHEELS

To enhance healthcare delivery, the use of electronic health records has become necessary for healthcare facilities to create a point-of-care environment where a patient's EMRs and all interfaces are available to healthcare providers together. Healthcare industries have large investments in computing technology to ensure that an electronic health record (EHR)-equipped computing device is present virtually at all doctor–patient interactions. Facilities are equipped with wall-mounted computers in their infrastructure to save space and computers on wheels (COWs) save cost also. Nurses carry a computer with them as they conduct patient interactions during a shift, thus enabling them and also the physician to access EHR for each patient (**Fig. 6**). Another benefit of COW is that the care provider can use the same computer throughout his/her shift, so COWs are cost effective as well as ensure that EHRs are always accessible at the point of care.

Helpful in Streamline Workflow

This is a common practice in healthcare facilities throughout the country that nurses and medical officers conduct clinical round with patient interaction, then come back to stationary computers at the nursing/physician station, and record all vital details of interaction and physician orders. COWs allow nurses and physicians at the point of care to record all vital information at the same time which streamlines the process. COWs are also helpful in reducing the multiple steps of the process. Radiological images of a patient can also be accessed from the hospital's internal network while interacting with the patient during morning or evening round, and an appropriate clinical decision can be taken instantly. Storage space can also be created in the same trolleys enabling nurses to bring supplies and medications with them to the patient's bedside and minimizing trips to the supply and medication rooms on each shift.

FIG. 6: Computers on wheels (COWs).

Helpful in Reducing Error and Improve Patient Safety

As discussed earlier, nurses and physicians record patient care data and record progress notes and patient interaction at the point of care which are helpful in reducing record-keeping errors and improving patient safety. By using COWs, nurses and physicians need not go back to workstation for data entry and they are less likely to forget an entry, leave out an important detail, or even be interrupted by an emergency that takes away their focus from the vital task of recording a patient interaction or the administration of medication. COWs are helpful in medication dispensing also as some manufacturers have customized storage drawers that contain medication, along with a barcode scanner. The wristband of the patient and medication is scanned to verify that the prescribed medicine is given to the correct patient and automatically generates an online record of the interaction. Complete medicine delivery systems are attached to the COWs, and the movement of medications from a secure loading station to the patient's bedside can be tracked through a barcode. With medicine delivery systems, dispensation errors can be drastically reduced because drawers are secured and only unlocked by scanning the barcode on the patient's wrist.

Promote Patient Engagement

Facilitating patient engagement throughout the healthcare delivery process is an important aspect for improving patient satisfaction and leading to improved healthcare outcomes. As we know, paper records were kept out of the reach of the patient at the nursing station and seldom shared with the patient. But with the help of COWs, reports and imaging can be shared and discussed with the patient as well as his/her illness during physician–patient interaction. In this way, patients and family feel engaged in healthcare processes and are also more likely to return to the facility where they had a good experience. Data can also be updated and shared with the patient and patient queries can be answered.

Outperform Other Technologies of Healthcare

Other technologies, such as wall-mounted computers and tablet smartphones, have similar functions to COWs but because of their versatility, practicality, and low cost, COWs are used in healthcare facilities. COWs deliver many of the same benefits as wall-mounted computers or tablet computers in the healthcare environment, so why is it that healthcare facilities everywhere prefer mobile computer carts? There are several reasons, but it ultimately comes down to cost, versatility, and practicality. Although tablets are light weight and many touchscreen tablets are incapable of facilitating rapid recordings of patient data in comparison to a traditional keyboard, poor battery life makes them inefficient for a healthcare environment. Tablets have a smaller size of screen and most of the emergency medical system strongly advise 24″ screens; EMR software is also not compatible with tablets. Wall-mounted computers are effective, but they have different ergonomic configurations from COWs. In contrast, COWs are both mobile and ergonomic. They can be connected with a powerful monitor/computer combination and can be configured with battery systems that provide enough power for an entire shift or longer. They are easy to transport between patients and provide more benefits to patient care workflows; hence, hospitals should invest in COWs rather than purchasing wall-mounted computers for every room in the hospital.

MEDICAL DRONES

Recently, the e-commerce giant Amazon made headlines when it promised drone-assisted package delivery; now, the healthcare industry is exploring ways to use drones in healthcare medical emergencies and healthcare supply deliveries (**Fig. 7**). The year 2020 started with a pandemic along with earthquakes, cyclones, and flood that destroyed road infrastructure and hence it was difficult to deliver the medical aids to rural areas. Drones are equipped with a global positioning system (GPS) and mapping system which allow the healthcare person to figure out the location where the people have taken shelter after a natural disaster; they are also able to assess the requirement of medicine, water, food, blankets, etc. Drones also help in reaching these affected people either by ground or by air. Drones can perform a variety of tasks as a disaster relief emergency responder to deliver drugs, vaccines, and medical aids very quickly.

In the future, you may call a drone through your device/smartphone in an emergency situation which can fly in with

FIG. 7: Medical drone.

life-saving medical equipment such as automated external defibrillators (AEDs), blood products, and prescriptions. Drones not only can transport medical equipment but also can provide instruction for cardiopulmonary resuscitation (CPR) to the performer.

DRIVERLESS AMBULANCE

With the development of driverless cars and the potential for turning cars into points of care, some governments are considering driverless ambulances as technology. These ambulances can work as "medical taxis." They can pick up low-risk patients and transfer them to the nearest hospital or clinic for treatment. The need for paramedic staff to respond to every call would be reduced and only be limited to critically ill patients. Initially, it would be uncomfortable to travel to the hospital in a driver-less ambulance but probably we have to get used to this concept. Vitals can be recorded passively and stored in the cloud and a driverless ambulance robot can notify to the hospital if there is an urgent situation that needs to be handled.

APPS SIMPLIFYING COMMUNICATION ADMINISTRATION AND IN-FLIGHT EMERGENCIES

Various apps simplify the communication in emergency care. During the medical transfer of a patient, apps not only help by calculating the estimated time of arrival based on the GPS, but users are also able to send pictures of the ECG, injury, medicine list of the patient, real-time data, and the parameters of the patient to the emergency physician in advance. An ED can be alerted by the paramedics before arrival with the patient. Similarly, the stroke team and ST-segment elevation myocardial infarction (STEMI) team can also be alerted that involves a neurologist, intervention neurologist, and intervention cardiologist. Advance information allows ED nurses and doctors to prepare much better and faster for the critically ill patient. Apps developed for resuscitation help in documenting the critical events during CPR and also measure time countdown according to protocol and help in optimizing the chest compression. Apps are also helpful in debriefing the case so that the team can learn from the collected data as well. A team of aviation experts can develop an app to help physicians, which includes the most common in-flight medical emergency situations that could be encountered during a flight. Apps also define the role of flight and cabin crew during in-flight emergencies as well as the medicolegal implications for volunteers who assist.

VIDEO GAMES FOR PRACTICING REAL SITUATIONS

Video game technology also applies to healthcare. The app allows the emergency physician to simulate the performance of airway procedures. Realistic endotracheal intubation scenarios can be created so that the emergency physicians can better prepare for difficult airway management. The app scores on the basis of the physician's skills displayed and also monitors the virtual patient's vital signs while the procedure takes place.

FUTURE OF EMERGENCY MEDICINE

As pressures mount for EDs to do more with less, many healthcare systems have turned to lean principles borne out of the manufacturing industry to cut waste and improve efficiency. Lean planning tools rely heavily on data analytics—both collection and management software. By tracking analytical data [such as movement times collected with real-time location system (RTLS)], administrators are able to identify optimal registration procedures, treatment process times, and staffing schedules. From a patient care perspective, lean principles seek to standardize work processes to ensure that outcomes are reproducible and predictable, improving patient outcome and departmental satisfaction scores.

Digital technologies support patients to receive quick and efficient care at the same time; they also support healthcare facilities to handle situations more safely and more confidently. Using self-driving ambulances, equipped with various sensors and wearable gadgets, healthcare workers and paramedics get a patient's vital data in advance and get more time to prepare for urgent situations.

In the coming years, emergency services will be more sophisticated, streamlined, data-based, efficient, and faster than ever before, while taking both the needs of the patient and the limitations of caregivers into consideration. So, hopefully, within a couple of years, no one will have to wait for proper care. Technological innovation, and its incorporation into ED design, has improved both the patient experience and care outcomes.

As advanced medical technologies are incorporated in the ED, high-tech products are designed to accelerate blood clotting and are available as a kit. Products with blood clotting technology slow blood loss after a person begins to hemorrhage. The kit comes with a tourniquet and gauze dressings layered with anticoagulants that control blood loss of penetrating trauma such as stabbings, gunshots, or vehicular rollover accidents. First responders commonly use the kits to treat when pressure is applied to the bleeding wound.

On one side, medical technology creates manufacturing jobs, improves patient health outcomes, and boosts the economy; on the other side, experts are apprehensive of rising healthcare costs. In spite of that, as new medical technology makes its way into EDs, it changes the way hospitals run their EDs. ED physicians, nurses, and first responders must continue to learn new skills to keep pace with all the high-tech changes.

SUMMARY

The ED is revolutionized by the inclusion of various advanced technologies such as online check-in, handheld devices, monitoring system, and telemedicine. Digital communication tools allow nurses and clinicians to uncover and track data in real time and adjust the course of treatment. Today, our emergency care system has multiple roles, not only to attend and manage urgent and lifesaving emergencies but also to maintain quality and safety standards, disaster preparedness, and public safety net care and to provide care even with increasing patient volume with limited resources. Implementation of advanced technologies in the ED is helpful in conducting the multiple roles of ED more efficiently. The newer technology has an acceptable wide range of roles and impact the ED within the larger hospital and healthcare system and can address wide range of issues.

MULTIPLE CHOICE QUESTIONS

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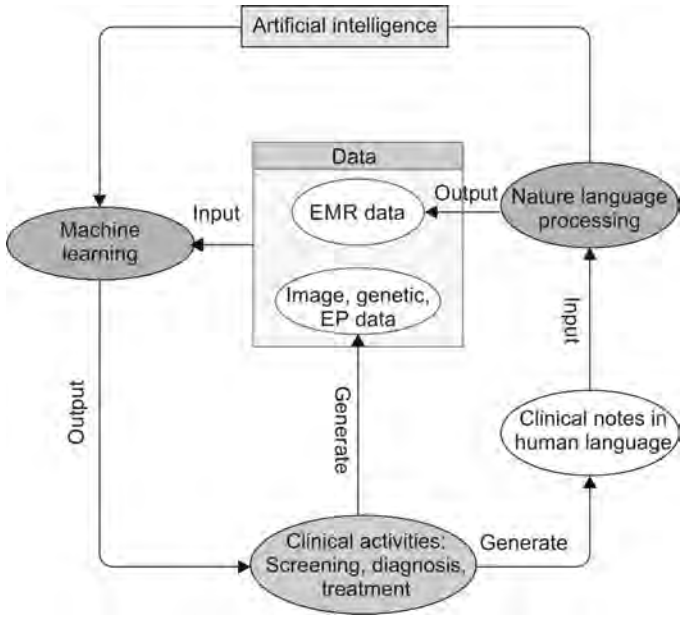
14
CHAPTER

Artificial Intelligence in Healthcare

Sandhya Shankar Pandey, Devendra Richhariya

INTRODUCTION

Over the last many years, some major changes have been occurring in healthcare. Technology has been involved in more precise, efficient, and impactful interventions in radiology and risk assessment, of chronic diseases and cancer, at exactly the right moment in a patient's care. Patients demand more from their providers, as payment structures evolve and the volume of available data continues to increase at a staggering rate. Artificial intelligence (AI) improves patient care. AI offers a number of advantages to diagnostics, care processes, treatment variability, and patient outcomes over traditional analytics and clinical decision-making techniques (**Flowchart 1**). More precise and accurate learning algorithms can be available as they interact with training data, allowing healthcare workers to gain unprecedented insights. Leading researchers and clinical faculty members foresee a major impact from AI in the various areas of the healthcare industry within the next decade and revolutionize the delivery and science of healthcare.



(EMR: electronic medical record; EP: electrophysiological)

FLOWCHART 1: Artificial intelligence in clinical data generation, machine learning, data analysis, and clinical decision-making.

MAPPING MIND AND MACHINE THROUGH BRAIN–COMPUTER INTERFACES

It is not a new idea to use computers for communication, but direct interface between technology and the human mind without the need for keyboards are being used nowadays and is a cutting-edge area of research and significant applications. Brain–computer interfaces (BCIs) backed by AI could restore patients' abilities to speak in neurological diseases and trauma to the nervous system and interact meaningfully with people and their environments. By using a BCI and AI, the neural activities of the affected hand can be decoded and allow that person to communicate the same way as normal people using a ubiquitous communication technology such as a tablet, computer, or phone. BCIs could drastically improve the quality of life for patients with amyotrophic lateral sclerosis (ALS), strokes, or locked-in syndrome as well as for those who experience spinal cord injuries.

ARTIFICIAL INTELLIGENCE IN DEVELOPING THE NEXT GENERATION OF RADIOLOGY TOOLS

Magnetic resonance imaging (MRI) machines, computed tomography (CT) scanners, and X-rays are noninvasive radiological techniques, helpful in diagnosing complex diseases. Physical tissue samples through biopsies are also required in many diagnostic processes for conclusion, which carry risks for infection. Experts predict that AI will enable the next generation of radiology tools that will replace the need for tissue samples with accurate and detailed results. AI allows clinicians to develop a better understanding about the aggressiveness of cancers and target treatments more appropriately. AI is helpful in knowing the phenotypes and genetic properties of tumors by creating image-based algorithms by enabling "virtual biopsies" and advancing the innovative field of radiomics.

ARTIFICIAL INTELLIGENCE IN EXPANDING HEALTHCARE IN DEVELOPING REGIONS

Developing nations around the world usually face shortages of trained healthcare providers, including ultrasound technicians and radiologists, which can significantly limit access to life-saving care. AI is now taking over some of the diagnostic duties that are typically allocated to humans, which could thus help mitigate the impacts of this severe deficit of qualified clinical staff. For example, chest X-rays with signs of tuberculosis can be screened by AI imaging tools, often achieving a level of accuracy comparable to humans. Technology could be deployed through an app available to providers in low-resource areas, reducing the need for a trained diagnostic radiologist on site. However, developers of the algorithm should be careful to account for the fact that different ethnic groups may have unique physiologies and environmental factors that will influence the presentation of the disease. It is very important to make sure that the data represents a diversity of disease presentations and populations and the algorithm should not be developed on the basis of a single population.

ARTIFICIAL INTELLIGENCE IN REDUCING THE BURDENS OF ELECTRONIC HEALTH RECORD

Digitalization of the healthcare industry by implementing electronic health record (EHR) has brought various changes including myriad problems associated with cognitive overload, endless documentation, and user burnout. Clinical documentation, order entry, and sorting consume most of the user's energy and time so EHR developers are now using AI to create more intuitive interfaces and automate some of the routine processes that consume less user time. Natural language processing (NLP), voice recognition, and dictation are helping to improve the clinical documentation process but have some limitations. AI may also help to prioritize tasks that truly require the clinician's attention, routine requests from the inbox, such as medication refills, and process result notifications.

ARTIFICIAL INTELLIGENCE AND ANTIBIOTIC RESISTANCE

Populations around the world are under the threat of antibiotic resistance due to overuse of these critical drugs, thus making changes in superbugs that no longer respond to treatments. Multidrug-resistant organisms can cause disaster in the hospital setting and community and claim thousands of lives every year. AI tools can help to identify infection patterns and highlight patients at risk before they begin to show symptoms and provide accurate and faster alerts for healthcare providers. Hospitals that are using EHR and creating mountain of data should use AI to the fullest potential, to create a smarter, faster clinical trial design to live up to the expectation for infection control and antibiotic resistance.

ARTIFICIAL INTELLIGENCE IN ANALYSIS OF PATHOLOGY IMAGES

Pathologists are one of the most significant sources of diagnostic data for healthcare providers across the spectrum of care delivery, and decisions are based on a pathology result. Right diagnosis depends on a more accurate pathology result and that is where digital pathology and AI has the opportunity to deliver. Digital pathology and AI can provide extremely large digital images which allow the providers to identify nuances that may escape the human eye. AI is now able to assess behavior of malignancy, rapid or slow progression, and patients can be treated based on an algorithm rather than clinical staging or the histopathologic grade. AI can also improve productivity by identifying features of interest in slides and directing us to the right thing to look at so that we can assess what is important and what is not. AI increases the efficiency of the pathologist and increases the value of the time he/she spends on each case.

ARTIFICIAL INTELLIGENCE IN MEDICAL DEVICES AND MACHINES

Smart devices are taking over the consumer environment, offering real-time video from the inside of the cars that can detect when the driver gets distracted. Smart devices are critical for monitoring patients in the intensive care unit (ICU) and in the healthcare environment, and inserting intelligent algorithms into these devices will ensure that patients receive care in a timely manner. Using AI devices can identify deterioration or give an alert for the development of complications which can significantly improve outcomes and may reduce costs related to hospital-acquired complications. AI can alert an ICU doctor to intervene early.

ADVANCING THE USE OF IMMUNOTHERAPY FOR CANCER TREATMENT

Immunotherapy is one of the most important modalities for cancer treatment. Patients may be able to beat stubborn tumors by using the body's own immune system, and oncologists still do not have a precise and reliable method for identifying which patients will benefit from this option; only a small number of patients respond to current immunotherapy options. AI with algorithms and data can analyze highly complex datasets and may be able to suggest new options for targeting therapies to an individual's unique genetic makeup.

ELECTRONIC HEALTH RECORD AS A RELIABLE RISK PREDICTOR

It is a challenge for providers and developers to extract and analyze EHR data in an accurate, timely, and reliable manner. It is very difficult to understand exactly how to engage EHR in meaningful risk stratification, predictive analytics, and clinical decision support as it is all dependent on data quality and integrity issues. A mishmash of data formats, structured

and unstructured inputs, and incomplete records will make the analysis complicated. Many successful risk scoring and stratification tools have been developed through EHR analysis by researchers by connecting deep learning techniques. But these algorithms should truly improve clinical care and should be devoid of any hidden biases in the data.

ARTIFICIAL INTELLIGENCE IN MONITORING HEALTH THROUGH WEARABLES AND PERSONAL DEVICES

Almost all consumers now have access to smartphones with sensors that can collect valuable data about their health with step trackers that can track a heartbeat around the clock. AI plays a significant role in extracting, collecting, and analyzing this data through apps and other home monitoring devices and offer a unique perspective into individual and population health.

MAKING SMARTPHONE SELFIES INTO POWERFUL DIAGNOSTIC TOOLS

The quality of smartphone cameras is getting better day by day and can produce images that are viable for dermatology and ophthalmology analyses by AI algorithms. Various tools have been developed by researchers that identify developmental diseases by analyzing the images of a child's face. Smartphone images will be an important supplement to clinical quality imaging, especially in underserved populations or developing nations. Most of the population are equipped with pocket-sized, powerful devices that have a lot of different built-in sensors; a craniofacial abnormality can be detected by evaluating a child's jawline, eye, and nose placement. In areas with a shortage of specialists, smartphone images of eyes, skin lesions, wounds, infections, and medications can be collected and transmitted to specialists which will be helpful in reducing the time-to-diagnosis for certain complaints.

BEDSIDE CLINICAL DECISION-MAKING WITH ARTIFICIAL INTELLIGENCE

Artificial intelligence by powering predictive analytics and clinical decision support tools can provide earlier warnings for conditions such as seizures or sepsis, which often require intensive analysis of highly complex datasets. AI with various algorithms in it allows healthcare to develop the processes that will enable proactive, predictive interventions. Clinical support decisions by learning machine can also be helpful in deciding whether to continue care for critically ill patients, such as a patient with coma after cardiac arrest by analysis of electroencephalogram (EEG). AI algorithms are helpful in risk scoring and early alert, clinical decision support. AI provides a new era of clinical quality and exciting breakthroughs in patient care.

ADMINISTRATIVE APPLICATIONS OF ARTIFICIAL INTELLIGENCE

There are a number of administrative applications of AI that provide substantial efficiencies in healthcare. As an administrative application, AI can be used in claims processing, clinical documentation, revenue cycle management, and medical records management. The use of AI in hospital administration settings is somewhat less appealing as compared to patient care.

SUMMARY

Artificial intelligence has already arrived in healthcare. Traditional healthcare providers are now opting for technologies equipped with algorithm with AI. AI promises great benefits to patients but it equally presents risks to patient safety, health equity, and data security. The active role of the doctors and those from across the wider healthcare is to reasonably ensure that the benefits are maximized and the risks are minimized.

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15
CHAPTER

Use of Simulation-based Education in Emergency Medicine

Asit Misra, Brad Gable

INTRODUCTION

Simulation is defined as "a technique that creates a situation or environment to allow persons to experience a representation of a real event for the purpose of practice, learning, evaluation, testing or to gain an understanding of systems or human actions" as per the healthcare simulation dictionary. Simulation-based education (SBE) became popular in emergency medicine (EM) in the last 20–25 years. SBE is one of the key components of the EM training curriculum in many countries, including the United States, Canada, the United Kingdom, and Australia. "The validity or value of simulation education and training has never been proven in any other industry." One of the forefathers of SBE, Dr David Gaba, once stated, "No industry in which human lives depend on the skilled performance of responsible operators has waited for the unequivocal proof of the benefit of simulation before embracing it."

Simulation-based education plays a vital role in developing competencies in the EM trainees by providing them opportunities to become proficient in high-frequency, high-risk situations and procedures as well as low-frequency, high-risk circumstances. This type of education also provides the trainees with a conducive and safe learning environment to practice and learn from their mistakes. SBE in recent years has proved to enhance not only the technical skills of the trainees but also the nontechnical skills of the trainees such as interprofessional teamwork, crisis resource management, communication, systems-based practice, and professionalism.

HISTORY OF SIMULATION

One could argue that simulation is as old as a primitive man. The trial-and-error method of learning is nothing more than a series of simulated events. However, modern medical simulation harkens to the middle ages when animal models were used for education. Examples of anatomic models and trainers span nearly all continents and cultures. In 1700s France, Angélique Marguerite Le Boursier du Coudray utilized a cloth birthing simulator to train midwives and surgeons. Modern medical simulation can trace its roots to anesthesia education in the 1970s. The first computerized full-body human simulator known as "Sim One" was developed by Drs Denson and Abrahamson in 1967. A year later, in 1968, Dr Michael Gordon unveiled the cardiopulmonary patient simulator "Harvey." Since that time, SBE has expanded into nearly all specialties and across the spectrum of allied health professions.

EDUCATIONAL THEORY

Simulation-based education in medicine is supported by various pedagogical and andragogical approaches as well as by learning theories ranging from the adult learning theory, constructivism, experiential learning model of Kolb, Dewey's experiential learning theory, deliberate practice, and mastery learning. A combination of these approaches and learning theories helps develop a learner's knowledge and skills needed to successfully perform and practice medicine.

Adult Learning Theory

Adult learners are self-directed and self-motivated. They want to know why they need to learn something, and they tend to relate the learning to their life experiences. The principles of adult learning, as described by Knowles are as follows:

- Adults like to be an active participant in the learning process.
- They have both intrinsic and extrinsic motivation to learn.
- They want to know the relevancy of the teaching with their job.
- They are self-directed and goal-oriented.
- They prefer a safe and respectful learning environment.
- They expect feedback on their performance in order to improve themselves.
- Adults prefer personal and informal learning environments.

Constructivism

Using the constructivist approach in SBE helps the learners to keep up with the changing nature of the information. It also prepares them to handle any uncertain or undefined challenges that they can face in real-life scenarios. As per Conner, constructivism is suitable for teaching something that is new (technology), sophisticated, and where time is

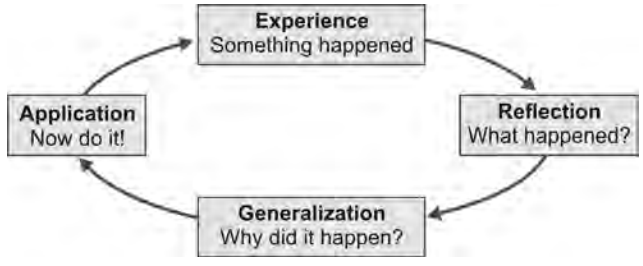
of the essence. The constructivist approach also helps the learners work around their understanding of the subject and to discover new ways to deal with the situation in reality, e.g., crisis resource management.

Kolb's Experiential Learning Model

This provides a basic structure for any SBE session by providing learning strategies applicable to adult learners. In this model, the learner(s) receives a specific experience in a simulation session followed by their reflection on this experience. This reflection helps the learners to develop some concepts and make suitable changes to improve. Later on, the learner(s) apply these new concepts or generalizations and test them in new or similar simulation scenarios or real-life situations. This continues in a cyclical process (**Flowchart 1**).

Dewey's Experiential Learning Theory

Previous research has shown that experiential learning promotes various important competency domains required for a healthcare provider to succeed, such as decision-making, critical thinking, problem-solving, teamwork, and system-based practice. One can define experiential learning as education gained by experiencing, interacting, and reacting to certain situations (scenarios). Dewey's experiential learning theory supports the theoretical claim that simulation-based medical education (SBME) can provide a platform for adult learners to build their knowledge base by experiencing new information and relating it to their own experiences. The learners can also apply their knowledge in different new situations or scenarios to experience different outcomes. SBE is helpful for learners to achieve higher levels of cognitive learning outcomes as per revised Bloom's taxonomy (analyze, define, create, evaluate) (**Fig. 1**).



FLOWCHART 1: Simple illustration of Kolb's experiential learning cycle.

Deliberate Practice

Deliberate practice is a term commonly used in SBE and is based on the principles of behaviorist learning theory. Ericsson and his team first used this term to describe the achievement of skills by the learners in different professions, including healthcare. They explained how repetitive practice with feedback on performance could improve a learner's skills to achieve set goals in various conditions. Deliberate practice is crucial in healthcare professionals' education, especially for those who are expected to perform in a highly stressful or demanding situation.

Mastery Learning

The origin of mastery learning can be linked to Carroll's model of school learning. McGaghie and colleagues contributed to developing the simulation-based model of mastery learning. The model is founded on three popular educational theories: (1) Constructivist, (2) Behavioral, and (3) Social learning. In simple words, mastery learning focuses on the achievement of a learner's competency to meet the set educational outcome (result) rather than how much time is needed to reach the same. For example, during a simulation-based educational session, learners, after practicing a skill while receiving feedback from content experts, are expected to perform the same skill to demonstrate their competency. Learners can practice alone and under supervision until they can demonstrate their mastery and competency in that skill. To that end, using mastery learning theory, some learners may achieve competency before traditional time-based milestones, while others may take longer.

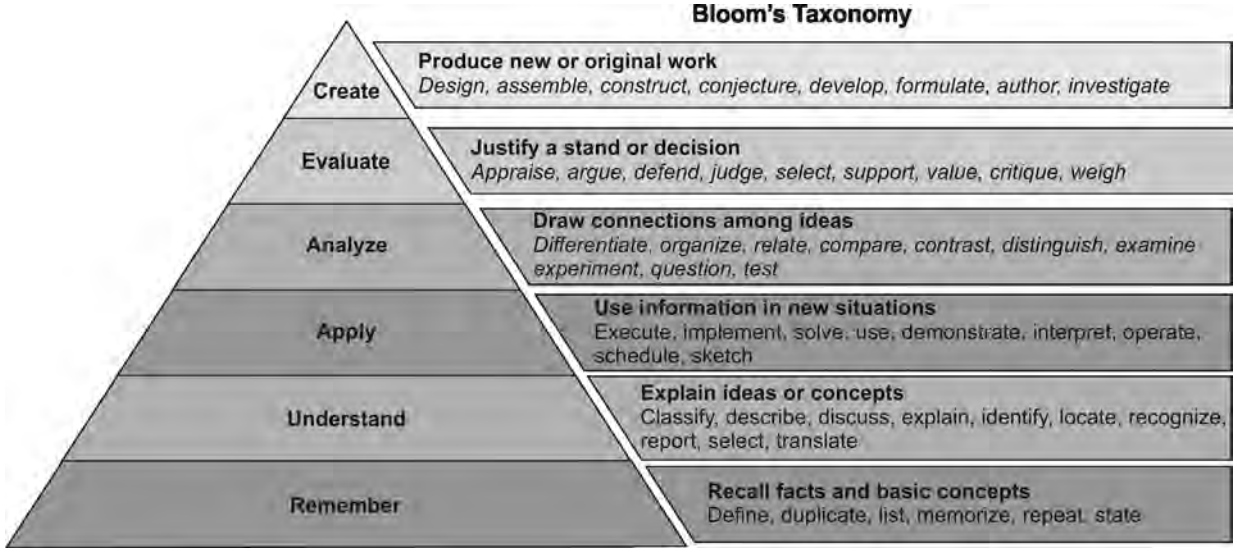

Bloom's Taxonomy
Create
Produce new or original work
Design, assemble, construct, conjecture, develop, formulate, author, investigate
Evaluate
Justify a stand or decision
Appraise, argue, defend, judge, select, support, value, critique, weigh
Analyze
Draw connections among ideas
Differentiate, organize, relate, compare, contrast, distinguish, examine
experiment, question, test
Apply
Use information in new situations
Execute, implement, solve, use, demonstrate, interpret, operate,
schedule, sketch
Understand
Explain ideas or concepts
Classify, describe, discuss, explain, identify, locate, recognize,
report, select, translate
Remember
Recall facts and basic concepts
Define, duplicate, list, memorize, repeat, state

FIG. 1: Bloom's revised taxonomy and descriptions of each category applicable to simulation-based medical education.
Source: Vanderbilt University Center for Learning, CC BY 2.0.

SIMULATION TYPES AND METHODS

Educators must choose the appropriate type of simulation and modalities of simulation according to their learners' training needs and the desired educational outcomes. Simulation sessions can be conducted in situ (at the place of work), in a simulation center (or a designated simulation space), or in a mobile environment (simulation vehicle).

The simulation was previously described in five categories according to a scheme proposed by Dr David Gaba. These designations are: (1) Verbal, (2) Standardized patients, (3) Part-task trainers, (4) Computer (virtual) patients, and (5) Electronic patients. With the exponential growth of technology in recent years, these categories would likely need to be expanded and further categorized. Below is an adapted list of Dr Gaba's categories:

- *Verbal*: Oral boards, tabletop simulations, communication skills
- *Standardized patients*: Objective structured clinical examination, communication skills
- *Part-task trainer*: Procedure skill training
- *High fidelity mannequins*: Full-body mannequins, mock code training
- *Tissue models (animal and cadaveric)*: Procedure training
- *Screen-based*:
  - *Augmented and virtual reality*: Phone-based, head-mounted
  - *Applications*: Downloaded to a phone
  - *Serious games*: Avatar simulations
  - *Telesimulation*: Learners/instructors participate remotely from the simulation

In addition to the acquisition of knowledge, simulation in healthcare can be used for other purposes such as process testing, identification of latent safety threats, verification of systems-based practices, equipment validation, and research and development.

Educators must consider providing appropriate realism to meet the learning objectives and suspend the learners' disbelief. Realism is defined as an ability to represent a situation that is observed during real-life conditions. Another term that is used along with realism in simulation is fidelity. Fidelity is defined as the degree of realism; the higher the fidelity, the higher the realism. However, a high-fidelity simulation session may not result in higher learning outcomes. There should be a relationship between simulation fidelity and its perceived value of the education session (**Fig. 2**). Although realism is important, it does not necessarily mean increased cost. Low-cost simulators and low-fidelity simulations can also improve the learner's knowledge, confidence, and skills. This is especially true when learning high-value procedures and concepts.

PLANNING A SIMULATION CASE

Simulation case development begins with the identification of a knowledge gap or a discrete learning objective. The number of objectives should be limited to allow learners to fully explore the objective and determine how the knowledge they gain will be applied to their practice. After the objectives are defined, the simulation faculty will then determine the following before writing the case:

- Location where the simulation will take place
- Type of simulation to be used

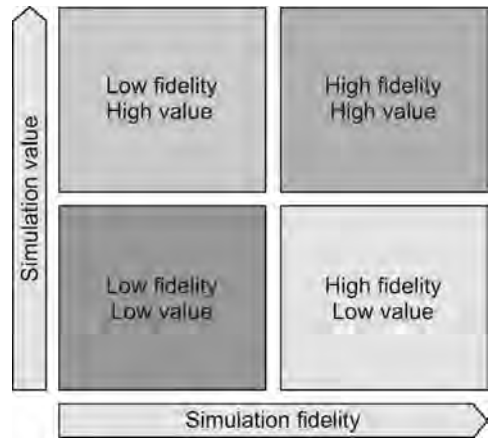


FIG. 2: Relationship between simulation fidelity and value.

- Number of learners
- Number of subject matter experts and debriefing faculty required

Once these are defined, the simulation faculty can begin writing the case. The case should be written in such a way that learners from various levels of expertise will have varied outcomes based on their interventions. Using the Dreyfus model of expertise, most residents will fall into the advanced beginner, competent, and proficient stages.

When writing a case, faculty members are asked to balance the signal-to-noise ratio. The signal-to-noise ratio is the balance of giving the learners the information needed to successfully manage the case while managing distracting or irrelevant information. Novice learners require a high signal-to-noise ratio as their educational focus should be on knowledge and skill acquisition. For example, a post-graduate year (PGY) 1 resident managing a patient in cardiac arrest should be given information such as the patient's oxygenation and should have staff provide clear closed-loop communication. As learners become more advanced, the amount of "noise" present in simulations can increase. Senior residents managing a patient in cardiac arrest may have to deal with "noise" such as updating the patient's family members, communicating with staff who are not using closed-loop communication, and calling consultants.

The single most crucial aspect of SBE is debriefing. This is a skill that, like all others, must be learned, coached, and continually practiced. In order for a debriefing to be successful, a prebrief is an essential element. It is within the prebrief where psychological safety and debriefing rules are established. In addition, debriefers may share their debriefing stance or "basic assumption." A number of debriefing models and approaches have been described. However, one of the most commonly referenced is debriefing with good judgment. Allowing learners the opportunity to reflect on their performance in a safe learning environment is paramount. Through this process, learners can reinforce the knowledge skills and attitudes that should be fostered while beginning to change those that require correction. Not only must this be facilitated by a trained debriefer, but adequate time must also be allotted for the debriefing. A ratio of 2–4:1 can be used when determining the amount of time necessary for debriefing relative to the time the simulation case requires. Therefore, a 10-minute simulation would require a 20–40-minute debriefing.

USE OF SIMULATION IN EMERGENCY MEDICINE

Evidence of simulation use to deliver training to EM trainees, physicians, and other staff working in the EM department can be found from early publications on its usage. Chapman et al. described how they used simulation to teach emergency thoracotomy to medical students, resident trainees, and physicians working in the emergency department and compared their performance by using assessments on written, computer, and animal models. However, there are other evidences of the early use of simulation in teaching EM department administration. The increase in adaptation and use of simulation in EM is seen from the year 2000 onward based on the number of publications reporting it. A publication on the rapid growth in the use of SBE in EM reported an increase of 62% between 2003 and 2008 in the United States.

Some uses of SBE in EM are as follows:

- Procedural skills training
- Mock codes and code blue response for decision-making and critical thinking, and resuscitation skills
- Human factors and crisis resource management (CRM) training to improve problem-solving skills
- Nontechnical skills training to address professionalism, interprofessional collaboration, team dynamics, communication, and ethics
- Overcrowding and patient flow management and multitasking
- Testing of process and system to identify errors
- Providing a safe environment for learners to apply clinical knowledge and practice skills for low- to high-risk scenarios and skills
- Assessment of trainees for the achievement of competency for skills and knowledge

Simulation-based education in EM helps to improve the attitude, confidence, and comfort of the trainees. It advances knowledge and skills, changes in behavior, and application of the skills in the workplace. The simulation also helps to reduce medical errors and complications and to improve clinical and patient outcomes. Some studies have been able to demonstrate the impact of SBE on clinical outcomes (**Table 1**).

TABLE 1: Studies demonstrating the impact of simulation on clinical outcomes.

Study	*Conclusion*
Barsuk et al. (2009)	Reported that simulation-based training for insertion of a central venous catheter (CVC) resulted in a significant reduction of procedure-related complications (number of needle passes, fewer arterial punctures, fewer catheter adjustments, and higher success rates) for actual CVC insertion in the medical intensive care unit when compared to the traditionally trained group
Biese et al. (2011)	Reported that simulation-based training resulted in a significantly decreased rate of inappropriate urinary catheter placement
Sauter et al. (2016)	Demonstrated how simulation-based training of emergency medicine clinicians and trainees for providing procedural sedation for reducing a subluxated shoulder joint resulted in significantly faster time to the procedure
Theilen et al. (2017)	A simulation-based training of a pediatric emergency medicine team resulted in a significant reduction of PICU admissions and PICU bed days with a significantly reduced hospital mortality rate

(PICU: pediatric intensive care unit)

HOW TO INTEGRATE SIMULATION EDUCATION INTO AN EMERGENCY MEDICINE CURRICULUM

Initiating simulation into an already existing curriculum will not be a "none to all" proposition, but this approach has been described previously. More likely, adding SBE will involve gradually adopting simulation into the curriculum and, at a minimum, will involve all of the following: (1) Willingness of the program to trial SBE, (2) Faculty champion, and (3) Buy-in and feedback from the learners to meet their educational needs. The absence of any of these three features will likely result in the simulation program not being successful. The first step in a gradual integration of SBE is likely to be either a desire of the program to adopt this method of education or a passionate faculty member to serve as the simulation champion.

When determining the type of SBE to use when beginning the integration process, it is best likely to look at features unique to the program that might make this process easier. If there are identified knowledge gaps or "holes" in the curriculum that simulation could easily fill, these would be of the highest value to the learners and the program. These are likely to be low-frequency, high-risk procedures, cases, or situations. The simulation champion should also identify local resources that might allow for cheap and easy models of education. A few specific examples of local resources include:

- Butchers who discard animal parts that can be used for procedure training (tracheas for cricothyroidotomy, skin for suturing)
- Academic institutions with access to unique technology (computer systems for developing applications or serious games, augmented or virtual reality systems)
- Industries that can donate supplies or equipment (gels or polymers for making models, plastics for constructing task trainers)
- Other programs that may share simulation resources [obstetrics and gynecology (OB/Gyn) program to share a birthing simulator, surgery program to share a thoracostomy trainer]
- Expired materials from within the hospital and health system

There is a litany of publications describing low-cost models that have blueprints and descriptions available for free online. In addition, many simulation companies offer grants and discounts to many new simulation programs.

A wholly integrated simulation curriculum may present in several different ways. It may involve low-stakes formative education and/or the use of high-stakes summative evaluations to promote learners to the next level of training. Below, we describe just one sample curriculum that involves simulation

in two ways. First, new interns are on-boarded through a simulation "Bootcamp." Second, SBE is integrated into the rest of the existing curriculum and comprises half of all didactic time.

Bootcamp models for resident education have been previously described. A sample 1-month curriculum is presented in **Table 2**. This describes a once-weekly training for a total of four sessions, with each session consisting of 4 hours of education.

Simulation education can be woven into the existing curricular framework. Here, we outline a year-long simulation curriculum that was integrated into the existing systems-based didactic model (**Table 3**). Each month, the first and third weeks were dedicated to traditional didactics. The second week was assigned to procedure-based education. The fourth week was designated as the large-scale simulation case education. From year to year, the procedure education would remain constant while the simulation cases would change.

TABLE 2: Postgraduate year 1 orientation bootcamp. Each session comprises 4 hours of simulation education. Session 4 comprises four simulated cases with professional debriefing.

Session	*Skills*
1.	Airway management, needle decompression, tube thoracostomy
2.	Central line placement, defibrillator/pacer, arterial line placement
3.	Slit lamp, genitourinary exam, intraosseous access, ultrasound
4.	Simulation cases: i. ST-elevation myocardial infarction with ventricular tachycardia arrest ii. Septic shock from pneumonia with respiratory failure iii. Ruptured abdominal aortic aneurysm iv. Severely injured trauma patient (requiring intubation, chest tubes, central line placement)

TABLE 3: Sample systems-based simulation curriculum divided into procedure training and simulation cases.

Months	*Topics*	*Procedures*	*Simulations*
July	Otolaryngology/ Dermatology	HEENT nerve blocks, cricothyroidotomy, oropharyngeal foreign body removal, lip laceration repair, ear laceration repair, dental reimplantation, laceration repair	Pediatric airway foreign body, expanding neck hematoma, facial trauma requiring cricothyroidotomy
August	Cardiology	Defibrillation, cardioversion, transcutaneous pacing, temporary venous pacemaker, pericardiocentesis, cardiac ultrasound	Patent ductus arteriosus, heart block requiring pacing, pericardial effusion with obstructive shock
September	Gastrointestinal	Focused Assessment with Sonography in Trauma, nasogastric tube placement, orogastric tube placement, gastroesophageal varices balloon tamponade, anoscopy, paracentesis	Pediatric intussusception, variceal hemorrhage with hypovolemic shock, ischemic bowel
October	Endocrine/Obstetrics-gynecology	Vaginal delivery, shoulder dystocia, uterine tamponade	Pediatric DKA, shoulder dystocia, eclampsia
November	Renal/Genitourinary	Renal ultrasound, pelvic exam, pelvic ultrasound, Bartholin cyst drainage, urinary catheter placement, priapism management	Pediatric sepsis from urinary source, Fournier's gangrene, cocaine overdose with chest pain and priapism
December	Hematology/ Oncology	Massive transfusion, vascular access, catheter troubleshooting	Pediatric hemophilia with head injury, tumor lysis syndrome, disseminated intravascular coagulopathy
January	Toxicology/ Environmental	Warm/Rewarming techniques, cooling techniques, prehospital equipment review	Pediatric tricyclic overdose, carbon monoxide poisoning, and concomitant hypothermia, organophosphate exposure
February	Vascular/ Musculoskeletal	Vascular ultrasound, venous cutdown, musculoskeletal ultrasound, splinting, casting, musculoskeletal apparatuses, hematoma blocks, joint aspirations/injections	Pediatric trauma with compartment syndrome, tracheoinnominate fistula, trauma with multiple fractures requiring emergent splinting/reduction
March	Neurology/ Ophthalmology	Nerve ultrasonography, regional anesthesia, lumbar puncture, ventriculoperitoneal shunt management, slit-lamp exam, tonometry, lateral canthotomy	Pediatric acute flaccid myelitis, hyponatremia with status epilepticus, Guillain–Barre syndrome with respiratory failure
April	Infectious disease/ disaster medicine	Abscess and cellulitis ultrasound, tabletop disaster drills	Neonatal herpes simplex virus infection, tetanus with respiratory failure, *Trichinella spiralis* with altered mental status
May	Pulmonary	Lung ultrasound, needle decompression, tube thoracostomy, thoracotomy, intubation, difficult airway	Pediatric bronchiolitis, tension pneumothorax, massive hemoptysis
June	Psychology/geriatrics	Delivering bad news, evaluating the agitated patient	Pediatric suicidal patient, altered mental status with basilar artery stroke, geriatric delirium

(DKA: diabetic ketoacidosis; HEENT: head, eyes, ears, nose, and throat)

SUMMARY

While SBE has existed as long as EM itself, recent advances in technology have made it more accessible. However, successful simulation education must still be rooted in sound educational theory and curricular design. SBE spans a wide spectrum of modalities with varying cost, fidelity, and realism. However, SBE has been demonstrated to be well received by faculty and learners and improves medical knowledge, skills, and attitudes. In addition, learners apply the knowledge they gain through simulation in clinical situations. This leads to improvements in systems-based practice, quality and safety, teamwork, communication, and crisis resource management. SBE when properly applied, has demonstrated improved patient-centered outcomes.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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16 CHAPTER

Overcrowding Management in Emergency Department

MI Nizami, Ashima Sharma

INTRODUCTION

Emergency department (ED) crowding is one of the leading problems in healthcare across the globe. Evidence shows a tremendous increase in the utilization of emergency services in the recent past. However, the capacity of the emergency healthcare system has not been well developed to respond to such high demands. This condition leads to crowding of the EDs, which in turn impose public health challenges related to the quality of healthcare and outcomes. In addition, the ED might be the only source of healthcare services to people, especially in rural areas. Delivery of timely care is compromised in crowded emergencies. Delay in initiating antibiotics, analgesia, or thrombolysis are all well established in crowded EDs. Crowding might also lead to the violations of the norms and service provision standards, which in turn result in patients leaving the facility without getting appropriate care.

A crowded ED creates problems for the prehospital services as the ambulance crew is unable to unload their patient. This reduces their resilience and capacity to respond to calls. Patients harmed by crowding in an ED continue to suffer even after getting admitted. There is evidence to suggest that patients admitted through crowded EDs have longer hospital stays. Patients are also more likely to be admitted when the ED is crowded because the department's ability to safely discharge patients is compromised. Crowding also harms the hospital personnel which manifests as absenteeism, staff sickness, and burnout. This results in junior staff delivering an increasingly busy and inefficient service. Resident and student education is also compromised and further recruitments into the department are hampered. **Box 1** summarizes the ill effects of overcrowding in ED.

BOX 1: Potential harms of ED overcrowding.

Effects on patients:

- Delayed assessment
- Delay in the initiation of treatment
- Increased walkouts due to perceived ED length of stay (LOS)
- Patients and attendant's frustration and fear
- Low patient satisfaction
- Poor pain relief and morbidity
- Frequent readmissions
- Prolonged hospitalization
- High cost of treatment
- Medication errors and adverse events
- High mortality

Healthcare delivery system process:

- Diversion of ambulance
- High workload
- ED personnel frustration
- Delayed service provision and decision-making
- Shorter time to investigate patients' condition
- Discharging patients with high-risk clinical features
- Prolonged time to transfer outpatients
- High patient readmission rate
- Decreased admission of patients due to crowding
- Overutilization of diagnostic imaging and laboratory tests
- Poor infection prevention and control measures
- Low compliance with standards of care
- Compromised quality of care
- ED fights and medicolegal cases

(ED: emergency department)

DEFINITION OF OVERCROWDING

Crowding is a situation when an identified need for emergency healthcare services exceeds the available resources to provide emergency care to patients within an appropriate time frame. There is not much consensus on the definition of overcrowding despite a large literature describing the consequences of crowding. Defining crowding is important, as it allows measurement, planning subsequent research, and policy evaluation. Access block refers to the delay caused for patients in gaining access to in-patient beds after being admitted. It is almost always associated with overcrowding. There are a number of crowding scales described in the literature, but many are limited by being country specific or lack a gold standard in development or are incompletely validated (**Table 1**).

TABLE 1: Scores for assessing ED overcrowding.

Scale	*Calculation*	*Score*	*Remarks*
ED occupancy rate*	$\frac{\text{Total patients}}{BT}$	ED occupancy rate above 1.0 indicates that there are more ED patients than treatment bays	• Total patients = Number of patients in the ED including those in the waiting room, boarding, hallway, and chairs • B_T = Total number of licensed treatment bays including fast track or observation units, excluding hallway locations
Emergency department crowding score (EDCS)†	• Number of attending emergency physicians • Number of staffed ED beds • Number of critical care patients • Number of total ED patients • Number of staffed hospital beds • Hospital occupancy rate	EDCS score >65 was found to be predictive of both ambulance diversion and the number of patients who leave without being seen by a physician	Generates an output score between 0 and 100
Emergency department work index (EDWIN)‡	$\frac{\sum n_i t_i}{N_a (B_T - B_A)}$	<0–1.5: Active but manageable 1.5–2.0: VERY BUSY but not overcrowded >2.0: EXTREMELY BUSY severely overcrowded	n_i = Number of patients in ED in triage category i t_i = Triage category (ordinal scale 1–5, 5 being most acute) N_a = Number of attending physicians on duty at a given time B_T = Total number of beds, or treatment bays B_A = Number of admitted patients (boarders) in the ED
Real-time emergency analysis of demand indicator (READI)§ scores	$DV = (BR + PR) \times AR$	• DV >7 indicates overcrowding, and further assessment is recommended • BR >1 indicates overcrowding • PR >1.5 indicates an understaffed ED • AR close to 4 indicates a severe burden of illness	$BR = \frac{\text{(total ED patients + predicted arrivals − predicted departures)}}{\text{ED spaces}}$ $PR = \frac{\text{Arrivals per hour}}{\sum\text{PPH for each physician}}$ $AR = \frac{\sum\text{(triage category) (patients at each category)}}{\text{Number of patients}}$

Continued

Continued

Scale	*Calculation*	*Score*	*Remarks*
National emergency department overcrowding study (NEDOCS)‖	$-20 + 85.8 \times \frac{\text{Total patients}}{\text{ED beds}} + 600 \times \frac{\text{Admits}}{\text{Hospital beds}}$ + 13.4 (ventilators) + 0.93 (longest admit) + 5.64 (last bed time)	• 0–50: Normal • 51–100: Busy • 101–140: Overcrowded • 141–180: Severe • >180: Disaster	• Total patients = Total patients in the ED, including those in the waiting room, fast track, or observation areas • ED beds = Total ED beds, including those in hallways • Admits = Total number of boarders/admitted patients in the ED at the time the score is calculated • Hospital beds = Total number of hospital beds • Ventilators = Number of patients in the ED on ventilators • Longest admit = The longest patient boarding time (in hours) at which the score is calculated • Last bed time = The time (in hours) from arrival to bed for the last patient assigned to a bed
ED work score¶	$3.23 \times \frac{P_{wait}}{B_T} + 0.097 \times \frac{\sum n_i t_i}{N_n} + 10.92 \times \frac{B_A}{B_T}$	Using the threshold work score = 4.77, predict the decision for ambulance diversion with 86% sensitivity and 80% specificity	P_{wait} = Number of patients in the waiting room B_T = Total number of beds or treatment bays available in the ED n_i = Number of patients present in the ED in triage category i t_i = Triage category (ordinal scale 1–5, 5 being most acute) N_n = Number of nurses on duty B_A = Number of admitted patients (boarders) in the ED

* Suggested to be the simplest and overall best indicator of crowding.

† Exact calculations for the EDCS are unclear. However, three variables were identified that independently predicted physician and nurse ratings of EDC: (1) the number of boarders, (2) the total number of ED patients, and (3) the number of critical care ED patients.

‡ The triage system used was an inverted emergency severity index (ESI).

§ Demand value (DV) provides an overall measure of demand based on current calculations of the three ratios.

i. Bed ratio (BR) assesses the demand per treatment space.

ii. Provider ratio (PR) calculates how many patients can be seen by the physician providers based on the average number of patients seen per hour (PPH) by each physician.

iii. Acuity ratio (AR) measures the relative burden of illness by averaging the triage categories of all patients in the ED.

‖ Generates an output score between 0 and 200; however, higher scores are possible.

¶ Sometimes referred to as the Boston ED work score. The triage system used was an inverted ESI.

(ED: emergency department; PPH: patients seen per hour)

CAUSES OF OVERCROWDING

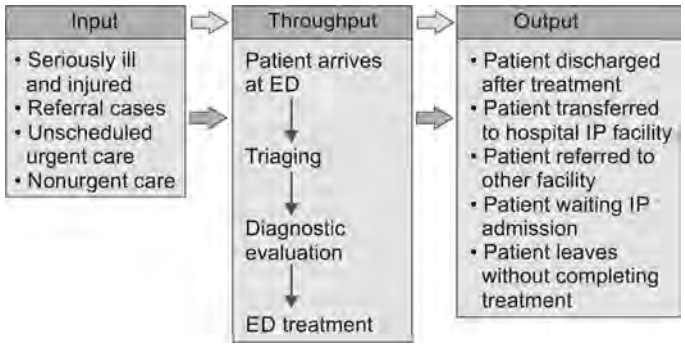
Crowding is caused by multiple factors. These can be best understood in terms of input, throughput, and output. Asplin's conceptual model illustrates the stages that can lead to ED crowding (**Flowchart 1**). Input factors include not only the volume but also the acuity and type of patients. The volume of patients attending EDs has increased dramatically over the last 20 years. The reasons for this are not well understood. With increased longevity, elderly people are requiring disproportionate care.[7] Patients with mental illness and chronically ill patients require extensive ED care. A small increase in any of these groups can have an add-on effect. Input problems do not cause crowding if the rest of the admission and discharge process works well.

Throughput factors refer to activities within the ED that can hinder patient flow. EDs are extremely complex systems and almost any activity can lead to crowding. Poorly designed EDs do not support patient flow and contribute to crowding. A linearly designed department with adequate corridor spacing is probably most efficient. Merely increasing cubicle spaces do not reduce crowding, if processes within the department and in the main hospital are not improved. Delay in diagnostic imaging and laboratory services also contributes to crowding. Inadequate number of medical and nursing staff is a major contributing factor in many underdeveloped healthcare setups. Increasingly stringent emergency protocols and extended care have further increased the workload of EDs. Analysis of the separate components of time a patient spends in the ED has shown that waiting comprises 51–63% of the total turnaround time. Major components are the time taken for radiological investigations, waiting time for the physician's first consultation, and waiting time for blood work.

Output factors are the main cause of ED crowding. Lack of inpatient beds is the single most important cause of crowding. Shortage of critical care beds leads to high acuity patients remaining in the ED. Worldwide, the trend has been to reduce inpatient bed capacity. There is a strong perception that hospitals prioritize more lucrative elective work over emergency admissions.

INTERVENTIONS

Interventions can again be grouped into input, throughput, and output. The strongest evidence comes from throughput solutions. It is important to identify the main causes of crowding in individual EDs. Failure to take this logical step leads to effort being expended on unnecessary interventions.



(ED: emergency department; IP: inpatient)

FLOWCHART 1: Flow diagram of patients through ED.

Input Strategies

Reducing inputs is attractive to administrators and policymakers; however, the evidence of effect is very weak. A substantial number of patients attending the ED can be adequately managed in an outpatient service. However, efforts on directing these patients away once they have arrived in the ED are rarely worthwhile. The effects of limiting the input of patients have not been shown to significantly affect overcrowding and diversion. Developing alternative sources of care away from EDs, such as walk-in centers, has probably met a previously unmet need. The concept of fast-track service evolved from the fact that most of the crowding in ED may actually involve low acuity patients such as those with minor injuries and illnesses. Therefore, fast-track services for such patients may be an important front-end operational strategy to relieve congestion. Few healthcare systems have incorporated emergency nursing practitioners with proper training for dealing with minor ailments in ED.

Throughput Strategies

There are a variety of throughput interventions to reduce crowding in EDs. Ensuring that patients are seen early by a trained emergency physician is helpful. Ensuring adequate training of the nursing staff and the emergency medical technicians cuts down the waiting time. However, these interventions help in lower acuity patients, but not in the critically ill ones. Triaging patients into broad acuity categories and managing them through separate processes can reduce the overall waiting time. Monitoring key bottlenecks, such as time for laboratory and radiology results to become available, is useful. Point-of-care testing is a rapidly evolving innovation which fastens clinical decision-making. Streamlining transfer policies and developing ambulatory care pathways to avoid admissions are important tools for effective disposition of cases in the ED. Appointing nonmedical supportive staff in the form of floor managers and counselors has proved to be a useful strategy in managing the issues of crowding.

Output Strategies

The biggest contribution to ED crowding and ambulance diversion is the inability to get admitted patients, especially those who are critically ill, out of the ED. No significant success will occur without hospital leadership making this a priority. Although ED admissions in many centers are looked at as less profitable, the financial benefit of ED admissions is significant. The possible causes of access block include:

- Disinclination for clinicians to discharge patients.
- Inefficient flow in the discharge process.
- Genuinely insufficient bed capacity.

Holding units are clinical decision units or observation units within the ED. Studies suggest that such units are able to alleviate access block and ED overcrowding.[13] They also contribute to the reduction in hospitalization and improvements in ambulatory care. Observation units have shown to play a significant role in selected clinical conditions, such as acute exacerbation of heart failure[14] and acute pyelonephritis.[15]

There is some evidence to support the role of *social workers* in helping the early discharge of elderly patients and reducing the readmission rate within 6–12 months without an apparent increase in mortality. Discharge lounges are areas

in the hospital for patients to wait until transport and other administrative discharge arrangements are completed. A study found that after the introduction of such lounges, there can be substantial savings in bed hours. Reverse triaging is a relatively new concept based on selecting patients who can be discharged safely with little risk of serious consequences. It has a high relevance in the event of a vast surge in demand for hospital beds.

SUMMARY

Administrators need to consider ED crowding as an unintended consequence of improper policies or their inefficient implementation. A systematic team effort focusing on the local issues in the background of globally acclaimed strategies can help in overcoming the issues of crowding in EDs.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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17
CHAPTER

Difficult Patient and Situations

AN Venkatesh

INTRODUCTION

One of the important aspects of the medical profession is interaction with patients and their families. This is one aspect of our care toward our patient which is present irrespective of specialty. But in our medical training, we hardly receive any formal training toward dealing with difficult patients. Though most of the interactions with patients and medical professionals are fruitful and healthy, there are about 15% of them which are described as being difficult by physicians. This number has progressively increased over the years and the current percentage of difficult interactions is much more than 15%. With ever-increasing incidents of complaints about medical professionals and abuse of medical professionals across the globe, it is imperative we look at this aspect of patient care—dealing with difficult patients.

DIFFICULT SITUATIONS

As with many of the difficult situations, patients become difficult patients as a result of culmination of various events during the course of their attendance or consultation. It is most of the times multifactorial (**Fig. 1**). The causative factors maybe as follows:

- Patients—unmet expectations, pain and distress, cry for help, fear of unknown.
- Physicians—work pressure, language difficulties, lack of communication.
- Situation/Circumstances—feeling not care for, concern of resources.

Patients come to healthcare facility seeking help and guidance for their discomfort. It has to be recognized that the patient's condition is an emergency to them. One of the early signs of patients becoming difficult would be anxiety, uncooperative, restlessness, demanding, and verbally abusive. Patients tend to become difficult patients over the course of their journey in the system. It is an important skill to identify early signs and try to resolve their grievance. Along with good diagnostic skills, it is equally important to have good communication skills. Having good and effective communication with patients is one of the most effective steps in managing a patient's expectations and addressing his/her anxiety. This would also help gain the patients' trust and confidence. A breakdown in communication between the physician and patient, if not identified and addressed appropriately, can easily snowball into a disturbing situation. One of the harsh examples of these is the recent increase in violence on healthcare professionals.

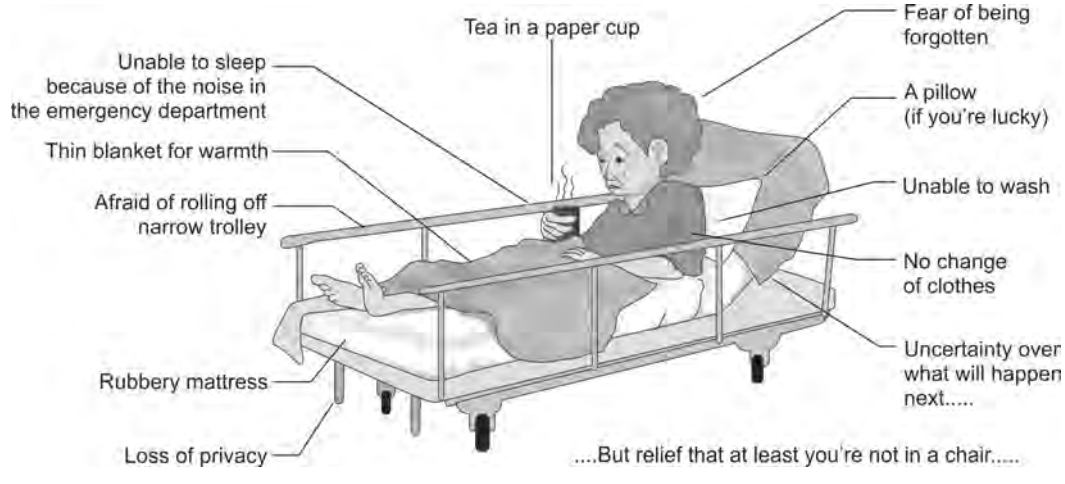
Tea in a paper cup
Fear of being forgotten
Unable to sleep because of the noise in the emergency department
A pillow (if you're lucky)
Thin blanket for warmth
Unable to wash
Afraid of rolling off narrow trolley
No change of clothes
Uncertainty over what will happen next.....
Rubbery mattress
Loss of privacy
....But relief that at least you're not in a chair.....

FIG. 1: Difficult situation and circumstances make a difficult patient.

TYPES OF DIFFICULT PATIENT

Although there is no classification of difficult patients, they can be broadly grouped into four types (**Fig. 2**):

1. Resistant patient
2. Manipulative patients
3. Patients who somatize
4. Frequent flyers

Resistant patients: These patients present to be angry or defensive. A change in behavioral pattern of becoming more irritable and responding aggressively can be noticed. With these patients, avoid conflict, modulate your interaction, have a chaperone, and keep in mind your personal triggers. If at any point you feel threatened, try to get away slowly and get help.

Manipulative patients: These patients tend to use rage and threats of legal action in an attempt to get what they desire. It is important to be nonjudgmental during interacting with these patients. If in doubt, seek advice from a senior colleague.

Patients who somatize: These patients often present with a plethora of vague symptoms with frequent exaggerated severity. They tend to be "doctor shoppers." Inexperienced clinicians are at an increased risk in dealing with such patients. They may fall prey to prejudice and tend to overlook a genuine illness. It would be advisable to be safe than sorry.

Frequent flyers: These patients pose a unique challenge in themselves. Empathy is vital with these patients. Identifying these patients and having an agreed plan in discussion with the primary treating team for these patients can ease the interaction with these patients. Keeping the patients informed of these plans and involving them in discussions help better acceptance.

Clinicians in specialties, such as emergency department, have to face patients with increased demands and expectations. It is important that clinicians and other healthcare professionals having increased patient interaction understand and learn to identify early signs of patients becoming disturbed. Some of the early signs could be patients or attendants asking questions frequently and patients getting angry for no apparent reason.

CLINICIANS AS CAUSATIVE FACTORS

Clinicians themselves may be contributing to patients becoming difficult patients. Some of the clinician characters which pose a risk in dealing with difficult patients and situation are as follows (**Fig. 3**):

- Being angry
- Being defensive
- Fatigued
- Stressed and strained

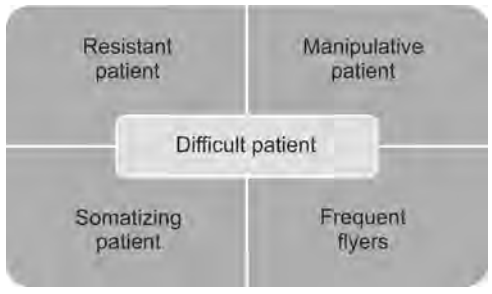

FIG. 2: Types of difficult patients.

When working in a team, it is important that any team members showing any of the above characters are given an opportunity to talk and seek help. It is also a key for the clinician to be aware of his/her own personal state. Dealing with difficult and challenging patients can be very demanding. One should never hesitate to ask for help. As noted by many clinicians, conflicts and stressful interactions are more common during busy periods and during the end of shifts rather than start of their shifts.

The situation in which the patient or family is can also have its influence in compounding the patient's dissatisfaction. It could be things which can be addressed such as overcrowding, making them feel neglected, or situations which can be readily addressed such as needing a glass of water.

There are many examples of difficult families and patients due to situations and circumstances. Clinicians may get a complaint from a concerned family member that the patient has been left unattended in a corner of the emergency department and he/she has been feeling cold and repeated requests for blankets have not got them anywhere. Working in busy shifts, it is easy to relate to such situations. It is easy to just say that we are all busy and we will get to it as soon as we can as we have more pressing patients to attend to athough this may be a factual statement. We can be better-caring clinicians if we get a blanket, apologize, and explain that department is busy. This not only will help us win back our patients' and families' trust and confidence, but also will help to get their cooperation in further care of their patient. We are now becoming aware of the increased number of incidences of patient–clinician discordance. Communication plays a vital role in this situation if your communication is healthy (**Fig. 4**).

HOW TO DEAL WITH DIFFICULT SITUATIONS?

Careful and considerate communication is one of the keys to avoid difficult patients. The importance of communication

FIG. 3: Characters of doctors which contribute to difficult patient.

FIG. 4: Make healthy communication.

cannot be overemphasized in dealing with difficult patients and families.

There is an increased need for guidance on dealing with difficult patients and families but with a varied spectrum of patients and factors involved, it has been a challenge to formulate a formal guideline. We can use certain basic understanding in interpersonal relationships and tailor it to the healthcare setting. When dealing with difficult patients and families, it would be a good idea to be empathic to patients and families. When patients or families are posing a challenge, it could be a culmination of various factors.

Listen to their concerns actively. It would be advisable to listen to concerns with open mind and ears. Let them speak freely; it would let them blow off steam. It would help them to start to settle and help work toward resolution of the difficult situation. Have a clear discussion and try to summarize their concerns. Let them feel in control of the explanation. Remind yourself that the patients may not be upset with you and their response is not personal (**Fig. 5**).

Stay calm. It is much easier said than done. But keeping calm would go a long way in resolving the situation. Be professional and confident but be mindful not to show overconfidence which can come across as being arrogant and can worsen the situation. For example, when talking to a patient or family member who is screaming in the middle of the department, it may be wise to talk in a low measured tone, take them off the shop floor to a quiet room, and offer them to sit. This will give them time to reflect and also ensure smooth running of the department by diverting the distraction.

Ask questions. If required, ask relevant questions to get a better understanding to gather more information rather than being intrusive. Be mindful to be gentle and sensitive. Try not to show any sudden reactions. Take time and answer any questions and do not make any defensive responses. Be gentle and caring. Try not to get too close, try not to touch them too early, and be attentive toward their body language. Apologize for their inconvenience. It will not make you guilty but it may present you to be sensitive. If you have identified any issues or concerns, address them straightaway. Keep the patient and family appraised on the progress. In an attempt to be helpful, be mindful not to make unrealistic promises or promises which you cannot keep up. Involve patients in any solutions, do not forget their families. As these situations at times turn violent, if you feel threatened or unsafe get help of security. Try to lead the conversation and resolve the situation. With the recent incidence of violence on healthcare professionals, it may be safe to get help when you feel unsafe.

Being involved in a stressful situation can be very draining and make you exhausted. Do not forget that you also need time and space to relax. Try and take time, sit out and have a drink, and let the stress of the event pass off before you move on.

ROLE OF EMERGENCY PHYSICIAN TO RESOLVE DIFFICULT SITUATIONS

There could be situation factors contributing to patients becoming difficult. With open access to the emergency department, patients tend to walk into the emergency department even for conditions which are not actual medical emergencies. It becomes important to have a robust triage system to attend to such patients and be able to communicate with patients appropriately, e.g., a person coming into a hospital for a fall from his bike last evening and having sustained grazed abrasion of his knees, wanting to get dressing done before he goes to his work. Although it is a priority for the patient, it has to be explained that he would be seen in a timely order depending on other acuity in the department where patients needing more urgent medical attention would be given priority. It is not uncommon to see patients and family members attending to emergency department seeking advice on a wide spectrum of issues. Some of them are unrelated to the emergency department, e.g., when will a consultant be available? And when they do not get a reply, they tend to get angry. We need to realize that their anger is a form of helplessness as they are not able to find the answer to their question.

It would be better if we could spend few minutes in having a sensible discussion with such patients rather than trying to answer a complaint from an irate patient (**Fig. 6**). In organizations where there is a need identified, it would be productive to have a patient's relations personnel to help in the smooth journey of the patient. As the saying goes "a stitch in time saves nine."

FIG. 5: Listen to the patient.

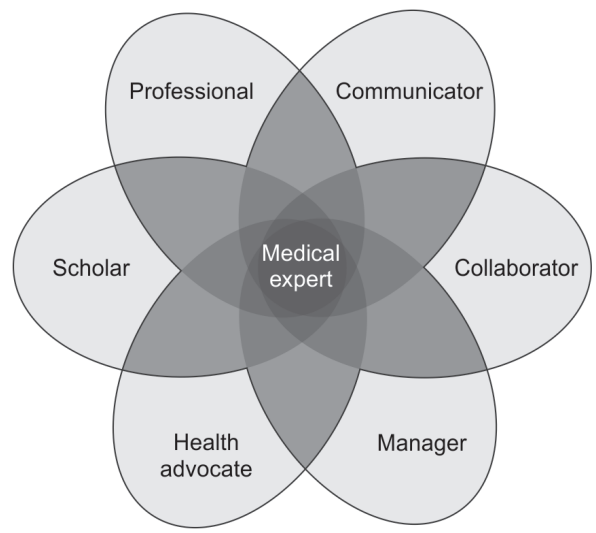

FIG. 6: Qualities required in dealing with a difficult situation.

SUMMARY

Interaction with patients is an integral part of day-to-day clinical practice. Patients presenting to the hospital, especially to the emergency, are already stressed. With a lack of trust in the profession and increased commercialization of healthcare, patients and their families are increasingly getting skeptical about the profession and healthcare delivery system. Patients or family members can become difficult at various stages of their presentation from the time of early registration to the time of their discharge. There is no trigger point can be mentioned for difficult patient and family members but helathcare professionals more so physicians, have to be more aware and vigilant about the early signs of patients or their family members starting to be defensive or difficult. Most of these situations can be resolved if we can recognize the early signs of a patient becoming difficult, such as change in body language, becoming angry and aggressive, and not being cooperative, and act on them. It is very important not to reciprocate or try to fight back. As medical professionals, we need to be patient and listen to their concerns, ask only relevant helpful questions to arrive at a resolution, and act and work to help and seek to resolve the patients' concerns (**Table 1**). It also important to be mindful that the patient's anger may not be directed at the person but it may be the process, the system, or the circumstances. They should not take any anger or comments personally. It may be good to let them talk and "let the steam off" so that they can cool down and a calmer environment is encouraged to have a productive discussion.

TABLE 1: Summary of dealing with a difficult situation.

Listen to patient	• What is the cause of anger • What are the concerns
Stay calm	• Be professional • Confident but not overconfident
Ask questions	• Facilitate understanding • Do not be patronizing

As these situations can at times be highly charged, it is important to assess the situation and get help of security at an early point to ensure the safety of staff and other patients. With incidents of violence on healthcare professionals, there is more awareness about dealing with difficult patients and family members. There is a need for a formal process of dealing with these situations. In the absence of these, we need to have a locally agreed process and have relevant training and education of healthcare staff, more so for frontline staff like the emergency department.

MULTIPLE CHOICE QUESTIONS

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18 CHAPTER

Medicolegal Cases and Writing Medicolegal Reports

Amit Nabar, Devendra Richhariya, Vivekanshu Verma

INTRODUCTION

For any successful investigation of crimes against a person (homicides and sexual offence), medicolegal evidence is the most critical event. It is, therefore, important to develop robust standard protocols and guidelines for medicolegal examination and reporting as well as update them from time to time. Medicolegal cases (MLC) are frequently encountered in everyday medical practice by Medical Officers. The MLCs are on rise; systemic examination and documentation of these cases as per the guideline are an important aspect to avoid legal complications. There are differences in the legal procedures being followed by different states, since law and order is a state subject. Medical Officers should be aware of the guideline/medicolegal procedures of the state in which they are serving. In the emergency department, while attending to a critical patient, the doctor should understand that his/her first priority is to save the life of the patient. He/She should do everything possible to resuscitate the patient and ensure that the patients is out of danger. All legal formalities stand suspended till this is achieved.

MEDICOLEGAL CASES

A medicolegal case can be expressed as any case of injury, disease or infirmity, or death in which law-enforcing agencies have to enquire into the matter and fix the responsibility of a person or a group of persons responsible for causing the said injury, disease or infirmity, or death and penalize as per the existing law of the land. Cases that are to be treated as medicolegal are as follows:

- All cases of injuries and burns, the circumstances of which suggest the commission of an offense by somebody (irrespective of suspicion of foul play)
- All vehicular, factory, or other unnatural accident cases, especially when there is a likelihood of the patient's death or grievous hurt
- Cases of suspected or evident sexual assault
- Cases of suspected or evident criminal abortion
- Cases of unconsciousness where its cause is not natural or not clear
- All cases of suspected or evident poisoning or intoxication
- Cases brought dead with improper history creating suspicion of an offense
- Cases of suspected self-infliction of injuries or attempted suicide
- Any other case not falling under the above categories but has legal implications

MEDICOLEGAL REPORTS

Medicolegal reports (MLR) are documents prepared by a government/private doctor, pertaining to injury, sexual offense, poisoning, or unexplained death. It contains all the facts, observed by the doctor and his/her opinion drawn therefrom. His/her opinion must be based upon the observations made by him/her and not on hearsay evidence. MLC writing comprises the following three parts:

1. *Preamble*: It includes the date, time, and place of examination, name of the patient, his/her residential address, occupation, name of the person/police official accompanying, DDR/FIR No., informed consent of the person being examined, two marks of identification, thumb impression, etc., wherever applicable (**Fig. 1A**).
2. *Findings/observations*: These include a complete description of the injuries/any other findings present; any investigations/referrals, etc., are asked for (**Fig. 1B**).
3. *Opinion*: It includes the nature of the injury, whether simple or grievous, weapon/force used, whether blunt or sharp, or firearms or burns, etc. The duration of the injuries is based on the characteristics of the external injuries.[8]

Preparation of Medicolegal Report

Medicolegal cases are like any other clinical conditions or injuries presenting to emergency department and a doctor's duty is to treat as well as document the details of injuries and communicate to the investigation officer of law-enforcing agencies under Section 39 of the Criminal Procedure Code (CrPC); failure to do so will attract legal penalty and liable to be prosecuted under Section 201 of the Indian Penal Code (IPC). Any doctor who possesses permanent registration with the Medical Council and who has the first contact with the patient should prepare a MLC report; in rape victims, the examination

Serial No.....

Medico Legal Report (Form-II)

MEDICO LEGAL REPORT NUMBER..... DATED.....
Consent for medico-legal examination (in case of accused, consent is not required u/s 53CrPC)

I, Dr. ..... Desegnation.....
PHC/CHC/Hospital/Dept. .....
examined Sh/Smt/Miss (First name).....(Last Name).....
s/o,d/o,w/o.....Age.....Sex.....Occupation.....
Address.....PS.....Distt.....
As per particulars given below:-

(A) Date and Time of arrival: .....
(B) Date and Time of examination: .....
(C) Place of examination: Casualty/Ward/OPD/Dept:.....
(D) Police request number and date (if brought by police):.....
Police informed (if coming direct) vide No:.....Date.....Time.....
(E) Brought by Police official .....No.....
PS.....Distt.....
(F) Accompanied by: Name .....Relation.....
Address.....PS.....District.....
(G) Name and address of the female attendant (in case of female patient).....
(H) Identification marks of the patient (1)

(2)

(I) OPD No.....Referred to.....
If admitted: (I)C.R. No. .....Date..... Ward.....
(ii) Date of Discharge .....
(iii) Where dying declaration is necessary, indicate steps taken:

(a) Whether the Magistrate was informed for recording Dying Declaration .....
(b) Name and Address of the Magistrate.....
.....
(c) Time at which the Magistrate arrived on the spot .....
(d) If magistrate not available, details of witnesses is whose presence the Dying declaration was recorded:
1. .....
2.....
(e) Dying declaration handed over to police official: Name .....

No.....PS.....District.....

(J) Material collected, preserved and handed over to police for chemical analysis etc. (write complete detail)

Amount of fee paid (if any) ₹.....to.....vide No.....

I List of incident as stated by the injured/inccompanying person

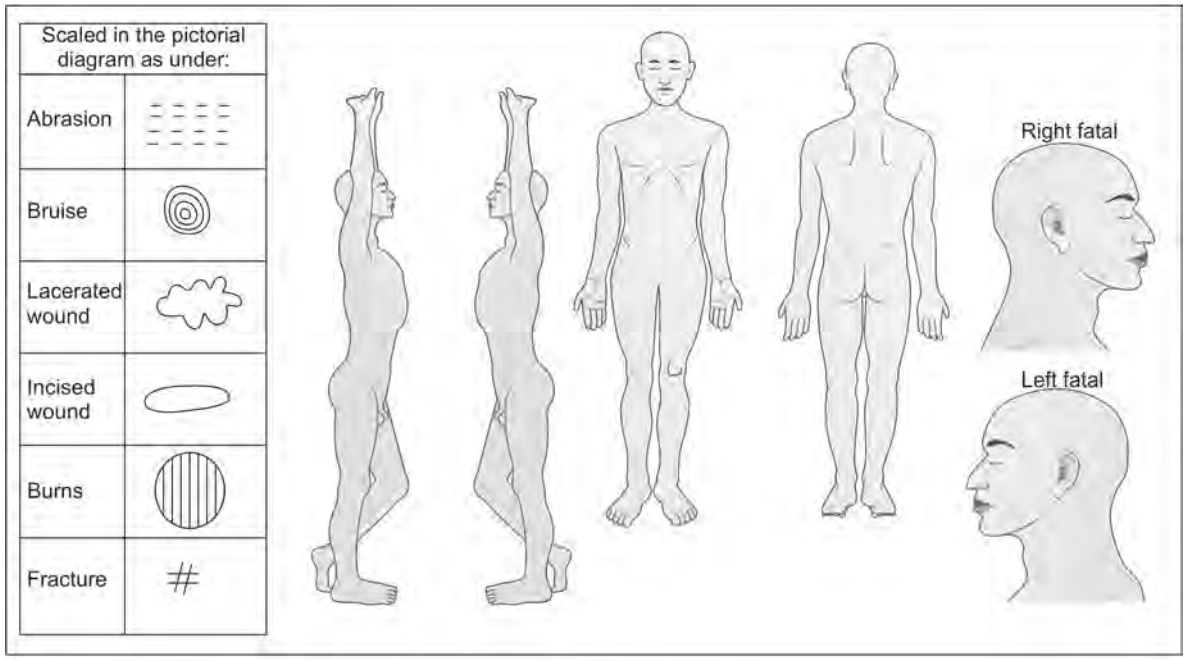
II General condition of the person, clothing etc.

III Particulars of injuries viz type, shape, dimension, location, nature, duration etc., and kind of weapon used:

1. Nature of Injuries_____
(Simple, grievous, Dangerous or pending for observation)
2. Probable duration of injuries _____
3. Kind of weapon used (Sharp, Blunt, Firearm, Fire, Position etc.)_____

SIGNATURE OF THE EXAMINING MEDICAL OFFICER
Name (in capital letters).....
Designation.....

FIG. 1A: Documentation of medicolegal report (general information and description of injuries).



Guidelines

As per section 320 IPC, any injury falling under following clauses in grievous:

1. Emasculation
2. Permanent privation of the sight of either eye
3. Permanent privation of the hearing of either ear
4. Privation of any member or joint
5. Destruction or permanent impairing of the powers of any member or joint
6. Permanent disfiguration of the head or face
7. Fracture of dislocation of a bone or tooth
8. Any hurt (i) which endangers life or (ii) which causes the suffer to be during the space of 20 days
   (a) in severe bodily pain, or
   (b) unable to follow his ordinary pursuits.

At the end in column no. 7 opine whether multiple injuries, individually simple, are collectively dangerous to life.

(CrPC: Criminal Procedure Code; IPC: Indian Penal Code)

FIG. 1B: Documentation of medicolegal report: description of injuries.

and preparation of MLC are done by female doctors. The emergency department is the area where majority of MLR are prepared, but sometimes maybe in wards, after detection of new findings. The consent for medicolegal examination is to be taken in written in all cases except for cases which are in brought by the police, e.g., being arrested on charge of committing an offense; in case of a person below 12 years/unsound mind, the consent of the guardian is to be taken. The institution of proper treatment to the patient and lifesaving is the prime responsibility of the doctor and the hospital in accident or MLC. There should be no delay in providing first-aid. The doctor should complete the injury sheet, which is a part of the assessment of the patient. Situations where a doctor prepare a MLR are as follows:

- Brought by the police for examination and reporting
- Already registered MLC referred from other healthcare system
- After history-taking and thorough examination, if the doctor suspects that the circumstances/findings of the cases are unnatural or mishap and need to inform the police department, e.g., road traffic accident rail, factories accident
- Suspected or evident homicides or suicides
- Suspected or evident poisoning
- Burn injuries due to any cause
- Injury cases where foul play is suspected
- Injury cases where there is a likelihood of death in the near future
- Sexual assault cases
- Suspected or evident criminal abortions
- Unconscious cases where the cause is not clear
- Brought in dead cases where there is a suspicion of foul play
- As per directive of the court

Consent for Medicolegal Report

Always take the consent of the injured person on the MLR form. If the patient is <12 years, take the consent of the guardian/accompanying person and get his signature/thumb impression; consent is not required in case of accused person u/s 53 and 53A of CrPC and even reasonable force can be used for his examination on the request of the police officer, not below the rank of a sub-inspector. If an unconscious/semiconscious patient is brought in an emergency along with family/guardian, the consent shall be taken from them. In case of refusal by the family/guardian, the medical officer shall mention on the MLR that the consent could not be recorded. (Write brief reasons.)

Completion of Medicolegal Record

Documentation is done in duplicate/triplicate in a set Performa as per the hospital policy. Separate Performas may be available for medical examination, examination of drunkenness, etc. All columns are filled up carefully and by the same doctor who had examined the patient. Each MLC is given a fresh MLC number sequentially or parallel series as per the hospital policy. The details are completed then and there only, leaving no provisions to be completed later on. After completion, doctors sign and mention his/her name in full with the designation. The police constable on duty is informed in each case. After registration of a case as MLC, all documents and requisition forms bear the same MLC number including the discharge slip.

Filling of General Details

Registration number, MLC no, name, S/D/W, age, sex, religion, occupation, residential address, details of the person who brought the victim, and mark of identification, the date and time of examination and name of the informed police station are noted and documented.

Filling of Examination Details

Alleged history should be precise and to the point, legible, and clearly written. Description of injuries such as minor injuries and multiple injuries in polytrauma and specialist consultation should be obtained and abbreviation should be avoided. As a part of the documentation of MLR or whenever the investigative officer requests the doctor for certifying the fitness of the patient by making a statement, the examining doctor will certify the same on the original MLC sheet. He/She will mention the date and time clearly with signature and name in full with designation below the certification. Opinion regarding injuries wheather simple grievious or dangerous are to documented based on history, physical examination, laboratory, radiological investigations and specialist opinion. A doctor cannot refuse to examine MLC on the basis of being a private practitioner or by citing a jurisdiction problem. The patient can be discharged after the initial treatment or admitted to the hospital or referred to other hospitals for expert management after being provided first-aid/stabilized and after completion of all necessary documentation.

Filling of Particulars of Injuries

The person should be examined from head to toe in a systematic way from both the front and the back. Always depict the site of the injury and the presence of stains and foreign material on the diagram. All the injuries should be recorded in a way as if you are giving a statement in the court. The following particulars of each and every injury must be recorded:

- *Type of injury* such as abrasion, bruise, wounds (lacerated, incised, punctured, etc.), fracture dislocation, or burns
- *Size*—exact dimensions (in centimeters) of each injury should be noted down in respect of its length, breadth, and depth wherever possible.
- *Shape* that is circular, oval, spindle, triangular, elliptical, crescentic, satellite, etc. Margins/Edges of wounds should be examined (by hands/lenses wherever necessary), regular or irregular having bruise on its vicinity, floor must be examined by just retracting the edges so that tissue can be seen, if any. Foreign matter such as grease, dirt, gravel, straw, coal, paint, glass, weed, metal, palettes, bullets, wads, clothes, and hair should be reported and must be preserved for further analysis.
- *Location and directions of injuries*
- *Age of injuries*—color changes and healing process
- *Duration of injuries*—time elapsed between the infliction of injuries and examination
- *Nature of injuries* such as simple/grievous/dangerous. Doctors shall specify the subsection of the Section 320 IPC as given in the note below for declaring the injury to be grievous. *Section 319 IPC*: *Hurt*: whoever causes bodily pain, disease, or infirmity to any person is said to cause hurt.

Note: As per section 320 of the IPC, only the following kinds of hurt are designated as "grievous injuries:"

- Emasculation
- Permanent privation of the sight of either eye
- Permanent privation of the hearing of either ear
- Privation of any member or joint
- Destruction or permanent impairing of the powers of any member or joint
- Permanent disfiguration of the head or face
- Fracture or dislocation of a bone or tooth
- Any hurt which endangers life or which causes the sufferer to be during the space of 20 days in severe bodily pain or unable to follow his ordinary pursuits
- "*Dangerous to life"* injuries are those which may be fatal if no surgical aid is available, e.g., tension pneumothorax, cardiac tamponade, liver and splenic laceration, deep incised wound in slit throat, stab wound in chest and abdomen, traumatic epidural hematoma and acute subdural hematoma with midline shift.
- *Dangerous weapons*: Dangerous weapon is defined under sections 324 and 326 of the IPC, as any instrument used for shooting, stabbing, or cutting or any instrument which, when used as a weapon of offense, is likely to cause death, or by means of fire or any heated substance, or by means of any poison or any corrosive substance, or by means of any explosive substance, or by means of any substance which is deleterious to the human body to inhale, to swallow, or to receive into the blood, or by means of any animal.

Medical Examination of Victims of Sexual Assaults (Section 164A of CrPC)

Examination should be done only by registered medical practitioner, without delay. Consent should be documented.

Complete history and examination, including genital examination and injuries should be documented. Standard protocols and guidelines should be followed. Preserve samples such as deoxyribonucleic acid (DNA) profiling. Emergency contraception should be given if required. Treatment/prophylaxis should be followed as required and opinion must be sought.

Guidelines for Preservation of Medicolegal Evidence

- Medicolegal evidence should be preserved and subsequently sent or handed over to the investigating authorities for forensic examination and production as evidenced in a court of law. All evidences will be identified,

sealed, and labeled properly. They will be kept in safe custody and handed over to the investigating officer of the case. Once collected, loss/destruction of evidence is a punishable offense. Failure to collect, destruction, or loss of such an exhibit is punishable under Section 201 of the IPC.

- The evidence required to be preserved is related to the nature of a case. In injury cases, the following articles should be preserved in sealed envelopes: (1) Clothing worn by the patient showing evidence of injury such as tears, bullet holes, cuts, and bloodstains. (2) In case of multiple tears, cuts, or holes, etc., each piece of evidence will be encircled and numbered with matching description in the MLC report and case sheet. (3) Bullets recovered from a body should be marked by etching an initial or a mark on the bottom before preservation. (4) All evidence collected should be mentioned in medicolegal documents to establish the chain of custody in a court of law subsequently.
- In cases of suspected poisoning, the following articles will be preserved and ensured that they are forwarded for forensic examination: (1) Gastric lavage/gastric contents/vomitus and soiled clothing and (2) Blood, urine, and any other relevant body fluid depending on the poison ingested.
- In cases of burns and carbon monoxide poisoning, the following articles should be preserved in sealed envelopes: (1) Articles soiled with inflammable substances such as burnt pieces of clothing and scalp hair and (2) Blood (and not serum) for carbon monoxide levels.
- In sexual offenses, the following articles should be preserved in sealed envelopes: (1) Clothing worn by the patient and showing evidence of blood stains or seminal stains, stains of mud, tears/cuts, etc., and (2) Vaginal swab preferably from the posterior fornix/anal swab.

Guidelines for Preservation of Medicolegal Documents

- Original copies of all medicolegal documents will be produced whenever asked for in a court of law.
- All original copies of certificates and reports issued for medicolegal purposes are to be preserved till the finalization of the case in the court of law.
- Medical Superintendent of the hospital will ensure that the documents are kept in the custody of an appropriate officer till the case is finally decided or cleared by the police and judicial authorities. In the case of units other than hospitals, the safe custody will be under unit arrangements.
- Documents pertaining to admitted fatal MLCs are to be processed and preserved as laid down in concerned policy letters.

Time Limit for Registering a Medicolegal Case

There is no time limit for preparing a MLR or registering a case as MLC. A case which otherwise qualifies to be a MLC was not registered earlier is to be registered as MLC by the concerned doctor. A case due to unraveling of new findings, history/clinical examination etc., which later on qualifies to be an MLC is to be registered by the concerned doctor. A MLC is registered as soon as a doctor suspects foul play or feels it necessary to inform the police, at any time after admission. A case is registered as a MLC even if it is brought several days after the incident. If the case brought is a referred case and is already registered as a MLC, fresh report is not required. If a patient hospitalized and later on some facts revealed on the basis of history physical examination and clinical document, medicolegal report (MLR) can be initiated by the concern attending clinician. If death is inevitable, an arrangement to take the dying declaration is made. All the materials such as vomit, gastric lavage sample, and blood urine in poisoning cases; vaginal swab and pubic hair in sexual offenses; and foreign bodies in wounds, etc., are collected. Samples are properly preserved, packed, and sealed and then handed over to the police.

Admission and Discharge of a Medicolegal Case

Whenever a MLC is admitted, the same is documented in admission papers and hospital records. When discharged, the same should be intimated to the police authorities of the hospital. Police is informed if a MLC is taking discharge against medical advice. At the time of discharge, detailed instructions to the patient regarding treatment, follow-up general care, diet, exercise, etc., are given in writing.

Death of a Person Admitted as a Medicolegal Case

The do's and don'ts in case a person admitted as a MLC expires are as follows. Police is informed immediately. The body is sent to the hospital mortuary for preservation, till the legal formalities are completed and the police releases the body to the lawful heirs. A death certificate is not issued, even if the patient was admitted. The dead body is never released to the relatives directly. *In case of a brought-in-dead patient,* police is to be informed. The number of injuries is noted in the MLC record. The article in possession is to be documented and handed over to police/relatives. The dead body is to be sent to the hospital mortuary and handed over to police.

MEDICOLEGAL CLASSIFICATION OF INJURIES

The wounds or injuries are classified as follows:

- *Estimating time since injury*: Time of injury can be estimated by changes in the injury over the period of time (**Table 1**).
- *Mechanical injuries:* Those caused by hard blunt weapons, fall, or friction with a rough surface, etc.: (1) Abrasion, (2) Bruise or contusion, and (3) Laceration.
- Those caused by sharp-cutting and/or sharp edge of sharp-cutting pointed weapons: *Stab wound* which may again be subclassified as: (1) Punctured, (2) Penetrating, or (3) Perforating.
- *Firearms,* e.g., (1) Shotguns, (2) Rifled gunshot weapons, (3) Improvised country-made weapons.
- *Thermal injuries*: (1) Dry heat—burns and (2) Moist heat—scalds and blisters
- *Chemical injuries*: These types of injuries are caused by corrosive acids or alkalis.

TABLE 1: Estimation of time since injury.

Time of abrasion	• Fresh abrasion—red, oozing with serum little blood, and no scab • 12–24 hours—dry exudation, reddish soft scab • 2–3 days—brownish scab • 4–5 days—dark brown and hard scab • 6–7 days—blackish scab dries up, shrinks falling off
Time of bruise	• Fresh bruise—intact skin, reddish color become bluish within an hour • Next 3 days—remain bluish for the next 3 days • 4th day—brownish/bluish black due to hemosiderin • 5–6th day—greenish due to hemotoidin • 7th day—yellowish-bilirubin and gradually fades away
Time of burn	• Fresh burn—erythematous and blister formation • 2nd day—erythematous around a blister or deep injury passes off • 3rd day—pus formation • 4–6th day—slough formation which sheds off by the end of the first week

HOW DOES THE LAW PROTECT THE VICTIM IN MEDICOLEGAL CASES?

The law states that concerns such as legal formalities, monetary considerations, or even the infrastructural restraints of the institution should not prohibit the institution or hospital from providing basic and emergency medical treatment. Here are a few things everyone should know:

- A hospital cannot deny emergency medical care to an accident victim under Article 21.
- It cannot deny treatment on the alleged reason of lack of facilities. The hospital has to provide emergency care and then transfer the patient safely in its ambulance to the nearest facility. This includes government and private hospitals. It also includes private clinics and nursing homes.
- The hospital cannot deny a patient emergent treatment on the basis that he/she is unable to pay the required fees or that there is no close relative to sign for consent (consent is overridden in an emergency).
- In the case of a rape or criminal abortion, the lady cannot be examined by a doctor without a written consent from her.
- In both cases, rape and criminal abortion, the doctor is bound by law to keep the patient's information, including her name, confidential.
- In cases where a woman is being examined, another woman must be present during the examination. In the case of males, another male has to be present at all times.
- In the case of suicide causing death, the doctor is obligated to report the matter to the police for further investigation.
- If the patient is alive and suicide is suspected, the doctor is not obligated to report the matter to the police.
- Please remember that, on visiting a hospital for a MLC, after the patient has received treatment, the doctor or hospital must inform the police about the case. It is advised to take an acknowledgment of receipt for future reference. If the intimation is given orally or via the phone, a docket number is provided which can be used as proof of intimation and is documented in the patient's records.
- Once the patient has stabilized and is fit to give a statement to the police, the patient is then required to authenticate the information that has been provided and the victim/patient will be visited by the police. They will take down the statement of the victim and confirm if a case needs to be filed or not. The doctor is responsible to give accurate information to the police which will assist them in their investigation. After the case is filed, the victim will get a receipt stating the file number and case number. If required, the victim can employ a lawyer to take the case forward.

PRACTICAL TIPS FOR MEDICOLEGAL CASE WRITING

Q. How to describe gunshot and shotgun wound in a medicolegal report?

A. Gunshot is a single bullet injury by a rifled firearm. Shotgun is multiple pellets injury by *desi katta*/improvised revolver. Indian Law enquires in firearm wound description—number of wounds and type of firearm projectile (bullet/multiple pellets), nature of injury (simple/grievous), killing range of firearm by blackening and tattooing, length × breath × depth, location and direction (circular/oval) of entry wound (inverted margins, blackening, tattooing, abrasion collar) or exit wound (everted).

Q. How to describe shotgun wound on the right lower limb in a MLC report?

A. Multiple punctured lacerated wounds of varying sizes 0.2 cm × 0.2 cm × muscle deep present in a diameter of 10 cm on the back of the right thigh 7 cm above the knee, circular in shape, with blackening and tattooing around the wounds, margins are inverted with active bleeding being present. Opinion reserved—X-ray and surgeon's operative notes for depth and grievousness. Opinion is reserved as not all firearm wounds on limbs are dangerous to life. In a distant range of firearm, it is just a laceration, if no fracture or vascular/nerve injury is caused.[6]

Q. How to describe 90% burn caused by kerosene?

A. Indian Law enquires in burn severity—type of burn (dry heat/scald), depth of burn, nature of injury (simple/grievous/dangerous to life), location and percent of burn and its duration. It should be described—superficial to deep burns with blackening and peeling of skin with singeing of hair with red line of demarcation over the following parts of the body. Head as a whole with singeing of scalp hair, face as a whole with singeing of eyebrows and eyelashes, neck and chest as a whole, abdomen in its whole circumference, genitalia in patches and both buttocks in patches with singeing of pubic hair, both upper limbs and both lower limbs, sparing the soles. Total burnt surface area is about 90%. Opinion of injury—dry heat flame burn of fresh duration and dangerous to life.

Q. How to describe chopped wound upper limb by a wooden axe in MLC report?

A. Indian Law enquires in wound description—type of wound to know the weapon (sharp/blunt and heavy/light), nature of injury (simple/grievous), length × breath × depth, location, margins of wound, fresh duration or not. So we can write—chop wound 5 cm × 4 cm × through and through deep, with clean-cut regular margins, and fresh blood oozing out, present over left forearm mid-part with missing of the distal part of left of the upper limb.

Q. How to write MLC findings of an acute poisoning case by suspected aluminum phosphide pesticide?

A. Patient is conscious, oriented with complaints of restlessness, vomiting of grayish color, intense thirst, burning epigastric pain, and dizziness with alleged history of pesticide poisoning? Celphos, amounting three tablets, ingested 1 hour ago at his home, as told by the conscious patient himself.

On examination—Glasgow Coma Score (GCS) = 15/15, moving all for limbs. Pupils are bilaterally equal in size and reactive to light. Blood pressure is 90 mm Hg systolic. Pulse rate is 160/min on a cardiac monitor and carotids are feeble on palpation. Respiration rate is 40/min. Chest—bilateral air entry present. Temperature is 97°F. Face is grayish-blue (cyanosed). Tongue is dry. There is garlicky odor of breath. Abdomen is soft and there is tenderness in epigastrium. Gastric aspiration samples and clothes of patient are sent for forensic science laboratory (FSL) lab analysis.

Q. How to write injuries in MLC report of sexual assault—rape?

A. Patient is conscious, oriented with complaints of severe pain in genitals and bleeding per vagina with alleged history of sexual assault 1 hour ago at her home, as told by the conscious patient herself. Injuries on the body (examined in the presence of female staff): Stains over external genitalia, matted pubic hair, vagina bruised in the posterior wall, labia majora and minora are both contused, edematous and inflamed, hymen torn at 6 o'clock position with fresh bleeding present. A written consent of the patient for examination of genitalia is mandatory in sexual assault cases. Take the consent of parents in case of minors (<18 years). Note marks of identification on the victim's face, such as black mole or any permanent tattoo mark on limbs or old scar mark, for future identification in court evidence. Vaginal swabs of patient should be preserved, sealed, and labeled.

- One glass slide (sealed in an envelope) smeared with the first swab from vagina
- One swab from cervix
- One swab from posterior fornix
- One sealed glass vial containing vaginal swab in normal saline
- One sealed test tube containing air-dried vaginal swab
- One sealed test tube containing air-dried swab of blood for blood grouping and DNA matching
- One sealed test tube containing air-dried swab of saliva for blood grouping and DNA matching[4]

Q. How to send samples to a police forensic laboratory for chemical analysis?

A. Samples are preserved in a sterile transparent container, sealed and labeled. These should be handed over to the police with a forwarding letter enlisting samples and patient's details. Samples include clothes and gastric aspiration samples in suspected poisoning, impregnated bullets, pellets, knife removed from the wound of patient, clothes, and vaginal swabs from a sexually assaulted victim.

Q. During court evidence, the most common question of a defense lawyer to a doctor (who made MLC) in an injury case is: Can this injury be caused by the falling of victim by self on a hard and blunt surface?

First case: Nitish Katara case: Homicidal physical assault by a blunt weapon—comminuted depressed skull fracture of frontal bone by a hammer. The defense lawyer proposed that it was a case of high-speed RTA as the victim was found by the police in the bushes near the roadside. Now the defense lawyer asked the first question: Can skull fracture be caused by falling on a hard and blunt surface?

The doctor replied: No. A wound of this nature could be caused only when a moving person hits a stationary hard surface which results in "countercoup injury" and results in a lesion in an area opposite to the point of impact. But no countercoup lesions were found in Nitish Katara's head. The lawyer lost the case.

Second case: RTA of a 30-year-old pedestrian, hit by a vehicle on the right lower limb while crossing the road, sustaining primary impact injury—Right lower limb deformity with fracture of femur, tibia, and fibula.

Now when the defense lawyer asked the first question: Can this injury be caused by falling on a hard and blunt surface?

The doctor replied: No. If the victim would have fallen from a height, then both his lower limbs would have got injured. There is no abrasion on the left side.

The lawyer asked: If the victim fell on his right side laterally? The doctor replied: Then he would have got injury over the right side upper limbs or trunk too, along with the lower limb. The lawyer lost the case.

Third case: RTA of a 25-year-old male driving a car, taking a turn over a crossing, hit by another car coming in high speed, sustaining whiplash injury of the cervical spine, leading to paraplegia of both lower limbs. Now the defense lawyer asked: Can this injury be caused by falling on a hard and blunt surface?

The doctor replied: No. The victim had no abrasions or bruises on any part of the body. If he would have fallen, then these injuries would be sustained along with deep injury over the neck. The lawyer lost the argument again.

So doctors should go through all the medical documents of the victim, before facing a defense lawyer, whose goal is to prove that the accused has not directly injured the victim and that the victim fell by self, so there is no proven crime and thus no nonfinancial claim for compensation is to be paid by accused. By using common sense during court proceedings, a genuine victim gets justice and compensation is demanded.

DO'S AND DON'TS IN MEDICOLEGAL CASE WRITING TO AVOID LEGAL PUNISHMENT

Doctors often perform a detailed physical examination but make the mistake of not thoroughly documenting the examination. The old medical maxim, "If it is not documented, it was not done," should be remembered. Remember that you may be cross-examined on your report; only write what you

would be prepared to say under oath in court. MLC reports should be prepared in duplicate preferably with a ball pen. Do not alter your report at the request of your patient or a third party; if you receive additional information or you have made a mistake, provide a supplementary report.

Common mistakes in MLC writing are when the wrong side of the body is mentioned, e.g., left limb fracture is noted as right side, relying on memory, and creating confusion and ground for discrediting MLC reports by courts. Disciplinary action is taken in such as a case which includes suspension from job and MCI notice for doctor's negligence. This can be prevented by properly proofreading their reports. The doctor should take all the steps necessary to catch and correct all: Misspelled words, transcription errors, and grammatical mistakes.

- MLC reports are confidential legal documents; any tampering or alteration in entries, such as antedate entries. Fabricating false evidence of crime—Section 191 IPC, punishable for 7 years.
- Issuing or signing false injury certificate—Section 197 IPC, 3 years of jail
- Do not miss the court date on summons as a arrest warrant will be issued. Contempt of court—Section 228 IPC, punishable for 6 months
- Do not state false findings. Giving false evidence under oath—Section 199 IPC, punishable for 3 years
- Always intimate the police about MLC promptly. Not informing police—to screen offender—Section 201 IPC, punishable for 3 years
- MLC report should be kept in safe custody. If lost/stolen or destruction of evidence—Section 204 IPC, punishable for 3 years

Do not rely on memory while writing MLC reports or giving court evidence. Always review and reply.

When writing your MLC report, it is important to remember that how you say it is just as important as what you are saying.

- Doctors, often inadvertently, use hedge words such as "it seems," "I think," "I believe," "it appears," "it could," or "apparently" in their MLC reports. These hedge words lessen the impact of their findings and conclusions.
- "Complete," "thorough," "meticulous," "exhaustive," and other such words should be used to describe the examiner's chart review, research, or examination. These self-serving words will hold the doctor and his/her MLC report at an extremely high standard.
- "Appears," "presumably," "supposedly," "is said," and "evidently"—these terms imply uncertainty.
- "Obviously" and "clearly"—these terms can be used to make the doctor appear patronizing or presumptuous.
- "Malingering"—sometimes police asks for an opinion on "victim of assault patient who are complaining of generalized body pain." In the majority of cases, it is usually better for the doctor to merely document exaggerated pain behaviors, inconsistencies, nonorganic findings, and lack of objective findings rather than making a diagnosis of malingering.
- "Alleged," "credible," and other words directly or indirectly opine on the credibility of the doctor. The doctor is a medical expert, not a credibility expert.
- "Dictated but not read" and "electronic signature"—these practices make the examiner appear to be more interested in cranking out reports and collecting fees than in precision and accuracy.
- Using incorrect, imprecise, or confounding language in the report will raise red flags and result in uncomfortable and unnecessary cross-examination by the lawyer.

SUMMARY

Writing a MLR is an important legal responsibility for doctors in prescribed cases which is helpful for the investigating authority. In MLR, relevant details are noted legibly and confidentially without abbreviation. Giving life-saving treatment is a priority in any MLC. The doctor's duty is to remain nonjudgmental about any case and examine the patient and document the injuries and findings and management. The onus of fixing responsibility of guilt is for the investigating authorities and court.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Medicolegal Issues in the Emergency Department

Adarsh Kumar, Vivekanshu Verma, Devendra Richhariya

INTRODUCTION

Whenever a patient is injured with suspicion of intention of foul play, it becomes a medicolegal case (MLC). When a patient is injured outside the hospital and he/she is brought for treatment, then the doctor has to inform the police and prepare an MLC. When the patient is injured inside the hospital, either due to slipping on a wet floor in the bathroom or due to lack of proper medical care, then it becomes a medicolegal issue for medical negligence. This adverse event should be reported to the legal department by the treating doctor so that proper documentation is implemented for future court litigation.

The issue of medical negligence is one of the most distressing medicolegal topics for the medical practitioners. To face the problem head-on, it is extremely important to thoroughly understand the concept. Medical negligence may be defined as an "act of omission which a reasonably competent medical practitioner, guided by such medical knowledge and practice as is commonly known at the time and at the place where he practices and further guided by such other considerations which ordinarily regulate the conduct of reasonably competent medical practitioners, would do, or doing something which reasonably competent medical practitioners would not do." It is the failure on the part of a doctor to exercise his/her skill and diligence, which are required of a medical professional resulting in harm to the patient. However, deviation from common practice is not necessarily an evidence of negligence. Similarly, a mere accident or error of judgment is also not evidence of negligence. Medical negligence is termed medical malpractice in the American legal system.

To label any act or omission by the doctor as negligence, all the essential ingredients of medical negligence must be present. The essential constituents of negligence include: (1) Duty of care toward the patient (doctor–patient relationship), (2) dereliction or breach in duty of care, (3) damage that results to the patient must be reasonably foreseeable, and (4) direct causation (direct relation between the breach in duty of care and the damage).

WHAT IS DUTY OF CARE TOWARD A PATIENT?

In order to charge a medical practitioner with negligence, the complainant must prove that the practitioner owed a duty of care to the person complaining of negligence. When a patient enters the clinic or hospital, and the doctor starts examining the patient, the duty begins. Even in charitable hospitals where no money is charged, a doctor can be charged with medical negligence. Not charging a professional fee does not protect the doctor from criminal negligence. Where no duty of care existed toward the person complaining of negligence, there would be no liability on the part of the medical practitioner, even where his action or conduct has caused damage to the complainant.

In *Laxman Balakrishna Joshi vs. Trimbak Bapu Godbole & Anr,* the Apex Court has held: A person who holds himself out ready to give medical advice and treatment impliedly undertakes that he/she is possessed of skill and knowledge for the purpose. Such a person when consulted by a patient owes him certain duties, namely (1) Duty to Care in deciding whether to undertake the case, (2) Duty to Care in deciding what treatment to give, and (3) Duty to Care in the administration of that treatment. A breach of any of those duties gives a right of action for negligence to the patient. The practitioner must bring to task a reasonable degree of skill and knowledge and must exercise a reasonable degree of care. Neither the very highest degree nor a very low degree of care and competence judged in the light of the particular circumstances of each case is what the law requires.

The doctor–patient relationship is absent with doctors in radiology, pathology, microbiology, and biochemistry. Because these doctors do not consult or examine patients, they just report the investigations. But in recent times, in intervention radiologic procedures such as ultrasound-guided stenting, radiologists examine and interact with patients and do procedures; hence, the doctor–patient relationship exists.

The doctor–patient relationship is not formed when the doctor sees the acutely ill patient for the first time in

the emergency room. So doctors giving life-saving drugs in emergency are protected by law from allegations of using dangerous drugs without discussing with the patient.

WHAT IS BREACH IN DUTY TO CARE?

It is expected of the doctor that once he/she has obtained the requisite qualification, he/she will acquire skill to treat the patient and exercise good care. It is assumed that he/she will exercise a reasonable degree of skill and care. He/she may not be the best in the community of doctors but it is assumed that he/she is average and his/her expertise should be at least average in his/her peer group. It is also understood that a doctor may not always know the latest in his/her field, but it is expected that he/she is aware of new techniques that are coming to his/her specialty.

Whenever a patient gets injured during patient care, either by wrong drug, wrong route, wrong site, wrong time, or wrong dose, then it leads to medical negligence. When a surgeon operates at the wrong site, by the wrong procedure, on the wrong patient, at the wrong time, or in the wrong surroundings, then it leads to surgical negligence.

In *Dr Ganesh Prasad & Anr. vs. Lal Janamajay Nath Shahdeo*, the National Commission held that "where proper treatment is given, death occurring due to process of disease and its complication, it cannot be held that doctors and hospital are negligent. Though death of the child is unfortunate, it cannot be said that there was negligence on the part of doctor."

WHAT IS DOCTRINE OF RES IPSA LOQUITUR?

Under certain exceptional circumstances where the doctrine of *res ipsa loquitor* applies, the patient is freed from the responsibility of providing the evidence to prove negligence by the defendant. The burden of proof shifts from the complainant to the medical practitioner who has to prove that damage did not occur from his/her conduct of negligence. The maxim res ipsa loquitor is derived from Latin which literally means "the thing speaks for itself." In context to medical negligence, this maxim applies where it is improbable that the damage complained of could have happened without the wrong of the medical practitioner.

In *Dr G. Vivekananda Verma vs. Chinta Bharamaramba & Ors.,* the National Commission held that "the Petitioner Surgeon gave anesthesia himself and has not shown how 'anoxic encephalopathy' occurred and whether immediate action was taken to avoid the complication and whether timely treatment was imparted to the patient to avoid anoxic encephalopathy. From the records of the Swatantra Hospital and NIMS, it is seen that the patient died due to anoxic encephalopathy suffered during Tonsillectomy. We agree with the findings of the state commission that there is deficiency in service and negligence by the Petitioner. It is clear that the doctrine of *res ipsa loquitur* applies in the present case."

In *Baby Geeta & Ors vs. Cosmopolitan Hospitals (P) Ltd. & Ors.,* facts of the case are that a post-term baby was delivered after administering "pitocin" to induce labor. The delivered child suffered high fever, convulsions, and breathing difficulties and within 16 hours of discharge, tests revealed birth asphyxia resulting in lifelong mental retardation, epilepsy, and physical disability of the child. The National Commission observed that proper antenatal monitoring was not done by the respondent hospital and the doctors. Admittedly special care was required but the case was treated as normal delivery. No appropriate care was taken despite the request of the mother that the baby suffering from tremors at times during the night and was not drinking milk actively. From the facts and the medical literature produced, the National Commission held that failure to take into account all warning signals and take immediate steps to prevent birth asphyxia indicates a clear case of deficiency in service and medical negligence. There is enough evidence to show case of *res ipsa loquitur*.

If it can be proved that the damage suffered by the patient was the possible consequence and is consistent with due care provided by the medical practitioner, then the maxim of *res ipsa loquitur* can be refuted. The medical practitioner has to prove that due care was shown toward the patient. In that case, the court will infer that the damage suffered by the patient was the result of misadventure or error of judgment and not due to negligence.

Jaswinder Singh vs. Santokh Nursing Home & Ors. (2012) 4 SCALE 170... was a case where two mops/gauges were left in the abdominal cavity and the patient died due to septicemia. *Gossypiboma* (retained foreign object) is the technical term for a surgical complications resulting from foreign materials, such as a surgical sponge, accidentally left inside a patient's body.

WHY MEDICAL SERVICES WERE INCLUDED UNDER THE CONSUMER PROTECTION ACT, 1986?

In a landmark case of *Indian Medical Association vs. V P Shanta & Ors,* the Hon'ble Supreme Court laid to rest the controversy whether the services rendered by the doctors/hospitals are covered under the Consumer Protection Act (CPA) or not. The Apex Court held that the services rendered by the doctors/hospitals are covered by the CPA unless such services are rendered by them entirely free of charge or to all the patients.

To clarify the concept and coverage of such services under CPA, the Apex Court has clarified the definition of "Service" under Section 2 (O) into three parts, namely:

1. The main part which says that service means service of any description
2. The inclusionary part which says: include the provision of facilities in connection with banking, finance...house construction, entertainment
3. The exclusionary part which says: but does not include rendering of any service free of charge or under contract of personal service

The Supreme Court further observed that "Contract for personal service implies a contract whereby one party undertakes to render services (professional or technical) to or for another in the performance of which he/she is not subject to detailed direction and control but exercises professional or technical skill and uses his/her own knowledge and discretion." Control of personal service implies a relation of master and servant and there is an obligation to obey the orders in the work to be performed as to the manner in which the work is to be performed. Services rendered by the doctors cannot be termed personal service.

A personal service necessarily implies that service is not only provided at the behest of the master but also that service is provided as per the direction of the master. In case of professional service, a professional such as a doctor advises his/her patient on the nature of disease and the treatment

required to be obtained. A professional may not necessarily follow the advice of his/her client while performing his/her functions.

WHAT KIND OF MEDICOLEGAL ISSUES ARE FACED IN DEALING WITH INTERNATIONAL PATIENTS?

Presently, India is seeing a boom in Medical Tourism Industry and gets patients from various countries who seek better medical facilities. When a hospital deals with an international patient, it must ensure that detailed records are kept including the reason for admission, transfer, and plan of care if required. Insurance companies have experts in their panel to cross-verify the line of treatment, and hence it is a good practice to have a team of specialists attend to a patient instead of looking at him/her individually. When any international patient is injured inside the Indian territory, then intimation to local police and MLC reporting are done as we do for all injured.

Then the doctor needs to inform the legal department of the hospital, who will coordinate with the concerned embassy for collection of material evidence of bullet, etc. When any person is injured or poisoned on board in an international flight, then medicolegal formalities need to be done according to the jurisdiction, as mentioned in the contract of flight carrying the person.

MEDICOLEGAL GUIDELINES FOR MANAGING A TERMINALLY ILL PATIENT IN THE EMERGENCY DEPARTMENT

Regulation 6.7 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002 provides:

"Practicing Euthanasia shall constitute unethical conduct. However, on specific occasion, the question of withdrawing supporting devices to sustained cardiopulmonary function even after brain death, shall be decided only by a team of Doctors, and not merely by the treating physician alone. A team of Doctors shall declare withdrawal of support system. Such team shall consist of the doctor in charge of the patient, Chief Medical Officer/Medical Officer in-charge of the Hospital, and a doctor nominated by the in-charge of the Hospital from the Hospital staff or in accordance with the provisions of the Transplantation of Human Organ Act, 1994."

In India, active euthanasia and assisted death continue to be illegal. Active euthanasia entails the use of lethal substances or forces which would cause the death of a person, e.g., a lethal injection given to a person with terminal cancer who is in terrible agony. Active euthanasia is a crime all over the world except where permitted by legislation. If a person consciously and voluntarily refuses to take life-saving medical treatment, the same is not barred by law. The Supreme Court has laid down guidelines with respect to nonvoluntary passive euthanasia (where a person is not in a position to decide for himself/herself, for instance, if he/she is in coma and is incompetent to take a decision in this connection) in the case of Aruna Ramachandra Shanbaug vs. Union of India, (2011) 4 SCC 454, which are as follows:

A decision has to be taken to discontinue life support either by the parents or by the spouse or other close relatives and in the absence of any of them, such a decision can be taken even by a person or a body of persons acting as a next friend. It can also be taken by the doctors attending the patient. However, the decision should be taken bona fide in the best interests of the patient. Even if a decision is taken by the near relatives or doctors or next friend, to withdraw life support, such a decision requires approval from the High Court concerned.

PATIENTS WITH WEAK FINANCIAL BACKGROUND IN A PRIVATE HOSPITAL

The Hon'ble Supreme Court in the landmark judgment of Parmanand Katara vs. UOI, 1989 (4) SCC 286, has held that every doctor, whether in a government hospital or a private hospital, is under a professional obligation to provide immediate medical aid to an injured person to save human life. However, the treatment should be supplemented by the same process of reporting to the authorities, as undertaken vis-à-vis any other patient of the hospital. The cost of treatment is covered under corporate social responsibility (CSR).

MEDICAL NEGLIGENCE

It is important to understand the difference between medical negligence and medical malpractice, as the two terms are at times used interchangeably. Medical negligence is an inadvertent medical misconduct which may occur due to technical insufficiency of the practitioner or due to lack of complete knowledge of a particular case or out of plain ignorance whereas medical malpractice is misconduct done on purpose and generally involves unethical behavior on the part of the medical practitioner. In the hospital and the likes of its setups, delayed medical attention, overdose, wrong medication, wrong surgical interventions, etc., lead to medical negligence. However, in medical streams other than the allopathic system of medicine where patients turn to, more as the last option rather than as a system of choice, which is, of course, a changing trend nowadays, medical negligence has a higher chance of occurrence. The existence of multidisciplinary treatment options has increased the risk to which any person might be exposed. Failure on the part of the doctors to inform/interact with/procure an informed consent form, the patients/attendants are the most common cause of claims of medical negligence. The discrepancy between the documentation, for instance, billing documents, discharge summary, doctor's notes, nurse's chart, etc., also result in claims for medical negligence. One of the common complaints in MLCs is that the patient or his/her family was not explained the risks involved prior to the procedure being undertaken.

Simplified Strategies to Prevent Medical Negligence During Patient Care

At the time of the admission of a patient, it must be ensured that all forms are properly filled and signed by the patient or by a first-degree relative. Uniform fact sheets and consent forms must be used by all the departments in a multidisciplinary hospital. Also, the history of the patients should be accurately recorded. Proper and accurate records are a must in preventing the chances of medical negligence. A doctor from the treating team must explain the risks and benefits of any surgical procedure/treatment that a patient has to undergo in that hospital. Doctor–patient/attendant communication

must take place between a doctor from the treating team and the family and should be recorded by the nurses. Patient–family education is also crucial. Negligence starts when the doctor carelessly prescribes management verbally without written orders, nurses forget in between the chaos of multiple emergency patients, and the individual patient does not get the appropriate treatment. Timely and correct documentation of advice by a doctor is the key to correct treatment.

How to Face a Medicolegal Complaint?

Medicolegal complaints are to be dealt with due caution and care. Facing a medicolegal complaint is something that needs preparation prior to the visit of the patient to the doctor, wherein, however small might be a doctor's setup, there has to be a provision in the system of the clinic or the hospital for appropriately facing the MLC(s) that might come up in the future. The key to fearlessly facing the cases is proper documentation. The legal counsel (in-house/external) should be immediately informed and provided copies of the relevant complaint/notice/summon/warrant. In a multidisciplinary hospital, it is necessary that there is a coordination between the various departments and, when a case arises, not to get into a blame game.

What Constitutes Medical Negligence?

In *Poonam Verma vs. Ashwin Patel,* while deliberating on the absence of basic qualification of a homeopathic doctor to practice the allopathic system of medicine, the Supreme Court held that a person who does not have knowledge of a particular system of medicine but practices in that system is a quack. The person is guilty of negligence per se, and no further proof is needed.

In *Nihal Kaur vs. Director, Postgraduate Institute of Medical Education and Research (*PGIMER*),* a patient died the next day after surgery and the relatives found scissors while collecting the last remains. A compensation of ₹1.20 lakhs was awarded by the State Commission Chandigarh on the ground that negligence was proved in handling the case.

What Does Not Constitute Medical Negligence?

In *Mrs Shantaben Muljibhai Patel & Ors. vs. Breach Candy Hospital and Research Centre & Ors*, the National Commission dismissed the complaint filed by the wife and two sons of the deceased Mr M M Patel who died in Breach Candy Hospital alleging negligence by staff and treatment administered by the surgeon and anesthetist. The deceased had undergone bypass surgery in 1988 and got the mitral valve replaced. Deterioration of 15% ejection fraction (pumping efficiency) was found in 1996. The operation was performed successfully. While undertaking postoperative treatment, there was extubation. As per the medical literature, such chances of extubation are between 8.5% and 13%. Extubation was swift and sudden and immediately noticed by the nurse. The expert doctor was called, but intubation was found difficult and the patient died due to cardiac arrest. The hospital was equipped with the necessary equipment and doctors performed their duties to the best of their ability with due care and caution. The deceased was a high-risk case and such accidental eventuality cannot be controlled. Every surgical operation is attended by risk. If something goes wrong, the conclusion of deficiency in service cannot be drawn. Reasonable care was exercised by the nursing staff. No negligence or deficiency in service was proved. While delivering its judgment, the National Commission has approvingly referred to the observations of Lord Denning in Roe and Woolley vs. The Ministry of Health and An Anesthetist 75: "Every surgical operation is attended by risks. We cannot take the benefits without taking the risks. Every advance in technique is also attended by risks. Doctors, like the rest of us, have to learn by experience; and experience often teaches in a hard way."

MEDICAL MALPRACTICE STRESS SYNDROME

Doctors sued for negligence are dismissed from the private hospital as it brings bad name in media. Doctors lose job and are harassed financially; they lose precious time in attending courts on dates of hearing and lose time in waiting for their turn that could be used in making progress in medicine. Doctors are stressed socially and psychologically. So prevention of negligence is better than facing the allegations in court.

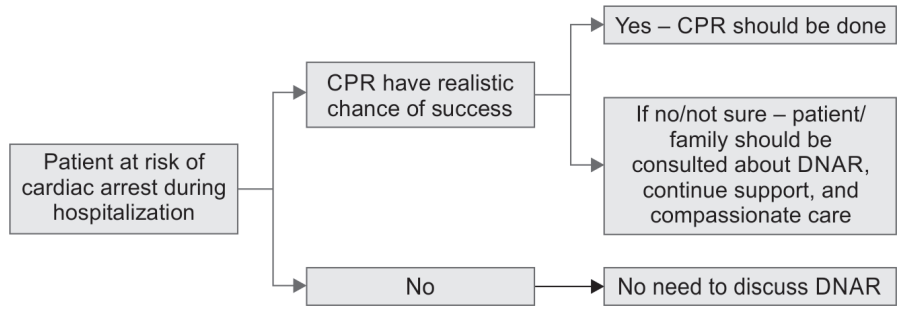
MEDICAL INDEMNITY INSURANCE

Medical indemnity insurance is provided by insurance companies to doctors, nursing homes, or hospitals to pay compensation to patients claiming for medical negligence and malpractice.

DO NOT ATTEMPT RESUSCITATION GUIDELINES

Cardiopulmonary resuscitation (CPR) is an emergency procedure performed in an attempt to revive a patient suffering from cardiac and/or respiratory arrest. In certain situations, providing CPR is likely to increase the suffering of a patient who has a serious and terminal illness. Doctors and hospitals are regularly faced with an ethical dilemma to perform CPR or not. Do not attempt resuscitation (DNAR) is an option that may be exercised by the treating physician in such a situation in the best interest of the patient. DNAR relates to CPR only and its limited value in a certain situation and not to other forms of treatment. The Indian Council of Medical Research (ICMR) guidelines aim to guide the treating physician and patient/surrogate in preserving dignity in death and avoid prolonged suffering to a patient through nonbeneficial CPR while continuing to provide other potentially curative and supportive care. Open communication and decision-making would enhance mutual trust and respect between the treating physician and patient/surrogate (**Flowchart 1**).

- DNAR would apply to a patient with a progressive debilitating, incurable, terminal illness where CPR would be inappropriate, nonbeneficial, and likely to prolong the suffering of the patient in the best judgment of the treating physician. DNAR should be discussed with sensitivity. Compassionate care is important while applying this principle.
- DNAR is distinct from withdrawal or withholding of other life support treatment, and advance directives do not come under the purview of this document


Patient at risk of cardiac arrest during hospitalization
CPR have realistic chance of success
Yes – CPR should be done
If no/not sure – patient/ family should be consulted about DNAR, continue support, and compassionate care
No
No need to discuss DNAR

(CPR: cardiopulmonary resuscitation; DNAR: do not attempt resuscitation)

FLOWCHART 1: Do not attempt resuscitation algorithm.

- There should be an adequate opportunity, time, and space to discuss with the patient and family in private and facilitate a clear understanding of DNAR and its implication. This should be done in anticipation of an impending cardiac arrest during current hospitalization.
- Teamwork and good communication are of crucial importance in decision-making. A combined decision may be taken with the help of another physician, psychologist, social worker, counselor, or hospital administration.
- The DNAR form should be available in the language understood by the patient/surrogate and treating physician. In case the patient/surrogate does not sign the DNAR form, the same should be recorded.
- Hospital administration should make effort to sensitize their healthcare professional on all issues related to DNAR.

EUTHANASIA

The word euthanasia is derived from a Greek word which means "a good death." In the current world, euthanasia has been defined as bringing about a gentle and easy death for someone suffering from an incurable and painful disease or in an irreversible coma (Pearsall and Trumble). Euthanasia may be classified on the basis of informed consent as follows:

- *Voluntary euthanasia*: Euthanasia conducted with the consent of the patient. It is legal in Belgium and Luxembourg.
- *Nonvoluntary euthanasia*: Euthanasia conducted where the consent of the patient is unavailable, e.g., child euthanasia which is illegal worldwide.
- *Involuntary euthanasia*: Euthanasia conducted against the will of the patient.
- *Passive and active euthanasia*: Passive euthanasia involves the act of omission which often involves withdrawing of life support measures, such as artificial feeding and antibiotics which are necessary to continue with life.

Legal Status of Passive Euthanasia in India

On March 7, 2011, the Supreme Court of India legalized passive euthanasia by means of the withdrawal of life support to a patient in a permanent vegetative state. The decision was made as a part of the verdict in a case involving Aruna Shanbaug who has been in a vegetative state for 37 years in King Edward Memorial Hospital. The High Court rejected the active euthanasia by means of lethal medication (injection) which is still illegal in India and most of the countries. In the absence of the law regulating euthanasia in India, the court stated its decision to become the law of the land until the Indian parliament enacts a suitable law.

DISCHARGE AGAINST THE MEDICAL ADVICE FROM THE EMERGENCY DEPARTMENT

Discharge against the medical advice is a common problem, in which a patient chooses to leave the hospital before the treating physician recommends the discharge. Discharge against the medical advice is a problem for many physicians who treat a hospitalized patient and expose the patient to the risk of inadequately treated medical problem and result in the need for readmission. Many physicians struggle with the desire to respect the patient's wishes to leave against the medical advice. In practice, managing this issue presents more complications than simply identifying and prioritization.

Physician–patient communication, informed consent, and underlying psychiatric issues are relevant in practical management. Understanding why a patient chooses to leave the hospital against the medical advice is important so that interventions can be done earliest in a high-risk patient to prevent morbidity and mortality.

Managing Against Medical Advice Discharges

An informed consent is one of the important elements of care in a patient who has decided to leave. An informed consent means that the patient has arrived at the decision in consultation with his/her physician and fully understands the risk, benefit, and alternatives of the decision. An informed consent in discharge planning can be straightforward if the steps are clear. Few questions should be included in the evaluation form of a patient who is leaving against medical advice, e.g., Does the patient understand the admission diagnosis, prognosis, risk, and benefits of leaving the hospital? Is the patient aware of alternative treatment? Can the patient communicate choice? Can the patient articulate reason?

Follow-up

After discussion and discharge with his/her physician and an informed decision to leave against the medical advice has been made, the physician's responsibility is to ensure that the discharge is safe and appropriate as possible, helping the patient to follow-up after discharge.

MEDICOLEGAL IMPLICATIONS OF A PRISONER ABSCONDING FROM THE EMERGENCY DEPARTMENT

Absconding of a patient from the emergency department is of great concern, especially if the patient is under trial or a prisoner. As a result of absconding, the treatment and safety of this patient as well as the safety of society is at risk. Absconding is associated with an increased risk of suicide, self-harm, homicide, and missing from the society. Broadly, absconding has been defined as leaving the hospital without permission. This might be due to differences in the inpatient clinical profile and hospital environment. The common diagnosis in the absconding group is psychiatric and related disorder and substance-use disorder. Whenever a prisoner admits into the emergency department for treatment, he or she is mostly accompanied by the police force. Most of the events occur during daytime, because at that time many more people move around and visit, making it less difficult to make way for the exit. Increase in staffing security in nursing care helps in improving the monitoring and observation of inpatient.

HOW TO DECLARE A PATIENT BROUGHT DEAD?

In every hospital, occasionally a patient is brought to the emergency department who is apparently dead or dead-on-arrival (DOA). Such cases may be natural death or unnatural death. Every doctor should be aware of the procedure to be followed in DOA cases, because such cases have legal, ethical, and social ramifications. Ethically and legally, a doctor should immediately declare a person dead once the diagnosis of death can be clearly established. Legally, the cause of death certificate has to be issued by the doctor in all natural death and after medicolegal autopsy in all unnatural death. The next to kin/relatives get the death certificate by municipality/corporation/panchayat.

Procedure to be Followed in Brought Dead (Dead on Arrival)

First and foremost, all cases of brought dead should be documented clearly in a death register or a brought-dead register; subsequently, adequate history should be collected regarding the event before death, related to disease, drug usage, and injuries, and complete examination of the dead body should be performed. If there is injury, poisoning, signs, or suspicion regarding the nature of death, the case should be registered as an MLC and jurisdictional police must be informed. The body must not be handed over to relatives; the dead body should be shifted to the mortuary (or an empty and safe room if no mortuary is available) and one must wait for the police to arrive and take necessary action.

If there are no injuries or poisoning sign and it looks like a case of natural death and was treated in the same hospital (any doctor of the same hospital), then the cause of death certificate can be issued by the hospital (after persuading all treatment notes, discharge summary, and case sheet), and the dead body can be handed over to relatives for final rites.

If there are no injuries or poisoning signs and it looks like natural death and if the case was not treated by any hospital or doctor, then the case has to be made medicolegal and jurisdictional police must be informed immediately. The body should not be handed over to relatives and they should be informed that this is the only way to get legally a cause of death certificate.

In some hospital, they issue only "brought dead certificate" certifying mere confirmation of death but not the cause of death, is unethical and illegal and misleading. This may lead to false statistics about disease and conditions.

GRIEF COUNSELING

Grief counseling refers to a specific form of therapy which focuses on general counseling with the goal of helping the individual grieve and address personal loss in a healthy manner. Grief counseling is offered by a psychologist, counselor, or social worker. The specific task of grief counseling includes emotional expression about the loss, accepting the loss, adjusting the life after loss, coping with changes within oneself, and the world after the loss. Typical feelings experienced by an individual and addressed in grief counseling include sadness, anxiety, anger, loneliness, guilt, isolation, confusion, or numbness.

The purpose of grief counseling is to help an individual work through the feelings, thoughts, and memories associated with the loss of loved ones. Grief counseling is generally directed toward positive adjustment following loss after the death of loved ones. Grief counseling helps an individual cope with the pain associated with the loss, feel supported through the anxiety surrounding life changes that may follow the loss, and develop strategies for seeking support and self-care.

SUMMARY

There is no doubt that advances in medicine have improved the quality of healthcare being provided to the patients. However, there has also been a rise in unrealistic expectations from the physicians. Many times, patients are not willing to accept anything less than complete recovery. The allegation of medical negligence is a stressful event for every physician, and even if the physician is not found guilty of medical negligence, a lot of suffering has already occurred. It is extremely important for physicians to understand the meaning, scope, and legal interpretation of the term "medical negligence" so as to face the problem head-on.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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20 CHAPTER

Examination of Sexual Abuse Victim

Nikhil D Datar, Meghna Shedge

INTRODUCTION

Rape is one of India's most common, injurious, and heinous crimes against women. Statistics state that every 15 minutes, a woman reports rape in India. It causes severe physical, mental, and social trauma to the victim. The effects are devastating, extending to consequences such as unwanted pregnancy, sexually transmitted infections, sleep and eating disorders, and other emotional and physical problems.

Health professionals play a dual role in responding to the survivors of sexual assault. The first is to provide the required medical treatment and psychological support. The second is to assist survivors in their medicolegal proceedings by collecting evidence and ensuring good quality documentation. For accurate examination and evidence collection, it is important that every doctor understands what constitutes the offense of rape.

DEFINITION OF RAPE

According to the provisions of the Indian Penal Code (IPC) further amended in 2013, section 375 defines rape as: A man is said to commit rape if he (a) penetrates his penis, to any extent, into the vagina, mouth, urethra, or anus of a woman or makes her to do so with him or any other person; or (b) inserts to any extent any object or a part of the body, not being the penis, into the vagina, urethra, anus, or any part of the body of such a woman or makes her to do so with him or any other person or; (c) manipulates any part of the body of a woman so as to cause penetration into the vagina, urethra, anus, or any part of the body of such a woman or makes her to do so with him or any other person or; (d) applies his mouth to the vagina, anus, urethra of a woman or makes her do so with him or any other person.

Under the circumstances falling under any of the following seven descriptions:

1. Against her will.
2. Without her consent.
3. With her consent when her consent has been obtained by putting her or any person in whom she is interested in fear of death or hurt
4. With her consent when the man knows that he is not her husband and that her consent is given because she believes that he is another man to whom she is or believes herself to be lawfully married
5. With her consent when at the time of giving such a consent, by reason of unsoundness of mind or intoxication or administration by him personally or through another of any stupefying or unwholesome substance, she is unable to understand the nature and consequences of that to which she gives consent
6. With or without her consent, when she is under 18 years of age
7. When she is unable to communicate consent

PRESENTATION IN AN EMERGENCY DEPARTMENT

A rape survivor may present to an emergency room in different situations:

- *In a critically ill condition (brought by police or any other person)*: The primary response of a healthcare provider should be to provide resuscitation and immediate treatment to the survivor irrespective of the fact whether a police complaint has been made or not. Admission, evidence collection, or filing a police complaint is not mandatory for providing treatment. The survivor is brought to the emergency room (ER) by the police. After a quick triage if found to be physically and mentally stable, examination and evidence collection may be undertaken after the consent of the victim.
- *The survivor comes directly to the ER without informing the police*: After a quick triage to confirm that the survivor is in a stable condition, further examination can be undertaken after the consent of the survivor. The hospital is responsible to notify the police of this serious and cognizable offense. If the survivor does not wish to pursue the police complaint, she may refuse to give consent for evidence collection. The refusal needs to be recorded in writing. It is the survivor's decision whether to file an FIR or not.

EXAMINATION

Who should carry out the examination of the rape survivor? Section 164 (A) of the Criminal Procedure Code states that: Examination of a case of rape shall be conducted without any delay by a registered medical practitioner employed by a government hospital or local authority.

Any registered medical practitioner can conduct the examination and it is not mandatory for a gynecologist to examine such a case. If in case a female doctor is not available for examination, a male doctor should conduct the examination in the presence of a female attendant. In case of a minor/person with disability, his/her parent/guardian/any other person with whom the survivor is comfortable may be present.

The Criminal Law Amendment Act, 2013, in Section 357C Criminal procedure code states that: Both private and public health professionals are obligated to provide treatment, and denial of treatment is punishable under Section 166 B IPC with imprisonment for a term which may extend up to 1 year or with a fine or with both.

Thus, it is clear that every hospital should be equipped to handle such an examination in a quick and effective way to provide uniform and comprehensive healthcare services. In order to achieve this, the following may be considered:

- Every hospital should have a standard operating procedure (SOP) for the management of cases of sexual violence and these must be printed and available to all staff of the hospital.
- The administrative guidelines regarding interdepartmental handling of such cases for examination and evidence collection should be clear to all the staff.
- The administration should simultaneously help the clinical staff to inform the police and complete medicolegal procedures.
- The hospital should have a uniform method of examination and evidence collection. A kit with required pro forma along with the utilities such as nail cutters, syringes, and swabs can be kept ready for immediate use. [The author was instrumental in setting up the Sexual Assault Forensic Evidence (SAFE) kit.]
- Health professionals need to maintain a clear and foolproof chain of custody of medical evidence collected and referring to appropriate agencies for further assistance (e.g., legal support services and shelter services).

QUICK ASSESSMENT

A doctor should ascertain the general condition of the victim and the vital parameters. Injuries and hemorrhage may put the victim's life at risk and if so, treatment must be initiated. The examining doctor should be well aware of the comprehensive care to be provided. As soon as the rape survivor reports to the hospital, initial resuscitation and treatment should be given, followed by consent, detailed history, evidence collection and documentation, and treatment (**Flowchart 1**).

Informed Consent

Consent should be taken for examination, evidence collection, treatment, and police intimation. The doctor shall inform the victim about the nature and purpose of examination and in case of a child, the child's parent/guardian/person in whom the child reposes trust will be informed. This information should include the following:

- Medicolegal examination is to assist the investigation and prosecution of those who committed the sexual offense. This may involve an examination of the mouth, breasts, vagina, anus, and rectum.
- To assist the investigation, forensic evidence may be collected with the consent of the survivor. This may include removing and isolating clothing, scalp hair, foreign substances from the body, saliva, pubic hair, samples taken from the vagina, anus, rectum, mouth, and collecting a blood sample.
- The survivor or in case of a child, the parent/guardian/person, in whom the child reposes trust, has the right to refuse either a medicolegal examination or collection of evidence or both, but that refusal will not result in denial of treatment to the survivor.
- As per the law, the hospital/examining doctor is required to inform the police about the sexual offense. However, if the survivor does not wish to participate in the police investigation, informed refusal will be documented.

The nature of forensic evidence collected will be determined by three main factors: (1) Nature of sexual violence, (2) Time elapsed between the incident of sexual violence and examination, and (3) Whether the survivor has bathed or washed herself.

The Statement

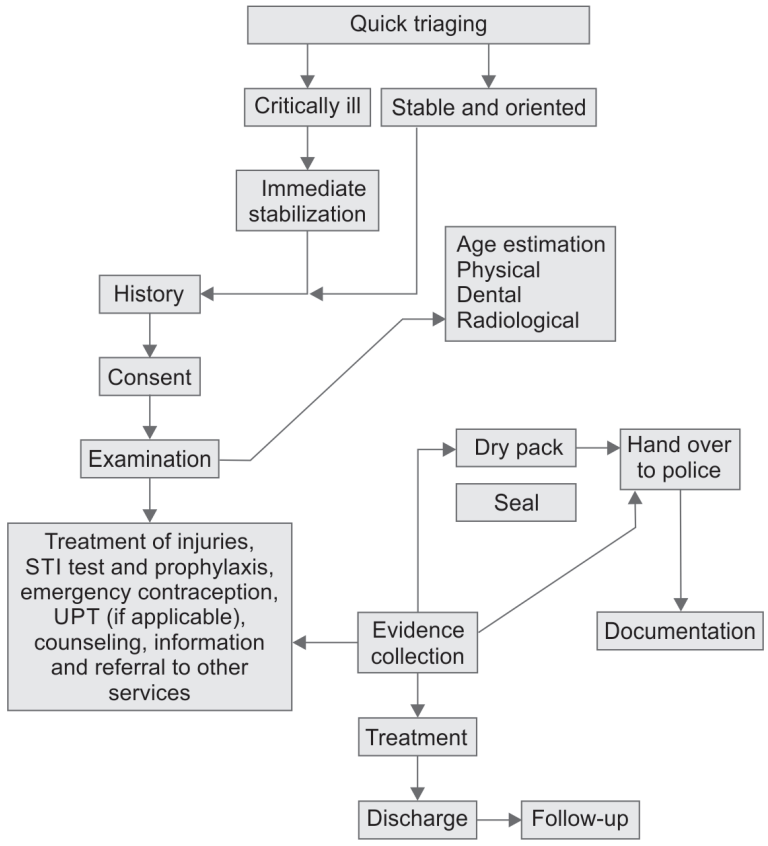
The examiner must be tactful and sympathetic to the victim while taking the statement. The exact narration by the victim is very important and the statement must be written down in her own words as near as possible verbatim. No false modesty should be allowed in writing. The statement may include direct questioning bringing out details about:

- The place and time of incidence
- The number of assailants
- The amount of violence
- Position
- Resistance offered
- Pain, hemorrhage, sensation of penetration, and emission
- Clothes which the victim has worn
- The statement must include whether the victim has changed clothes, urinated, or douched her vagina.

Clothes: The corroborative evidence on clothes speaks for itself. Examining the clothes when the victim has not changed them is very important. The tear in the fabric, marks of mud, stains of blood, and semen should corroborate with the statement of the victim. Clothes should be looked for foreign hair and pieces of clothing different from one worn by the victim (which could belong to the assailant). The clothing should be retained, labeled, and sent for examination.

GENERAL EXAMINATION AND INJURIES

At the time of history taking, examination, and evidence collection, any police personnel should not be present. The whole body must be examined for marks of violence. The victim should be requested to undress herself. Special attention should be given to the nature of the injuries.



(STI: sexually transmitted infection; UPT: urine pregnancy test)

FLOWCHART 1: Summary of managing a sexual abuse victim in the emergency department.

Common injuries are as follows:

- *Head*: Blow on the head or head injury due to fall
- *Neck*: Gripping of throat
- Injuries on cheeks, lips, breast, and chest are common.
- Generalized bruises, lacerations, contusions, bite marks, nail marks
- The marks of rope knots on the wrists and ankles

The examiner should strive to ascertain the following:

- Whether these marks are of injuries or self-inflicted
- Apparent development of the victim's body
- Amount of resistance offered
- Corroboration with the statement of the victim

Examination of the Nails

Scraping from the nail beds constitutes important evidence. Tags of epithelium, hairs, pieces of clothes, and bloodstains are important to collect.

Gait

A note of the victim's gait must be made. If consent is available, the victim's blood should be collected for grouping. This will help in ascertaining whether bloodstains are of the victim or the assailant. A second examination after 48 hours may reveal deep bruises, which may not be evident at the first examination.

Examination of Genitals

A gynecological examination should be conducted in a lithotomy position and in good light. The history of the last menstrual period must be asked for to differentiate menstruation from bleeding due to injuries.

Local Signs of Violence

Pubic hair: Pubic hair may be combed for foreign hairs. Pubic hair matted due to seminal stains, blood, or secretions may be cut and preserved. Stains of blood or semen from the skin must be scraped bluntly and preserved.

Collection of Vaginal Secretions

Instillation of 15 mL of normal saline in posterior fornix can be done and aspiration of contents can be collected and examined. A wet preparation when studied under a microscope may reveal motile or nonmotile spermatozoa. The absence of a spermatozoon does not mean the absence of intercourse. Ziehl–Neelsen staining of another slide may reveal acid-fast, rod-shaped organisms, which are smegma bacilli.

Evidence of Venereal Disease

The examiner should keep in mind signs of various venereal diseases such as syphilis, gonorrhea, and chancroid.

Injuries

Hymen: Especially in a virgin victim, examination of hymen is important. Signs of recent rupture of hymen are ragged edematous edges of the hymen and hemorrhage.

Examination of vagina: Distensibility of vagina should be noted in relation to the number of fingers it admits. The character and extent of injury will vary in proportion to the following:

- Disproportion of male and female organs
- Whether the victim is virgin or not
- The extent of penetration
- Amount of force

Lacerations of the posterior fourchette are very commonly associated with forceful intercourse, especially with a virgin. Finger penetration may lead to lateral vaginal wall tears. Bruising and lacerations in the vagina also must be recorded properly. The absence of injuries may be due to the inability of the survivor to offer resistance to the assailant because of intoxication or threats. Pictorial representation of these injuries can be very helpful for corroborative evidence.

DOCUMENTATION

The collected samples for evidence are properly packed, sealed, and preserved in separate envelopes in the hospital till the time police are able to complete their paperwork for dispatch to a forensic laboratory for tests including DNA. A copy of all documentation (including that pertaining to medicolegal examination and treatment) must be provided to the survivor free of cost.

TREATMENT

Medical treatment should include:

- Measures should be taken to prevent the sexually transmitted diseases
- Emergency contraception
- Prophylaxis for tetanus, hepatitis B, and HIV
- Treatment of wounds
- Counseling and psychological support

Survivors of sexual violence should receive all services completely free of cost. This includes outpatient department (OPD)/inpatient registration, laboratory and radiology investigations, urine pregnancy test (UPT), and medicines. The casualty medical officer must label the case papers for any sexual violence case as "free" so that free treatment is ensured. Each survivor copes up differently and hence psychological support and counseling can help in overcoming trauma and recovery from sexual assault.

EMERGENCY CONTRACEPTION

Emergency contraception can stop pregnancy before it starts. Emergency contraception is a safe way to prevent unintentional pregnancy due to unprotected sex, contraceptives failure, condom rupture, slippage diaphragm, forgotten oral pills, or following sexual assault. Rape resulting in unintended pregnancies causes mental and social burden to the women and society as a whole. Emergency contraception intervenes and prevents a number of unwanted pregnancies by reducing the maternal mortality and morbidity. Emergency contraception is also known as morning-after or postcoital method. It is similar to oral contraceptive but hormone doses are higher. Developing embryo or an established pregnancy is not affected by emergency contraceptives (ECs). EC is effective only if taken on the first few days of unprotected sexual exposure before the sperm fertilizes the ovum.

Emergency Contraceptive Use in India

India was a part of research trial by the World Health Organization (WHO) in 1995–1997 and 1998–2001. Report and recommendations were released in 2001 and EC was approved by the Drug Controller General of India. Nowadays, EC is an important method of contraception for unprotected sex and is most effective if taken within 12 hours of unprotected sex. Awareness is required among women about the timing of dose of the EC. This method is one-time use only so efficacy cannot be calculated by the Pearl Index. In India, maternal mortality is high and mostly due to unsafe abortion. Judicious use of EC plays an important role in reducing mortality and morbidity due to unsafe abortion.

Types of Emergency Contraceptive Pills

Ulipristal: It is more effective than progestin-only or combined pill in preventing unprotected pregnancy. It was approved in 2010 and can be taken up to 120 hours after unprotected intercourse.

Progestin-only: Progestin levonorgestrel 1.5-mg single dose or 750 μg 12 hours apart in two doses can be taken up to 72 hours.

Combined pill: It contains both estrogen and progestin in a higher dose. It delays the ovulation and is the most effective if taken within 3 days of unprotected intercourse.

Emergency Contraceptive Use

History of the last menstrual period, length of cycle, time since the last unprotected intercourse, any history of chronic illness, and physical examination are not generally required; however, Urine Pregnancy Test is recommended if pregnancy is suspected. Follow up after the use of emergency contraceptive if menstruation occurs within 7 days or expected periods; counsel and encourage for regular methods. If no menstruation occurs within 7 days or expected periods, perform a Urine Pregnancy Test; if it comes negative, wait for 1 more week and, if positive, counseling is recommended. There are no serious side effects of EC but only mild, which resolve within 24 hours. Mild side effects are nausea, vomiting, mild headache, mild tenderness in breast, dizziness, fatigue, and delay in menstruation.

SUMMARY

The aim of the examination is to provide holistic health advice and to collect evidence for forensic examination. The legal duty of the doctor is to collect accurate evidence regarding the use of force and the signs of offense. The judiciary has to pronounce the verdict if the crime of rape has occurred or not. All efforts must be made to carry out the examination in a quick, uniform, and systematic manner keeping in mind the

dignity of the woman. Any physician from the government or private sector may conduct the examination. In case a female physician is not available, a male physician can conduct the examination in the presence of a female witness. The Ministry of Health and Family Welfare of the government of India has made uniform guidelines and ready pro forma to assist the physician in dealing with sexual assault survivors and their examination. These can be downloaded from https://main.mohfw.gov.in/reports/guidelines-and-protocols-medico-legal-care-survivors-victims-sexual-violence.

MULTIPLE CHOICE QUESTIONS

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21 CHAPTER

End-of-life and Palliative Care in the Emergency Department

Naeem Toosy

INTRODUCTION

Emergency medicine is the acute specialty dealing with undifferentiated patients. Other than initiating the diagnostic process, identifying patients who may deteriorate, and resuscitating patients, the specialty has a holistic remit that extends to public health. Emergency departments (EDs) provide an access point for patients with chronic illnesses as well as those who are approaching the EOL. Easy access means that these departments are well placed to provide a safety net for patients who fall through the cracks of a healthcare system increasingly fragmented between various specialties and subspecialties.

Though many patients who know they are dying express a preference to remain at home during their final journey, the fact remains that many actually end up visiting an ED in the last few months of their life. Among the reasons for this often is inadequate communication in the lead-up period from the various specialists with their curative focus, the inability of patients or their families to cope with symptoms, inadequate social support, and cultural factors. The ED assumes an important role at this juncture of their lives as decisions about the trajectory of hospital care and initiation of life-sustaining interventions (e.g., mechanical ventilation and dialysis) are influenced by what happens in the ED.

The World Health Organization (WHO) defines palliative care as "*an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual.*" Investigations such as the SUPPORT trial (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment—JAMA 1995) have shown that currently, the ill or dying patients receive care that often, unfortunately, does not meet their expectations. This may be due to the fact that in the ED environment, it can be a challenge to address the EOL needs of a patient and his/her families.

However, by engaging the patient and his/her families in conversations about their goals of care, the trajectory of their illness, option in palliative care, and its associated hospice services, the emergency physician can significantly improve the quality and experience of patients approaching the end of his/her life. Such activity is in keeping with recommendations of international organizations such as the American College of Emergency Medicine (ACEM). The American College of Emergency Physicians (ACEP) on its website suggests a screening tool. Such tools can be used by anyone in the healthcare team, i.e., physician, nurse, and social worker, to screen and flag patients who may benefit from palliative care.

An ACEM expert consensus group placed core topics in palliative care that the emergency physician should be cognizant of into the following three groups:

1. Recognition of the EOL needs of the patient
2. Essential primary palliative care skills
3. A logistic understanding of palliative care delivery in the ED

TRAJECTORY OF DYING AND END-OF-LIFE DECISION-MAKING

Despite the challenges of predicting life expectancy accurately, it is still useful to recognize when a patient has entered the final stages. This is especially important when we realize that a significant proportion of healthcare spending is incurred in the final few months of a patient's life, without necessarily giving patients or their families satisfaction or contentment with the healthcare system.

Four dying trajectories have been described: *Terminal illness, organ failure, frailty,* and *sudden death.* Familiarity with these trajectories can assist the physician to contextualize these illness presentations and improve the recognition of the end of life. An example of terminal disease is metastatic cancer. Patients with metastatic cancer whose prognosis is poor nevertheless tend to maintain relatively good function until the very end. Once these individuals are significantly weakened by the illness, then their final trajectory is reasonably predictable.

Congestive heart failure and chronic obstructive airway disease are common EOL organ-failure diagnoses. Though patients who suffer from such conditions have a decline in their overall health over time, there are often sharp spikes of

deterioration but also unexpected recoveries. It is, therefore, challenging in the short term to prognosticate on their final decline. In addition, there may be other considerations such as the eligibility of such patients for organ support technology, e.g., ventricular assist device or extracorporeal membrane oxygenation (ECMO), which can be a bridge to transplantation or recovery. In these cases, unless the goals of therapy have been clearly defined before acute deterioration, it may be beyond the emergency physician to initiate palliative care. The emergency physician may be in a position to initiate such a discussion with the patient or family.

Frailty is characterized by the patients who reside in long-term care facilities or who are dependent on family care which might be due to advancing dementia or other severe incurable neurologic conditions. Often, a patient may be profoundly disabled for months to years prior to his/her ultimate demise, which often occurs from complications of the underlying illness rather than the disease itself. These complications are often the reason for their attendance to an acute care facility. Though a single hospitalization may not portend the final trajectory, a number of hospitalizations over the recent past can be a red flag that gives an opportunity to explore the patient's goals of care.

Although not common, sudden cardiopulmonary arrest is another trajectory as patients, who experience sudden or dramatic deterioration in the community, most often are brought to the ED. The resuscitative attempt and the intensive care admission for those who achieve a return of spontaneous circulation (ROSC) are often resource-intensive but without the outcome one would desire. This is especially true in those patients who are already critically ill (e.g., end-stage cancer) or who have an exceedingly low chance of either survival or return to a functionally independent status. Massive myocardial infarction, especially in the setting of previous myocardial damage, intracranial emergencies, and traumatic brain injuries, are other examples of conditions from which the prospect of meaningful survival may be limited and decisions on withdrawal of life-sustaining treatment may be necessary. This is why in patients with underlying health issues, a proactive approach to discussing these issues should be adopted so that there is time for them to consider their decisions and come to terms with them.

At the heart of EOL, care is understanding the patients' and families' preferences. The fact that some of the interventions are time-critical make it much more of a challenge to explore these preferences in the ED. As a majority of patients lose decision-making ability near the EOL, then this is the only critical time for emergency physician to decide.

- If there is an advance directive, and
- If not, to ensure that the patient's appropriate surrogate decision-maker is identified

Clearly, knowledge of the laws of the jurisdiction one is working in is useful as these directives can take the form of living wills, out of hospital DNR [do not resuscitate orders, physician orders for life-sustaining treatment (POLST)], etc., in different places.

When no written directives exist, then previously expressed wishes from an appointed decision-maker or surrogate (on occasion, a legally appointed healthcare proxy) may be sought. In many developing countries, there may not be formally established mechanisms to register these decisions or there may be cultural, religious, or legal challenges.

PALLIATIVE CARE AND BIOETHICS

The basis of decision-making in these situations is guided by bioethics. Specific bioethical issues relevant to EOL care include the principles of:

- Autonomy and self-determination
- Futility
- Justice
- Declaration of death and organ donation

Autonomy refers to an individual's right to make the decision about his/her own healthcare. However, in order to exercise this right, an individual should be competent and has the capacity. Capacity can be determined by medical and/or psychiatry professionals; however, competence can only be determined by a court. It is important to realize that even a surrogate decision-maker should only make decisions that they believe represent the patient's own wishes.

Decisions on the futility of therapy require trust between the family of the patient and clear and open communication with the medical team. Occasionally, due to either lack of trust of the patient or his/her family's religious or cultural beliefs, there is an impasse between medical professionals and the patient or his/her family. In these situations, a family may wish to seek another opinion or transfer the patient to another accepting healthcare facility. In rare cases, courts have been called on to mediate or make decisions. These processes are generally beyond the scope of the EDs and it will be necessary to involve palliative care professionals and/or the institution's ethical committee.

The principle of justice revolves around the stewardship of resources, especially intensive care unit (ICU) beds. Improper utilization of ICU beds can take up precious resources that could have been utilized for patients who are likely to benefit from advanced interventions such as extracorporeal life support, dialysis, and transplants. However, resource allocation is something that needs to be decided at a macro level and is often beyond the scope of the individual clinician. Trust, transparent communication, and cooperation are needed between regional institutions in order to utilize these resources efficiently.

Organ donation and declaration of death require clear pathways and legislation. Investment in these is worthwhile as it means organs can be recycled to help individuals with end-organ failure. In an ED, it is not uncommon to pronounce circulatory death in a patient not responding to resuscitative measures; however, the diagnosis of brain death is more involved and requires several physicians performing tests generally beyond the scope of an ED.

COMMUNICATION AT THE END OF LIFE

On a practical level, communication is one of the cornerstones of EOL care. These skills are needed by emergency physicians involved in these challenging but important conversations with patients and their families. The goal of effective communication is to enable "*shared decision-making,*" defined by the Institute of Medicine as "*care that is respectful of and responsive to individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions.*"

The concept of "*decision frames*" is a key one because the way information is presented to patients can have a significant impact on the decisions they make. In 1981, Tversky and

Kahneman suggested the prospect theory. According to this theory, when choices are presented in terms of the possibility of further gain, then people are less likely to take risks; however, when the choice increases the possibility of losing something, people are willing to take more risks. This is often because if the available decision is framed wrongly, then a patient with even a vanishingly small prospect of benefit may end up being intubated and ventilated.

In communication, the general principle is to use an "*Ask-tell-ask" approach*, allowing patients to express their emotions and feelings as well as their reservations and fears. There are several guides for the way to structure a goals-of-care discussion. The ACEP suggests one on its palliative care web page. Other examples include the guide proposed by Buckman and Kason or the six-step approach that uses the *SPIKES acronym* (**Box 1**).

A structured approach to responding to the participant's emotions is summarized by the *NURSE* acronym which reminds us to *Name* the emotion that the participant seems to be experiencing while showing *Understanding* of the emotion and *Respecting* it. It is also important to *Support* the participant and *Explore* an aspect of his/her emotion in order to establish an empathetic connection.

Although these skills can be taught and improved, the physician also needs to be genuinely empathetic and caring for this not to be a hollow exercise. It is important to be aware of communication behaviors that impact the encounter negatively. These include avoiding difficult topics, lecturing the patient with facts while failing to deal adequately with the emotional content of the conversation, colluding with the participants in avoiding difficult topics, and offering reassurance prior to allowing the patient to express his/her emotion fully.

BOX 1: SPIKES guide to a goals-of-care discussion.

Setup (S): Key preparation step to ensure that interruption-free and private conversation can take place

Perception (P): It is important to start by exploring the patient and family's perceptions

Invitation (I): The participants should be invited to share how much information they want to disclose

Knowledge (K): The information should be presented in a clear way in common language allowing time for comprehension and questioning

Empathy (E): It is important to let participants express their emotions and to empathize with them

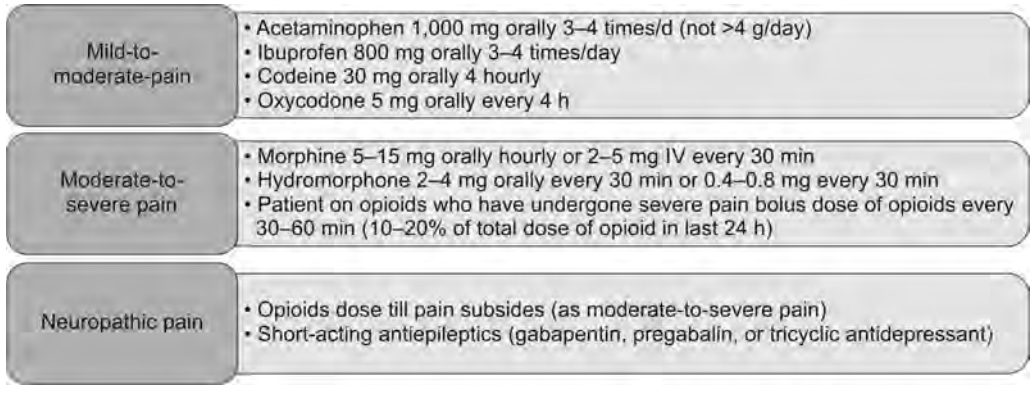
Summarizing (S): Summarizing the conversation to ensure that there is agreement on what has been discussed

END-OF-LIFE SYMPTOMS MANAGEMENT

On a practical level, a patient with an EOL trajectory often comes to the ED to seek relief symptoms that have overwhelmed him/her, his/her family, or his/her caregivers. The emergency physician needs to confirm the patient's diagnosis and prognosis, ascertain what arrangements are already in place, and initiate an open empathetic dialogue. It is important, therefore, for an emergency physician to have an understanding of common and distressing EOL symptoms and some of the ways in which these may be relieved.

It is important to realize that good palliative care dictates an active strategy that aims to relieve the patient from distress, e.g., pain (**Flowchart 1**). Common distressing symptoms at the EOL include *dyspnea, increased respiratory secretions, managing pain, fatigue, anxiety, delirium,* and *common gastrointestinal (GI) symptoms such as nausea, vomiting, constipation, or diarrhea* (**Table 1**). Although it is important to consider treatable disease processes that may be the cause of these symptoms, it may well be that no significant pathological process is found after a thorough assessment.

As an example, although a patient complaining of dyspnea may have treatable pathology such as pulmonary embolism, often the cause of the patient's symptoms may be subjective. In the absence of hypoxemia, the use of oxygen therapy is controversial, though it may be needed for patient appeasement. If needed though, high-flow nasal cannula or noninvasive ventilation should be considered prior to invasive mechanical ventilation. Simple measures, such as a fan, may also make a significant difference. Liberal use of opioids or benzodiazepines for air-hunger and anxiety, antipsychotics for agitation, antimuscarinics such as glycopyrrolate to control respiratory secretions, and medication to control gastrointestinal symptoms can be helpful. In an emergency situation, a distress protocol using a cocktail of drugs as suggested by Godbout may be considered to obtain rapid relief, giving time to consider the other factors.


Mild-to-moderate-pain
• Acetaminophen 1,000 mg orally 3–4 times/d (not >4 g/day)
• Ibuprofen 800 mg orally 3–4 times/day
• Codeine 30 mg orally 4 hourly
• Oxycodone 5 mg orally every 4 h
Moderate-to-severe pain
• Morphine 5–15 mg orally hourly or 2–5 mg IV every 30 min
• Hydromorphone 2–4 mg orally every 30 min or 0.4–0.8 mg every 30 min
• Patient on opioids who have undergone severe pain bolus dose of opioids every 30–60 min (10–20% of total dose of opioid in last 24 h)
Neuropathic pain
• Opioids dose till pain subsides (as moderate-to-severe pain)
• Short-acting antiepileptics (gabapentin, pregabalin, or tricyclic antidepressant)

(IV: intravenous)

FLOWCHART 1: Acute pain management during end-of-life care.

TABLE 1: Symptomatic treatment during end-of-life care.	
Nausea and vomiting	• Gastroparesis induced—metoclopramide (10–20 mg orally or IV every 6 h) • Medication, uremia induced—metoclopramide, haloperidol (0.5–2 mg IV 8 hourly), ondansetron (8 mg orally every 8 h) • Raised ICP-induced vomiting—dexamethasone (4–8 mg orally/intravenously once daily usually combined with other antiemetics) • Bowel obstruction induced—octreotide (100–200 µg subcutaneously 3 times per day), dexamethasone (4–8 mg orally/intravenously once daily)
Anorexia	Dexamethasone (2–4 mg orally/intravenously once daily)
Constipation	• Senna glycoside 1–2 tablets as a single dose per day • Bisacodyl 10 mg rectally once daily • Polyethylene glycol (PEG)
Dyspnea	Oxygen BiPAP morphine (2–4 mg IV every hour), nonpharmacological approach, e.g., breathing training, opening window for ventilation, elevation of head, end-of-the bed
Cough	• Codeine 30 mg orally every 6 h • Morphine 2–4 mg IV every hour as needed
Excessive oral secretion	Glycopyrrolate 0.2 mg IV every 4 h (maximum 4 doses)
Oral care	Pilocarpine 5–10 mg tablet orally 3 times daily, antimicrobial mouthwash, oral hydration mouth swab, lip balm humidifier
Fever	• Acetaminophen 650–1,000 mg orally/IV every 6 h, maximum 4 g/day • Naproxen 250–500 mg orally twice daily
Anxiety insomnia	Lorazepam 0.5–2 mg orally/IV every 6 h, psychological intervention will be more helpful, risk of fall may increase with sedation
Delirium	Haloperidol 0.5–1 mg orally/IV every hour. Agitated refractory cases, additional antipsychotics agents, and benzodiazepines and careful monitoring

(BiPAP: bilevel positive airway pressure; ICP: intracranial pressure; IV: intravenous)

SUMMARY

Although palliative and EOL care traditionally is considered to be the remit of oncologists, specialists in palliative care, and intensive care doctors, increasingly some of the responsibility for the assessment and care of these patients is falling on emergency physicians. As improvements in public health, nutrition, and healthcare increase the proportion of the population that is elderly or has chronic health conditions, it is essential that all medical professionals have an understanding of the balance between the quantity and the quality of life.

As the ED is often at the interface of healthcare specialties and society, it is imperative that EOL and palliative care principles, communication, treatment options, disposition choices, and medicolegal aspects are incorporated into an emergency physician's training curriculum.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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ONLINE REFERENCES

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22
CHAPTER

Death Declaration

Rammohan Radhakrishnan, Sahanya Ramesh Shetty

INTRODUCTION

Certain aspects in the emergency department (ED) prove to be an uncomfortable and challenging part in resuscitation efforts; one such aspect is that of delivering the news of the deceased patient to his/her relatives. It is evident that sudden death in emergency rooms is a common phenomenon; however, most physicians find it to be a daunting task due to being undertrained in this aspect. Even after the regularity in experiencing sudden death in ED, physicians generally draw skills from their own past experiences and each has his/her own manner of delivering the bad news. Situations are trickier when it involves the death of a child. Hence, delivering bad news along with appropriate care after the death is a systematic and meticulous pattern one must follow in order to ensure peace and harmony amongst the relatives.

POSSIBLE CIRCUMSTANCES OF DEATH

Whatever the prognosis of the patient, death in a hospital takes place in two scenarios. (1) One is where the death of a patient may be expected. In this case, the relatives are aware of the long-standing condition of the patient and the chronic ailments he/she is suffering from. Somehow, this becomes a more justifiable cause of death in the eyes of the relatives. It is much commonly seen and much easier to be accepted by the family members. (2) The second is sudden death of the patient in the emergency room. This does not really give much time for the family members to anticipate such an outcome. Hence, it is too sudden and unexpected for them to deal with it lightly. These are scenarios where the relatives can get a little violent or frisky, if the situation is not being handled with much compassion and care. The attack of healthcare personnel involved is very likely to occur in such situations. The emergency consultant involved should be the one delivering the news with care, keeping in mind the state of mind of the family members.

EFFECT OF DEATH ON SURVIVORS

Situations may arise where the traumatic series of events may take a toll on the members of the family involved in the accident or attached very closely with the deceased. In such cases, immediate efforts must be put to make sure of their well-being physically and psychologically.

- Suicidal intentions must be taken seriously as the loss of a near and dear one can produce a sense of survivors' guilt. These can be more common in situations where the patient died of suicide. Turning down these conversations may not be therapeutic for the survivor and further add on to the process of grieving. Counseling regarding guilt and responsibility of the death of deceased must be started early.
- Spouses of patients, especially ones from many years of marriage, have an undying attachment with each other. They have a higher risk of dying after a short while.
- The most common symptoms presenting would be hallucinating the presence of deceased (auditory, visual), denial, prolonged hysteria, and/or anger. Such patients require psychiatric consultation.
- Asking for sedative medications for sleep or to reduce anxiety is also prevalent. Usually, they do not need to be treated with sedatives; rather they require verbal and behavioral therapy to help change their process of thought.
- Threats to other members of the family, such as criminal gang threats, are of a serious concern for the safety and security of the other family members. The police should be notified at the earliest.
- Usually, when one of the parents dies, the other parent is overburdened with the responsibility of taking care of the children. In such cases, the surviving parent does not get the time or opportunity to grieve for his/her spouse. This pattern must be observed by other family members, and time and space should be provided for the spouse to accept the loss of the deceased.
- In any of the above scenarios, where one might think of a need for help, possible methods would be: Psychiatric consultation, if required need for hospitalization, calling on relatives for care and support, or making sure that at least a helper is present at all times.

EFFECT ON EMERGENCY DEPARTMENT PHYSICIANS

Emergency physicians are on the go constantly at handling multiple patients with acute ongoing crises simultaneously.

Hence after declaring a death, physicians consider it mostly their own professional failure. With recent advances in medicine, death can be prevented in most scenarios; hence, physicians consider it as a defeat failure on their part at a patient's death. Physicians also may fail to answer some questions posed by the family members. The blame of death can also be put on the physician, which may add on to the fear of death or unresolved fears of death that may make the physician even more uncomfortable. Healthcare providers are often taught how to save lives during courses such as advanced trauma life support (ATLS), advanced cardiovascular life support (ACLS), and pediatric advanced life support (PALS). However, they are not prepared for the consequences in the event of the death of a patient and how to handle and deal with it. However, these matters can be resolved by adequate education of breaking the bad news to the family, which prevents in leaving a negative impact on them after the loss of the deceased.

COMMUNICATION STRATEGIES

Prior to Death

Update on Deterioration of a Patient's Condition

It is advisable to constantly update the family members at regular intervals about the condition of the patient. It should include information regarding the initial condition of the patient when the patient presented in the ED, medical intervention required, if resuscitation is underway, and prognosis of the patient. It is difficult task to constantly update the family about the patient condition. In the event of procedures, such as endotracheal intubation, defibrillation, and other invasive procedures, someone from the ED team can be sent to update the family. In very few cases, the patient's family is allowed to view the resuscitation efforts going on from a distance. This practice is not widely accepted and encouraged. It is quite debatable about the presence of family members at the time of resuscitation. Carefully explain to the family about the deterioration in condition and the possible causes of it and patiently listen to their questions and answer them. Try to develop a sense of trust between the family members and yourself. In order to enable an *efficient and considerable technique to communicate to the family*, a patterned mnemonic *ABCDE*, after Rabow and McPhee's, is established.

- *A—Advance preparation*:
  - Acquaint yourself with adequate clinical information about the patient. In the event of it, carry a few medical documents with basic clinical findings of the patient, i.e., laboratory results, medications administered. This will help in providing a clearer picture of the prognosis and treatment given, to the family.
  - Allocate a spate room where disruptions in conversation can be prevented. If possible, instruct staff not to interrupt, unless it is an emergency.
  - Prior preparation in mind about how to deliver the news to the family may help in maintaining a calm and composed conversation. It is always advisable that the attending consultant should deliver the news to the family. The ones with less experience may observe and learn from the experience.
  - Mentally prepare yourself about all possible outcomes from the family members.
- *B—Build a therapeutic environment/relationship*:
  - Prior to meeting all family members, ensure who wants to and who does not want to be a part of such conversations.
  - Before starting the conversation, introduce yourself to all present and ask for family members to introduce themselves too.
  - Be clear and discreet in delivering the news. You may also foreshadow it by saying, "I am sorry to say, but I have bad news."
  - Acknowledge cultural differences and personal considerations. Avoid touching the relatives if they prefer not to. Avoid using phrases of humor or irrelevant discussions not pertaining to the patient.
  - Try to develop a space for comfort during this conversation. This enables the relatives to ask any questions or doubts they have about the treatment provided. This helps in building a more trustful relationship between the doctor and the patient's family.
  - Avail for your time in the future as well. Family members may go through a tedious process of grief. Accept to be available to provide information in the near future if necessary.
- *C—Communicate well*:
  - Prior to informing the patient's condition, ask the relatives about what they know. Try to be a good listener to what they already know. This can help you anticipate the reaction from them after getting the news.
  - Care and compassion should be considered while talking to them. Avoid the use of medical terms that they may not be able to understand. Prefer words such as cancer and death.
  - Compose yourself in a calm state of mind. Allow them some space and silence to react to the news. Avoid showing your own expression of sadness or emotion at such stages.
  - Collect their queries and questions regarding their understanding of the cause of death. Help them in clearing their doubts if they have any. Repeat and clear out the statement for better understanding.
  - The initial shock of the news may not help in retaining the information provided by you. Establish a way of communication by sketches or diagrams that may help them in understanding the medical condition of the patient. If necessary, repeat information for them to retain it.
  - Conclude by delivering basic information about what was the initial condition of the patient and the treatment provided. Allot follow-up if required.
- *D—Deal with patient and family reactions*:
  - Response to any bad news (sudden/expected) must be expected. Initial cognitive coping mechanisms such as denial, anger, disbelief, and intellectualization are likely to occur. Be aware of the possibilities. Any intuition of possible suicidal ideation or intention should be noted and made known to other family members.
  - *Empathy*: Express your sadness at their loss. Do not overindulge in expressing emotions as this may entitle your weakness and emotional capability.
  - Avoid blaming other colleagues or staff for their shortcomings or knowledge.

- *E—Encourage and validate emotions*:
  - Extend an understanding of the family's reaction to the news. Ask for any emotional and spiritual needs, if required. Provide references, if required.
  - Establish a meeting with the patient and family members after the conversation. This helps family members to accept the loss and grief.

After Death: If Family is Not Present

- In many situations, such as road traffic accidents, the family may not be present with the patient. In the event of such a scenario, one must be careful about providing initial information to the relatives over the telephone.
- Introduce yourself, the name of the treating facility, and the patient's name. Confirm the name of the person and if he/she is a relative of the patient. Acquire information of what the relative/close friend already knows.
- Inform about the event leading to the ailing condition of the patient to the relative over the telephone. There is no clear-cut consensus on whether the news of death should be conveyed over the phone. However, it is advised to deliver the news of the death of a patient in person to the family. The relative should be asked to reach the hospital at the earliest and to drive safely during the commute. Confirm if the relative attending the call is an adult. If not, kindly request him/her to hand over the number of an adult who is in close relation to the patient.
- Confirm whether the relative has understood the information provided to him/her. Encourage any questions he/she might want to ask and answer them patiently. For medicolegal reasons, it is advisable to have such a conversation face to face.
- Ask the family member to meet you once he/she reaches the hospital. Encourage to bring any parent or spouse along with him/her. Provide directions and complete address of the hospital.

VIEWING OF THE BODY

- Prior to viewing, ensure that the appearance is presentable. Cover the patient with appropriate clothing and bedsheet.
- Blood should be cleaned and removed from all parts of the body. Jelly used for procedure such as electrocardiogram (ECG), defibrillator, and echocardiography must be wiped off.
- Life support, such as endotracheal tubes, central line, and cardiac monitors, must be disconnected and kept away from the patient. Make sure that secretions or blood spills are not present.
- Ensure that emotionally viable relatives do not view the patient as they may collapse on seeing the deceased patient.
- Heavily mutilated patients may have injuries at different body parts. Bandaging the injuries with clean dressing should be done.
- Explain to the family that the deceased may look different from their expectations.
- In the event of the death of a child, it is advisable to ensure that another family member is present along with the parents. Consolation of parents of young deaths is necessary. Always wrap the child in a clean blanket or bedsheet.
- Avoid using terms such as "it" or "body" for the deceased patient. Respect the dead and acknowledge the loss of the family.
- Reluctant and unwilling members of the family must not be forced to view the body. Only members of the family willing to see the deceased should be allowed in a private area away from other patients.
- Rather than disturbing the family, allow them to express their emotions by providing them space. Conclude by assuring them that every effort was put in saving the patient's life.

MEDICAL EXAMINATION: AUTOPSY

Once the news of death is delivered to the patient, there are many tasks to be completed. In case of medicolegal situations (such as traumatic brain injuries, mutilation, abuse, or suicide), it is mandatory to do autopsy of the patient. Family members need to be notified about the autopsy. In other cases, if the family insists on an autopsy, it should be carried out by informing the respective departments. A member of social services can assist the family with the paperwork and funeral home assistance. Articles and clothing on the patient's body should be handed over to the family members. Careful handover should be done in case of blood-soiled clothing, as this would be a hurtful experience for the family members.

ORGAN DONATION

Organs such as lungs, heart, liver, and pancreas should be recovered only if adequate tissue perfusion is present. Usually, it is done in patients declared brain dead in the intensive care unit. However, tissues and organs such as skin, bone, cornea, fascia, cartilage, veins, heart valves, and corneas can be harvested up to 24 hours, if the body was refrigerated 4 hours after death. Apart from patients with oncological ailments or infectious diseases, all patients up to the age of 80 years are suitable for organ donation. Organ procurements in the hospital have to be notified. Members from the organ procurement team must speak to the family members about organ donation, and necessary arrangements should be done.

ORGAN DONATION: DEATH OF A CHILD

- In recent studies, it is indicated that parents are more appreciative than overwhelmed when asked about organ donation of their deceased child, if approached at the right time and by skillful team members.
- In pediatric patients, the size of the organ poses a major concern for organ procurement teams. The donation can be taken as giving meaning to the death of the deceased. It should be considered as a life-giving measure for other pediatric patients suffering from acute, unanticipated, and tragic causes.
- Hence, timely notification to trained personnel should be ensured. It is advisable if the member of organ procurement directly speaks to the parents of the deceased child about organ donation after giving them adequate grieving time. Ideally, supportive staff such as a social worker, chaplain, and child life specialist should be present while talking to parents.

SUMMARY

Notifying death can be a daunting and difficult experience for emergency residents and physicians. However, with adequate training to reduce anxiety and education about the possible outcomes to be expected, negative impressions on the family can be avoided. Emergency doctors should follow an organized approach to breaking the news in a calm, composed, and professional manner. Careful consideration to the grieving process of the family members and assistance to survivors should be provided. Aftercare, including administrative help or paperwork, should be availed by family members. This helps in reducing the stress that the family undergoes after the death of a close one. Careful handling of pediatric death must be ensured. The key to an efficient physician is to provide a clear picture of the cause of death of the patient along with adequate care and compassion to the grieving family. This can reduce a large number of violent attacks witnessed in ED after the death of a patient.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Brain Death

Bhawana Sharma, Devendra Richhariya

INTRODUCTION

Different countries produce comprehensive practical documents for the neurological determination of brain death; each describes the detailed systematic process and tests needed to confirm brain death. Individuals should obviously adhere to their own jurisdiction and legal protocol requirements. Despite much attention to the differences in codes of practice for determining brain death around the world, it is in fact the similarities that bind them. Neurological determination of brain death guidelines generally has fundamental clinical components—evidence of sufficient intracranial pathology to cause permanent coma, absence of reversible or confounding factors, absence of cortical or brainstem-mediated motor responses, absent brainstem reflexes, and loss of capacity to breath.

PATHOPHYSIOLOGY OF BRAIN DEATH

Regardless of the injury that causes alteration of the brain physiology, brain death occurs due to lack of blood flow to the brain. The common pathways involved in all are progressive intracranial hypertension, tissue damage, and edema (**Fig. 1**).

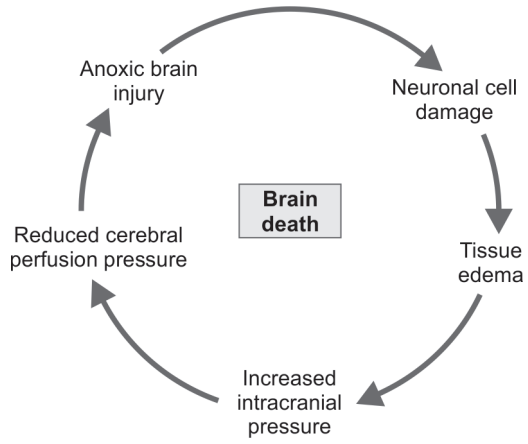


FIG. 1: Pathophysiology of brain death.

RECOMMENDATION

Australian and New Zealand Intensive Care Society (ANZICS) recommendations are as follows:

- *ANZICS recommendation 1*: Neurological determination of death is carried out by two doctors, who must each independently determine death according to the statement and meet the requirement of jurisdictional legislation.
- *ANZICS recommendation 2*: For neurological determination of death to take place, there must be the definite clinical neuroimaging evidence of acute brain pathology consistent with deterioration to permanent loss of all neurological function. In the cases of all hypoxic-ischemic brain injury, clinical history may alone provide sufficient evidence.
- *ANZICS recommendation 3*: There is a minimum 4-hour observation period prior to neurologic determination of brain death using clinical examination alone. Throughout this observation period, all preconditions are met, the patient has a Glasgow Coma Scale (GCS) of *3*, with pupils not reactive to light, absent cough/tracheal reflexes, and apparent apnea on the ventilator. Following an acute hypoxic-ischemic brain injury or hypothermia (<35°C) of duration greater than 6 hours, there should be a waiting period of 24 hours before determination of death using clinical examination.
- *ANZICS recommendation 4*: When imaging to demonstrate the absence of brain perfusion is required, it must be preceded by those parts of the clinical examination that are possible and responsiveness to all testable brainstem reflexes and breathing efforts must be absent.
- *ANZICS recommendation 5*: If the assessment of brain perfusion is required, three- or four-vessel angiography or radionuclide imaging is preferred. Computed tomography angiography (CTA) is acceptable if recommended radiological guidelines are followed. Magnetic resonance imaging (MRI) or angiography and transcranial Doppler (TCD) should not be used.
- *ANZICS recommendation 6*: Documentation of neurological determination of brain death should be made using a specific form to demonstrate explicitly that all criteria set out in this statement are met, whether or not donations occur. The same criteria should be listed in local hospital forms.

The international guideline development for the determination of brain death has been underway since 2012. *This group proposes a single operational unified determination of brain death based on cessation of brain function which occurs over two pathways, either permanent absence of circulation or subsequent to catastrophic brain injury. A harmonized international clinical practice guideline would reduce variation of practice between countries and improve public and professional confidence in the process. It seems unclear currently whether a worldwide consensus for either the definition or the criteria is achievable given complex challenges identified by the World Health Organization (WHO).*

DEFINITION

Brain death: A legal term (in most countries), defined as the irreversible cessation of the entire brain function that includes brainstem.

Medical and legal definitions: No standard definition exists internationally for the term "brain death." Medicolegal guidelines and definition of brain death are internationally inconsistent. Health care providers should know the local laws, institutional regulations, and guidelines before the declaration of brain death.

In 2014, a summary was published outlining the development of international guidelines for the diagnosis of brain death with the phrase "cessation of neurologic function" being used in lieu of brain death or brainstem death.

PREREQUISITES

Determination of brain death starts with documenting an irreversible and proximate cause for coma in a patient who is on invasive ventilator support with continued cardiac functions. A combination of the clinical history of the present illness, findings on clinical examination, radiologic imaging, and laboratory data is necessary to establish irreversibility and proximate causes. The patient's history and/or central nervous system (CNS) radiologic image findings should be suggestive of the mechanism of brain injury that may completely stop brain functions. The range of these clinical states may include circulatory arrest with no cerebral perfusion to a penetrating injury to the skull or a severe CNS infection with global cerebral edema with tentorial herniation. The patient's clinical examination with no sedative agents should be that of a comatose patient who is defined as having eyes closed and no appropriate interaction to external environmental stimuli. Hypothermia, CNS depressants, and neuromuscular blocking (NMB) agents may obfuscate the clinical examination and need to be systematically excluded. Furthermore, severe electrolyte or endocrine abnormalities may also impact a patient's mental status and need to be corrected before the diagnosis of coma.

After some prerequisites, *three essential steps* are mandatory for its determination (**Fig. 2**).

1. *Documentation of irreversible coma* due to a known proximate cause
2. *Documentation of absence of brainstem reflexes*
3. *Documentation of apnea—the apnea test*

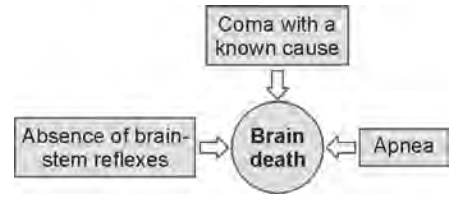


FIG. 2: Three essential steps in diagnosing brain death.

DOCUMENTATION OF COMA

Diagnosis of brain death by neurologic criteria based on current medical guidelines – Clinical, laboratory values, and radiological findings. The examination shows that the patient's eyes are not held open voluntarily and that no movements are made to verbal or noxious stimuli. A standard point of noxious stimulation includes nail bed, supraorbital, or temporomandibular pressure.

Confounders of brain death:

- Severe hypothermia, core temperature ≤32°C
- Severe hypotension—systolic blood pressure (SBP) <100 mm Hg
- Drugs—alcohol, poisons, recent sedation, NMB agents
- Severe dyselectrolytemia
- Hypoglycemia
- Acid–base abnormalities

Documentation of coma:

- Absence of motor response to a standardized painful stimulus
- Beware of local spinal reflexes causing spontaneous or stimulus-related motor movements

DOCUMENTATION OF ABSENCE OF BRAINSTEM REFLEXES

- Brainstem reflexes are lost in a rostral to caudal direction.
- Reflexes in the medulla oblongata are the last to cease.

Documented Tests

- Absent pupillary reflexes (nerves—optic and oculomotor)
- Absent oculocephalic movement—doll's eye reflex (nerves—vestibular part of vestibulocochlear, oculomotor, and abducens)
- Absent oculovestibular reflex—cold calorie test (nerves—vestibular part of vestibulocochlear, trochlear, and abducens)
- Absent corneal reflex (nerves—trigeminal and facial)
- Absent cough reflex (nerves—glossopharyngeal and vagus)

Pupillary Response (Cranial Nerve II)

Pupillary responsiveness should be assessed using bright flashlight. An ophthalmoscope should be used for magnification to look for the subtle pupillary response. The pupils are usually round or oval in mid position. Dilated pupils may suggest intact spinal sympathetic pathways or the release of stored norepinephrine from presynaptic terminals in the orbit. Infrared pupillometry may detect small pupillary responsiveness that may not be visible by the examiner.

Assessment of Eye Movements (Cranial Nerves III, VI, VIII)

Cervico-ocular Reflexes ("Doll's Eye Maneuver")

This maneuver can be performed only after the cervical spinal injury has been excluded. With the patient's eyelids held open, the head is rapidly turned 90° from the mid-line to the right and the left. If the patient is intubated, the endotracheal tube should be moved with the patient to avoid laryngeal damage or accidental extubation. The term "doll's eyes" refers to the expected conjugate horizontal movement of the eyes in the direction opposite to the head movement. This reflexive movement will only occur if the frontal cortex is not providing any input, such as in a comatose patient with intact brainstem reflexes. The absence of eye movements in a comatose patient during head movement is consistent with either upper brainstem dysfunction or a diagnosis of brain death.

Vestibulo-ocular Reflexes ("Cold Caloric")

Once the cervico-ocular reflexes are determined to be absent, or in circumstances in which these reflexes cannot be tested due to cervical spine instability, vestibulo-ocular reflexes should be assessed using cold caloric. First, the external auditory canal should be examined to ensure the absence of any obstruction. Given the clinical implications of diagnosing brain death, the presence of tympanic membrane perforation should not inhibit cold caloric testing. The patient's head end of the bed should be raised to 30°. Ice cold water of about 60 mL should be placed in a syringe and instilled into the ear while the patient's eyelids are held open. The amount of water is less important than its temperature; the goal is to decrease the temperature of the internal auditory canal. In a comatose patient with intact brainstem reflexes, the eyes should deviate toward the side of the cold-water stimulus. The absence of eye movement is present in a patient who is brain dead. The eyes should be examined for 1 minute after the ice water irrigation. After 5 minutes, the procedure should be repeated in the opposite ear.

Facial Sensation (Cranial Nerve V) and Facial Motor Response (Cranial Nerve VII)

Reflexes involving the cranial nerves V and VII need to be absent before the diagnosis of brain death can be made. The corneal reflex can be assessed by placing a gentle stimulus across the cornea of each eye individually to assess for a blink response. This can be accomplished with a wisp of cotton; however, some prefer a drop of saline to prevent the development of corneal abrasions, which may prevent tissue donation. A jaw jerk can also be assessed by the examiner striking his/her finger (cranial nerve VII) placed on the chin to assess for jaw closure (cranial nerve V). The absence of a grimace response to the noxious stimulus of the supraorbital ridge or temporomandibular joint should also be tested.

Gag or Cough Reflexes (Cranial Nerves IX and X)

The gag response may be difficult to establish in an intubated patient. Besides, the absence of a normal gag reflex in a significant proportion of healthy subjects renders this test less than useful in a comatose patient. So cough in response to deep endotracheal suctioning should be evaluated. By the neurologic criteria, the cough reflex should be absent to determine brain death.

DOCUMENTATION OF APNEA

Once the above-mentioned criteria are met, the physician should proceed to apnea testing to fulfill the diagnosis of brain death. An arterial catheter should be placed if one is already not in place due to the potential need of frequent arterial blood gas (ABG) analysis and hypotension during the apnea challenge. The patient's SBP must be ≥100 mm Hg with appropriate intravascular volume repletion and vasoactive drugs if required.

Apnea test: This should be done only after documentation of coma and documentation of the absence of brainstem reflexes.
Steps of apnea test:

- Preoxygenate with 100% oxygen for at least 10 minutes to obtain a PaO_2 of >200 mm Hg. Longer periods of preoxygenation may be required.
  Although the actual trigger for breathing during the apnea test is a decrease in the arterial pH, the test has traditionally been based on the rise in $PaCO_2$.
- Get an arterial blood gas.
- Disconnect the patient from the ventilator to prevent the false interpretation of artifactual breathing on the ventilator.
- Continue to oxygenate through an oxygen insufflation catheter which should be inserted in the endotracheal tube placed at the level of carina with the delivery of 100% oxygen @ 6 L/min to provide apneic oxygenation.

Those patients who have poor baseline oxygenation can be placed on 10 cm of H_2O continuous positive airway pressure (CPAP) or on an appropriate level to optimize their baseline oxygenation.

The patient is closely inspected for chest wall expansion, clavicle elevation, and abdominal excursions.

- To keep oxygen saturation > 95% (if SpO_2 <95%, abandon the apnea test)
- $PaCO_2$ is allowed to rise. If we assume a normal baseline $PaCO_2$ (35–40 mm Hg), the maximum respiratory drive is believed to occur at a $PaCO_2$ of 60 mm Hg.
- Repeat the ABG after 8–10 minutes.
- If an ABG shows a rise in $PaCO_2$ of 60 mm Hg or greater with continued apnea, the diagnosis of brain death is met.
- Alternatively, a rise in $PaCO_2$ by 20 mm Hg from its baseline level also meets the criterion. The rise in $PaCO_2$ and lack of respiration are documented.
- With an expected $PaCO_2$ increase of 3–6 mm Hg/min, a target $PaCO_2$ of 60 mm Hg should be observed within 8 minutes after discontinuation from the ventilator. Occasionally, it may take longer to establish this cutoff value. The rate of CO_2 production may be affected by the patient's core body temperature and hemodynamic status. Since pH is the main determinant of respiratory drive, an equivalent change in pH may be more specific than a change in $PaCO_2$.

The pH should primarily be considered in patients with an abnormal baseline $PaCO_2$ such as those with an underlying pulmonary disease. In the event, the apnea challenge cannot be finished due to cardiac arrhythmia, worsening hypotension,

or arterial desaturation and ancillary tests must be performed. Perform additional tests, which are optional in adults, recommended for age < 1 year. Some countries mandate this test by law to confirm brain death.

ADDITIONAL TESTS

Ancillary tests are necessary to declare brain death if the apnea challenge is difficult to perform or if there is a doubt regarding the reliability of parts of the neurological tests. The validity of these tests is yet to be determined. In many countries, these ancillary tests are required by law or left to the discretion of the physician. CT angiogram, electroencephalogram, Transcranial Dopplar and radionuclide imaging are some additional tests.

Conventional Cerebral Angiography

It remains the "gold standard" to know the intracranial blood flow. However, the specific radiographic features to define brain death are lacking. The absence of intracranial blood flow on angiogram at the level of entry of vertebral artery and carotid artery to the skull has been suggested to be consistent with brain death. The presence of contrast in the external carotid artery tree should be present to confirm appropriate contrast injection. In upward of 30% of brain-dead persons, there was a proximal opacification of the intracranial arteries observed with none having deep venous drainage.

Computed Tomography Angiography

This remains an issue of debate whether a computed tomography (CT) angiogram can be utilized as an ancillary test to declare brain death. The sensitivity for brain death seems to be the highest (99%) with the absence of opacification of the internal cerebral vein.

Transcranial Doppler Ultrasonography

This can be a useful tool for bedside assessment of cerebral blood flow (CBF), especially in an unstable patient in whom conventional angiography or CTA is not possible at that time. A specific pattern of oscillating flows or systolic spikes can be seen on TCD by experienced persons. Occasionally, absence of flow can also be seen. But a physician should be aware of the fact that in upward of 10% of patients, a thicker temporal bone window may not allow adequate insonation. TCD can be helpful in deciding the optimal time to send an unstable patient for ancillary brain death testing.

Radionuclide Imaging

Both planar scintigraphy and single-photon emission computed tomography (SPECT) are used in ancillary testing to diagnose brain death. Either of these radioisotopes, Tc-99m hexamethylpropyleneamine oxime (HMPAO) or Tc-99m ethylene cysteine diethyl ester (ECD), can be used. Intracranial blood flow cessation or brain death is diagnosed when there is an absence of radioisotope uptake into the brain parenchyma. Similar to other ancillary tests, "false-negative" cases for brain death have been reported in the literature.

Electroencephalogram

The "electrocerebral silence" on EEG may be consistent with brain death as per neurologic criteria. But EEG will be affected by some confounding factors, such as physical examination hypothermia, and effects of sedatives. Artifacts on an EEG can be produced by other electrical activities present on a critically ill patient. Limiting factors may include the availability of technical expertise. Many contemporary series of patients have shown a minimal difference between a clinical diagnosis of brain death and EEG findings.

OTHER TESTS

There is limited experience with MRI of brain so it cannot be recommended at this time. Somatosensory evoked potential (SSEP) can be absent due to severe drug intoxication or hypothermia. Therefore, SSEP should not be used for this purpose. Follow institutional protocols for certifying brain death. Most places mandate two sets of brain death tests. The second test is typically done in a minimum of 6 hours after the first test in adults to declare brain death. In neonates and pediatric group, this interval is 12–48 hours. There is no consensus about how long a patient needs to be observed before being certain that the brain functions have ceased irreversibly.

BRAIN DEATH MIMIC

Brain death mimic is important to differentiate various conditions (vegetative state, locked-in syndrome, coma from brain death) (**Table 1**). Brain death mimics can be roughly divided into two groups:

1. *Wrong-diagnosis mimics*: These are the most concerning. These are patients with an *unrecognized alternative diagnosis* which causes the patient to appear brain dead:
   a. Unrecognized intoxication (e.g., tricyclics, lidocaine, baclofen, barbiturates, paralytics, anticholinergics, organophosphates)
   b. Locked-in syndrome
   c. High C-spine injury
   d. Hypothermia
   e. Fulminant Guillain–Barré syndrome

   These patients have conditions which are often treatable and consistent with long-term survival. Accurate diagnosis is essential. One important clue to wrong-diagnosis mimics is that they are generally associated with *normal* neuroimaging.
2. *Wrong-severity mimics*: They do indeed have catastrophic, irreversible brain damage. Wrong-severity mimics have no likelihood of a meaningful recovery. However, they are not brain dead due to the persistence of some brainstem functions. An example would be a patient who has profound anoxic brain injury with marked cerebral edema. The patient has an isoelectric EEG for several days with no confounding factors (e.g., no sedation or hypothermia). The patient has no cranial nerve reflexes or responsiveness to pain. However, the patient does continue to generate a respiratory rate on apnea examination. This patient has no likelihood of awakening from coma. However, the patient

TABLE 1: Differentiating various conditions from brain death.

State	*Vegetative state*	*Locked-in syndrome*	*Coma*	*Brain death*
Awareness	Absent	Present	Absent	Absent
Sleep-wake cycle	Present	Present	Absent	Absent
Response to stimulus	±	Present (eyes only)	±	Absent
GCS	E4 M1-4 V1-2	E4 M1 V1	E1-2 M1-4 V1-2	E1 M1 V1
Motor functions	No purposeful movement	Volitional vertical eye movement or eye blink	No purposeful movement	None (reflex spinal movement)
Respiratory functions	Typically preserved	Typically preserved	Variable	Absent
EEG	Slow-wave activity	Typically, normal	Moderate to severely reduced	Severely reduced
Cerebral metabolism	Severely reduced	Mildly reduced	Moderate to severely reduced	Severely reduced
Prognosis	Variable	Depends on a cause/full recovery unlikely	Recovery/vegetative state/ death	Already dead

(EEG: electroencephalogram; GCS: Glasgow Coma Scale)

is *not* brain dead due to the absence of apnea. The injury is not quite *severe* enough to qualify for brain death.

MOVEMENT OBSERVABLE AFTER BRAIN DEATH

Brain death liberates the spinal cord from any supervision or suppression from the brain, causing spinal motor reflexes to run amok. This produces a variety of bizarre movements, often in response to stimulation. For example:

- *Triple flexion*: It is probably the most common movement observed. Stimulation of the feet causes flexion at the ankles, knees, and hips. This may appear to be a volitional withdrawal response to painful stimulation of the feet.
- *Myokymia:* It is localized quivering of a muscle (may involve facial or ocular muscles).
- *Lazarus sign:* It is flexion at the waist

These movements are alarming to family members and medical personnel who are not experienced with brain death. It is common for a brain death diagnosis to be inappropriately delayed or missed due to such movements.

BRAIN DEATH DECLARATION AND ORGAN DONATION

Who should Declare Brain Death?

Brain death should be declared by the medical superintendent of the hospital or an independent medical practitioner nominated by the medical superintendent, neurologist or the neurosurgeon nominated by the medical superintendent, or the treating doctor on duty. It should be assessed by two physicians and one of them must be consultant. No one should be from the transplant unit. Inform the family as soon as the patient is nearing brain death. Maintain the patient in a hemodynamically stable state. Approach for organ donation as per the regulation of the state law. If there is no transplant coordinator or grief counselor in the hospital, the neurosurgeon should also discuss with the family the option of the patient being an organ donor.

Brainstem Death and Indian Law

India enacted a law in 1994 to legalize the recognition of brainstem death. Maharashtra has recently mandated the notification of brain-dead cases. The Government Resolution underlines the responsibilities of hospitals registered under the Transplantation of Human Organs (THO) Act 1994, that is, they are authorized transplant centers. As a large number of brain deaths occur in hospitals not authorized to do transplants, the appropriate authority (Director of Health Services) has registered all hospitals in the state that have an operation theater and intensive care unit (ICU) as nontransplant organ retrieval centers (NTORCs). These hospitals are permitted to certify brain death as per the prescribed procedure and then conduct organ retrieval for therapeutic purposes; however, they are not permitted to perform an actual transplantation. Thus, it is now mandatory for all NTORCs and authorized transplant centers in the state to certify and notify the brain-death cases to the Zonal Transplantation Coordination committee. This is a strong step to streamline the procedure for cadaveric organ retrieval and transplantation. Medically and legally, the patient is dead, if brainstem death (brain death is used as a synonym for the latter) has been certified. The doctors involved in the diagnosis should in no way be connected with the transplant surgeries concerning the "brainstem dead" cadavers. The certification should be done on the laid-out forms (Form No. 8) as per the THO Act. The declaration of brain death must be recorded in the medical notes with the date and time. The legal time of death is the time at which the second prescribed clinical tests are carried out. Comprehensive reviews of brainstem death and brain death from an Indian perspective have also been documented.

CARE OF THE POTENTIAL ORGAN DONOR

"Care of the donor" is associated with "the care of multiple recipients." A brain-dead patient with a potential organ donor requires the similar intensity of care in order to preserve organ perfusion and improved quality of grafts. Improved quality of care and titration of inotropes and fluids with the use of invasive lines is mandatory in intensive care.

Potential donor: A potential donor is one who becomes brain dead due to a catastrophic brain injury, and the physician and the family expressed an intention to withdraw life support. The organ procurement organization initiates counseling the family by using "presumptive strategy" wherein grief counselors established communication with the family and explain that organ donation is the natural thing in the interests of the potential donor as well as the pool of recipients.

Pathophysiological Changes after Brain Death and its Importance in Organ Preservation

Fluctuating donor hemodynamics complicates the declaration time of brain death from the time of diagnosis. When the time to organ retrieval from the diagnosis of brain death is longer, the chances of hemodynamical instability are greater. Optimum donor care should be ensured in the ICU, in view of hormonal and inflammatory changes accompanying brain death to avoid graft dysfunction and chances of rejection. However, in the last two decades, outcomes have improved following transplant surgery due to increased awareness of donor management.

Cardiovascular System

In all patients with brain death, reflex hypertension and bradycardia (Cushing's reflex) occur due to medullary ischemia as a reflex attempt by the body to maintain the CBF. Following this, a period of intense vasoconstriction and tachycardia with increased circulatory catecholamines occurs, which can increase visceral and myocardial ischemia.

The effects of the catecholamine surge on the myocardium can be documented by the fact that 20–25% of brain-dead donors showed evidence of myocardial ischemia and 40% have echocardiographic evidence of myocardial dysfunction. Catecholamine surge contributes to the challenges in the maintenance of organ perfusion (reflex hypertension, bradycardia, myocardial dysfunction) in brain death. In order to maintain the organ perfusion management, include maintenance of BP with minimal use of inotropes, optimizing the fluid management.

All potential donors should undergo an echocardiogram and pulmonary artery catheterization (PAC). It is indicated for donors with an ejection fraction (EF) <45%, more in the background of cardiac and lung transplants. The hemodynamic parameter should be maintained as shown in **Figure 3**.

Respiratory System

An endogenous epinephrine rise causes a rise in pulmonary hydrostatic pressure damage to the pulmonary endothelium resulting in pulmonary edema. The ventilatory management should include minimal FiO_2 needed to maintain a PaO_2 > 100 mm Hg, SpO_2 > 95%, $PaCO_2$ of 35–40 mm Hg, and pH 7.35–45. Earlier recommendations were to use liberal tidal volumes 8–15 mL/kg, but current ventilation strategies recommend similar ventilatory strategies used for acute lung injury (ALI). The use of PAC in intensive care for a brain-dead potential donor may restrict excessive fluid use and pulmonary edema.

Endocrine System, Stress, and Metabolic Responses

With brain death, the endocrine responses of the body are lost and the rationale for hormone replacement therapy for brain-dead patients. After brain death, the posterior pituitary function is lost early in comparison to posterior pituitary function with the occurrence of diabetes insipidus associated with polyuria and hypernatremia. As a replacement, arginine vasopressin and desmopressin can be given. Thyroid hormone level decreases and condition become similar to critical illness "sick euthyroid" state.

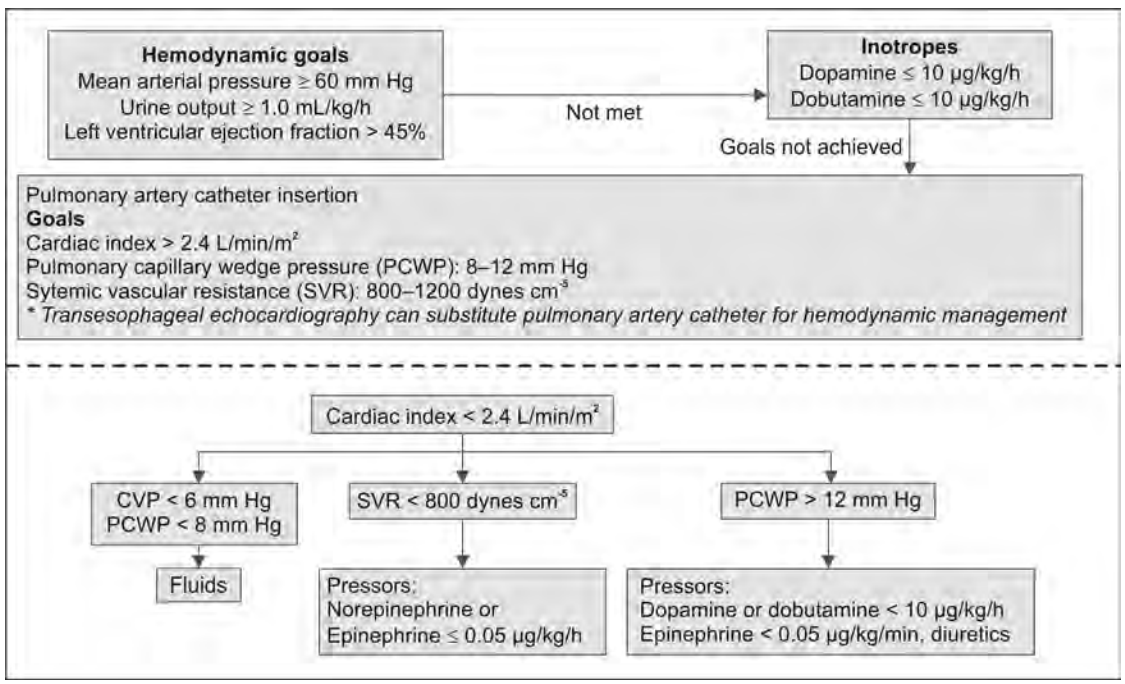

Hemodynamic goals
Mean arterial pressure ≥ 60 mm Hg
Urine output ≥ 1.0 mL/kg/h
Left ventricular ejection fraction > 45%
Not met
Inotropes
Dopamine ≤ 10 µg/kg/h
Dobutamine ≤ 10 µg/kg/h
Goals not achieved
Pulmonary artery catheter insertion
Goals
Cardiac index > 2.4 L/min/m²
Pulmonary capillary wedge pressure (PCWP): 8–12 mm Hg
Sytemic vascular resistance (SVR): 800–1200 dynes cm⁻⁵
* Transesophageal echocardiography can substitute pulmonary artery catheter for hemodynamic management
Cardiac index < 2.4 L/min/m²
CVP < 6 mm Hg
PCWP < 8 mm Hg
SVR < 800 dynes cm⁻⁵
PCWP > 12 mm Hg
Fluids
Pressors:
Norepinephrine or
Epinephrine ≤ 0.05 µg/kg/h
Pressors:
Dopamine or dobutamine < 10 µg/kg/h
Epinephrine < 0.05 µg/kg/min, diuretics

FIG. 3: Recommended hemodynamic parameters in a potential donor.

Other endocrine changes are a decrease in insulin levels, hyperglycemia worsening with stress, and alteration in carbohydrate metabolism. Insulin levels normalize subsequently with an increase in C peptide levels. A strict euglycemic state should be maintained as hyperglycemia-induced pancreatic cell damage may affect the pancreatic graft. Hyperglycemia can adversely affect the outcomes of renal transplantation.

Temperature regulation is also affected in a brain-dead individual displaying a pattern of initial hyperthermia followed by hypothermia. Lack of shivering, peripheral vasodilatation, and a decrease in the metabolic rate complicate the hypothermia. Hypothermia can worsen acidosis and coagulopathy and increase the risk for arrhythmias and cold-induced diuresis besides causing a leftward shift in the oxygen dissociation curve.

Systemic Inflammatory Response

A systemic inflammatory response mediated by inflammatory mediators from an ischemic brain, ischemic reperfusion injury, metabolic changes that occur during the catecholamine storm, and an inadequately restored cardiovascular state is quite severe after brain death. Increased plasma levels of interleukin-6 in the donor correlate with the poorer graft utilization and graft dysfunctions. After brain death, due to the release of tissue thromboplastin from the necrotic brain, tissue-disseminated intravascular coagulation occurs.

Protocols for Donor Management

The general principle of the "Rule of 100" is applied to maintain the circulatory and biochemical variables suggesting targets of SBP ≥ 100 mm Hg, urine output ≥ 100 mL/h, hemoglobin ≥ 100 g/L, PaO_2 ≥ 100 mm Hg, and blood sugar targeted at 100% normal. Other elements of donor management are listed below:

- *Temperature*: Prior to organ donation, the aim is to keep the core temperature > 35°C. Circulating hot air blankets, warmed intravenous fluids, and adjustments of ambient temperature may be used to achieve this goal.
- *Fluid management:* These patients often have polyuria and are severely dehydrated due to vasoplegic state which ultimately leads to central volume depletion. Traditionally among fluid therapy, crystalloids are the first choice and balanced salt solutions (Ringer's lactate, Plasmalyte-A, Ringer's acetate, half-normal saline with sodium bicarbonate) which do not produce hyperchloremic acidosis may be superior to normal saline. Hypernatremia should be corrected to avoid graft losses after liver transplant. Hydroxyethyl starches can damage renal epithelial cells and cause early graft dysfunction in the transplanted kidneys and are contraindicated in organ donors. There is little evidence to date supporting the use of gelatins in donors.
    - In the context of lung transplant, a fluid restrictive strategy with monitoring of filling pressures may be beneficial. Studies have documented the impact of fluid loading on outcomes in lung transplantation. This does not affect the quality of the renal graft for transplantation. Hemoglobin of 10 g/L could improve tissue oxygenation indices. Guidelines of critical care should be followed during the replacement of blood and blood products.
- *Inotropes and cardiovascular system*: Dopamine has beneficial effects on the renal graft and is the first choice of inotrope in hypotension unresponsive to volume. Although dopamine may predispose to arrhythmias and has no renal protective effect, the beneficial effect of dopamine is probably related to preservation injury and inflammation, donor cardiovascular effects, or recipient treatment. In transplanted hearts, noradrenaline doses >0.05 μg/kg/min adversely affect cardiac contractility and decrease the right ventricular performance.
- *Ventilatory management:* The principles are along the lines of management of ALI (low tidal volume 6–8 mL/kg, minimum plateau pressure, lung recruitment). The use of the lowest possible FiO_2 and optimal PEEP with a restrictive fluid strategy improves graft harvesting for lung transplants.
- *Replacement of hormones after brain death*: Standardization of hormone therapy after brain death in combination with a central venous pressure < 10 mm Hg significantly improved utilization of the heart and lungs for transplant without affecting other organ systems. The recommended replacements are:
    - Vasopressin 1 U bolus followed by an infusion of 0.5–4.0 U/h (desmopressin intranasally has a selective action on the V_2 receptors and a half-life varying from 6 to 20 hours)
    - Methylprednisolone 15 mg/kg immediately after diagnosis of brain death and 24th hourly thereafter
    - Insulin 10 U in 50% dextrose followed by an infusion to maintain blood glucose between 80 and 150 mg
    - Thyroxine (T4) 20-μg bolus followed by infusions of 10 μg/h. Tri-iodothyronine (T3) given as a 4-μg bolus followed by an infusion of 3 μg/h. T4 improves hemodynamics and prevents cardiovascular collapse in hemodynamically unstable organ donors.

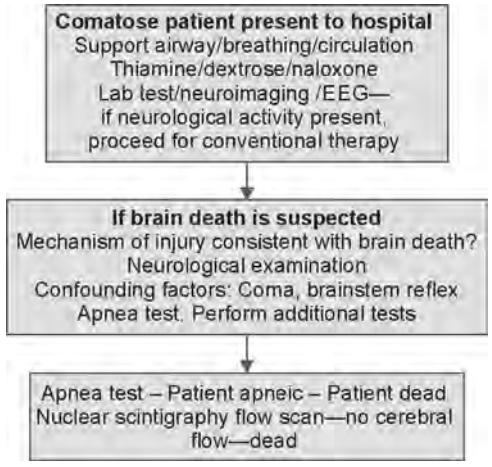
An analysis of 10 years of data of several hormone replacement modalities in the United Network for Organ Sharing (UNOS) data showed that the combination of thyroid hormone, corticosteroid, insulin, and antidiuretic hormone was the best for multiple organ procurement.

Other Concerns and Considerations

Donors with bacteremia or fungemia are not absolute contraindications to donations except overwhelming sepsis. However, infections with human immunodeficiency virus (HIV), herpetic meningoencephalitis, and T-cell leukemia-lymphoma virus should not go for organ donation. Transmission of HIV and rabies from infected donors has been documented.

SUMMARY

The ICUs are available to the wider population and more cities in India; a large number of seriously ill patients are now being


Comatose patient present to hospital
Support airway/breathing/circulation
Thiamine/dextrose/naloxone
Lab test/neuroimaging /EEG—
if neurological activity present,
proceed for conventional therapy
If brain death is suspected
Mechanism of injury consistent with brain death?
Neurological examination
Confounding factors: Coma, brainstem reflex
Apnea test. Perform additional tests
Apnea test – Patient apneic – Patient dead
Nuclear scintigraphy flow scan—no cerebral
flow—dead

(EEG: electroencephalogram)

FLOWCHART 1: Approach to suspected brain death.

revived. While many recover, a significant number end up being brain dead (approach to suspected brain-dead patient is shown in **Flowchart 1**). Brain death has created a new class of dead people who do not conform to the society's expectations of normal death and dying. Brain death also causes great stress for the family and friends. It is important to provide ample time to the family which helps them to adjust with the sudden tragedy and hopelessness of the situation. This helps them develop trust in their physician and in the diagnosis. An effective communication with the family members, as well as caring and providing support for them, is crucial before the request for organ donation is made. The only rational reason for continuing treatment after confirming brain death is for organ donation. Once the permission from family members is obtained, the transplant team takes over further care. The law in India is still not clear if the support system can be withdrawn once the family refuses organ donation.

MULTIPLE CHOICE QUESTIONS

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24 CHAPTER

Organ Donation and Transplantation

Devendra Richhariya, Bhawana Sharma

INTRODUCTION

Over the years, the pattern of diseases has changed and so the treatment options are. With improved healthcare facilities, the survival of citizens of India has also improved. Healthcare facilities in India are mostly focused on particular problems such as diabetes, hypertension, obesity, and ischemic heart diseases, but the burden of chronic organ failure and end-stage diseases (end-stage renal disease and end-stage liver disease) is also rising at a significant pace. Treatment options of chronic end-stage diseases are limited, expensive, as well as resource-consuming; therefore, national apathy also coexists toward these diseases. The cure of the chronic end-stage disease is *"organ transplantation"* but majority of the patients cannot afford it. The benefits of transplantation are still far away from the reach of the large population of the country. Most of the patients with end-stage renal disease are on long-term dialysis and have poor quality of life. Dialysis facilities are expensive, limited, and not freely available in most centers; >90% of patients die within a month of the diagnosis. It has been estimated that a very small percentage of patients in India actually end up getting a transplant for end-stage organ failure. Similarly, in our country, with the enormous rise in end-stage liver disease and the absence of other definitive therapies, a pool of patients for liver transplants is also rising. Liver transplant is a highly skilled procedure and only few centers in India perform this.

The organ transplantation topic is always in the focus of the discussion in terms of ethical practice, especially in India where poor people are attracted to sell their organs for financial gains. In a country such as India where the prevalence of chronic end-stage disease is high and the cost of managing chronic illnesses such as end-stage renal disease is unaffordable by poor, e.g., limited facilities of free of cost hemodialysis or peritoneal dialysis, organ transplantation is the best mode to improve the quality of life. Patients who need organ transplantation are more than the available organs so transparency in the process of distribution is the key to the credibility and success of the organ transplant program along with social, cultural, religious, and political support.

HISTORY OF ORGAN TRANSPLANT: WORLDWIDE AND IN INDIA

In 1954, Dr Joseph Murray performed the first successful kidney transplant at Peter Bent Brigham Hospital in Boston. For the first time in 1962, immune-suppression drugs and tissue typing were also used for a human kidney transplant. In India, the first-ever renal transplant was done in 1965 at King Edward Memorial Hospital, Mumbai, from a deceased donor in a hypernephroma patient, while the first live donor renal transplant in India was done in 1971 at CMC Vellore. In India, the first kidney transplant was performed in the 1970s and these activities were picked up in the 80s and 90s as more centers were established and more trained staff started to be available.

In 1960, as an experiment, a liver transplant was performed from a deceased donor. The first successful liver transplants were done in the USA and the UK, respectively, in 1967 and 1968 from deceased donors, while in Australia (1989), the first successful liver transplantation was done from a live donor followed by in Japan (1994) and later by the USA (1999). In India, the first live donor liver transplant was done in 1998 from father to child.

In 1965, the term *"brain death"* was introduced and in 1968 it was defined as a complete cessation of mid-brain and cortical brain function.

Organ transplant in India is relatively new as compared to developed countries, although cornea (eye donation) from a dead patient is popular in the Indian society for the last few decades. Every healthy human being has two healthy kidneys and one kidney is sufficient for survival, so living donor kidney transplant is being performed frequently in India. Liver transplantation is also being performed from the living donors in which a part of the liver (250–650 g) is removed and transplanted in the patient suffering from end-stage liver disease (advanced cirrhosis and acute fulminant hepatic failure) and in the next 8 weeks' duration, the liver grows to normal size in both the donor and the recipient.

As live donors are not available to every patient and risk to life is also involved in donors along with various ethical issues, organ transplantation from cadaveric, deceased donors

is more relevant in India. In many states of India, it is claimed that deceased organ transplantation led to reduction in commercial transplantation. Retrieval of organs such as liver, kidney, and heart can also be done from the brain-dead patient (patient is certified brain death -heart beating and no question of survival of patients).

In 1994, the Transplantation of Human Organ Act (THOA) was passed in the Indian Parliament, which allowed the removal of organs such as liver, kidneys, and heart from a brain-dead patient for transplantation. One of the main aims of the act was to stop the illegal trade of organs for financial gain.

EVOLUTION OF LAW: TRANSPLANTATION OF HUMAN ORGAN ACT

As discussed earlier, the first kidney transplant in India was done in the early 70s and the activities picked up in the 80s. It is important to note that initially there was no law regarding human organ transplantation. Overseas patients rushed to India for transplantation from paid donors. Small hospitals along with some big private hospitals started performing the transplantation in substandard conditions resulting in poor outcomes. A significant section of nephrologists and transplant surgeons were also involved in unlawful activities.

The media reported these scams and medical bodies such as medical councils and other regulatory bodies had no answer. A section of the population started justifying "paid organ donation" by giving ideological rationale of free-market philosophy, while others advocated for regulations. However, at the ground level, it was realized that the donors should be protected from the middlemen in this "paid organ donation market"; on the other hand, studies also suggested the poor quality of life in unrelated donor transplantation. Success was also claimed by countries with the state-sponsored regulated model.

As a response to various controversies, the government of India in 1991 constituted a committee to prepare a report for all India legislation on organ transplant. The committee focused on brain death and suggested that human organ trading be made a punishable offense. In 1994, the government of India came up with THOA and enacted it in 1995. According to THOA, commercial trading in organs is banned. An unrelated donor is only permitted with permission of the authorization committee on the ground of altruism. Brain death is also legalized in India by THOA, so organs can be procured from brain-stem dead donors and deceased organ transplantation can be encouraged. The criteria for determining brain death have also been issued. According to the rules, brain death can be declared only in the state-recognized institution by four individuals unrelated to transplant and tests are to be done twice within a gap of 6 hours. THOA rules were also amended in the years 2008, 2011, and 2014.

CHALLENGES

Interpretation of the Transplantation of Human Organ Act

In THOA, brain death is defined for a specific situation and that is in the context of organ donation. The Act authorized only those institutions to declare brain death who are doing organ transplant. Later in 2011 Act amendment and rules in 2014, few other institutions who do not perform organ transplant have also been recognized to declare brain death. These are known as "nontransplant organ retrieval centers"; organs can be retrieved in these centers and then transported to transplant-recognized centers. A peculiar situation arises at the ground level if brain death is diagnosed and the family has not given consent for organ donation but instead asked for the handover of the body after removal of the ventilator; such a request is turned down as there are no instruction and guidelines in the Act. Because of problematic interpretation of the law, most of the time, relatives accused healthcare institutions and hospitals of keeping the dead body on ventilators and making money.

Ground Reality and Resource-constrained Scenario in India

The ground reality in India is different when it comes to deceased organ transplantation. Only major cities of India have modern state-of-the-art intensive care units, where "brain death" can be declared and the subsequent donation can be processed, and facilities to keep the brain-dead patient's organ working with mechanical ventilation and intensive monitoring. In a given scenario where ICUs are understaffed and nursing staffs are overburdened, another conflict of interest that arises is where to use resources, on a sick patient who needs life-saving care or on a brain-dead potential donor. A major change in attitude is also required as both conditions require the same attention. It has been observed that low priority is given to the process of declaring brain dead and taking consent from the families of potential organ donors.

Disparity in Organ Demand and Availability

The main issue of concern is the huge number of patients waiting for the transplant. Shortage of organs is a global issue and the only solution is deceased organ donation. The social worker of the hospital approaches the relatives of the patient who is declared brain dead and explains that three lives can be saved by donating two kidneys and one liver. Close relatives give written permission. Road accident fatalities in India comprise about 1.5% of the total fatalities and about 50% of death are due to head injuries. Even if 5–10% of these opt for organ donation, the problem of organ shortage can be solved.

Lack of Organizational Support, Educated Transplant Coordinators, and Effective Communication

Deceased organ transplant got a setback due to nonavailability of an adequate number of transplant centers, staffs, and educated transplant coordinators who have adequate knowledge of organ donation procedures and who could approach the family members of the brain-dead sympathetically and take consent. Many hospitals lack any protocol regarding the declaration of brain-death. They also do not have good dialysis backup, research, and health insurance plan. Even the medical fraternity has poor knowledge about organ donation.

Negative Coverage by the Media

Philosophy of altruism and mutual trust is the entire concept of the deceased organ transplant. Any negative propaganda breaks the trust and creates a hurdle for the whole process.

How to Encourage Deceased Organ Donation

The cost of maintenance is also an issue as most of the donors are in private sectors and how one can bill a family who has given consent for organ donation. Various incentives for the donor's family such as waiver of donor's hospitalization cost, providing preferences in a job, and children's education support should be included in the Act because the recipient and the hospital performing the transplant are the beneficiaries. Another thought is that any amount of compensation commodifies the Act and in an unequal Indian society, this will be a soft form of trading even in deceased donors. Political will is an important requirement for an accessible and affordable transplant to all end-stage organ failure patients. Frequent interaction between government and stakeholders and necessary legal and administrative help through regular orders are behind the success of a deceased organ transplant in the state of Tamil Nadu, especially in Chennai. Till date, Tamil Nadu, Andhra Pradesh, Maharashtra, Kerala, and Gujarat are the states where the highest number of deceased organ transplants is done.

Inequality in Recipient Pool and Transplant Pattern in India

In India, quality healthcare is largely owned by private sectors; the same is true for the organ transplant. Very small numbers of hospitals in public sectors are even doing the simple straightforward renal transplant. Similarly, <1% of public sector hospitals are doing liver transplant in India. Over the years, the deceased donor program poorly developed in India in comparison to the live donor liver transplantation because of no backup for end-stage liver diseases such as dialysis in end-stage renal disease. The high cost involved in transplantation along with very little funding by the government is another cause for poor progress in a deceased donor transplant.

As the deceased organ donation depends on the altruistic philosophy and, principally, organs do not belong to any hospital or city but belong to society, a transparent approach should be enforced by the state in distribution to a needful person. Instructions are clearly given in THOA about who can donate the organs but not about how the organ would be distributed to the needful person.

India is a vast country, and the deceased organ allocation policy differs in every state. It is not clear how an organ is allocated, severity-wise, waiting-period-wise, or institution-wise. A centralized approach for the allocation of the organ may also not work because of diversity in the country.

HOW TO CURB THE PROBLEMS

National Organ for Tissue Transplant Organization (NOTTO)

The National Organ for Tissue Transplant Organization was set up under the Director General of Health Services, Ministry of Health and Family Welfare, which evolved as a national network for organ sharing. The National Human Organ and Tissue Removal and Storage Network is a subdivision of this group which is expanding to other states as well for coordination and networking for retrieval and distribution of organs and tissues. This institution also maintains registry of organs.

Public–Private Partnership

A public–private partnership with the help of educated and effective transplant coordinators is significantly contributing to improving the organ procurement and transplant rate, such as in the southern states (Tamil Nadu, Andhra Pradesh, Kerala, Puducherry) where Multi-Organ Harvesting and Networking (MOHAN), a non-governmental organization, has been working since 1997. This organization also established the Indian Network of Organ Sharing (INOS) to promote organ sharing across the country.

Organ Transfer and Green Corridors

When donor and recipient are in different hospitals, or the transplant experts are not available where organs are harvested, organs are transported to other facilities. Road transfer is the conventional method in India for patient and organ transfer. Special road routes (Green Corridors) are created for the transfer of harvested organs where street signals are manually operated, stoppage at red lights are avoided, and traffic is diverted to ensure rapid transportation. If the distance is more commercial, airlines can be used for the transport of organs.

SUMMARY

India has a huge potential for deceased organ donation. If proper attention is given, it will fill the gap of organ demand within the country and provide an alternative to living transplant program. There is also a mismatch between potential donors and actual cadaveric donors. The actual decision is changed by the family members due to lack of awareness and miscommunication within family members or with hospital staff. That is why awareness needs to be generated among the general public toward deceased organ donation by nongovernmental organizations and religious leaders. Public awareness is the key to promote deceased organ donation.

The National Organ for Tissue Transplant Organization, a central organization, has to play a decisive role in coordinating the activities of deceased organ donation and make transplant accessible, ethical, and affordable in India. Effective communication between stakeholders is an important factor. Transplant coordinators and counselors should be involved in the early stage and at an appropriate time, a discussion about donation should be a part of the end-of-life care. Setting up more and more tissue banks with improved facilities for sterilization of preserved organs is the need of the hour.

MULTIPLE CHOICE QUESTIONS

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Section 4: Prehospital and Disaster Management

25
CHAPTER

Ground Medical Transfer

GV Ramana Rao

WHAT IS GROUND MEDICAL TRANSFER?

Ground medical transfer refers to the transportation or movement of a sick/injured person, from one place to another under medical care. If the patient is moved from one place to another without any medical care, it is often referred to as "patient transport." It can be from home, workplace, or roadside to the hospital or from a lower level hospital to a higher level hospital. It can be elective or emergency transfer. Elective ground transport may or may not have a paramedic or medical oversight. A fine line of difference, hence, exists in the use of these terms; ground transport refers to physical movement while transfer refers to "movement with medical care." Ground medical transfer, emergency medical services (EMS), and prehospital care or out-of-hospital care are terms which have certain similarities and overlaps. Transport of critical patients has become a well-established practice of EMS worldwide and there is a growing need. Critically ill transfers demand the presence of doctors who can carry out detailed monitoring and advanced life support interventions. A critical patient during transfer is at a higher risk.

SALIENT HISTORICAL MILESTONES

At the global level, medical transfers of the modern era were created by Napoleon's doctor Jean Dominique Larrey in 1793, who established a system to transport and treat injured French soldiers. Mahatma Gandhi, during the Boer war in South Africa in 1892, started National Indian Ambulance Corps to help injured British soldiers. It had over 1,000 members as volunteers of stretcher bearers. Gandhi was bestowed with the title of "Kaiser-i-Hind" by the British for his ground medical transfers in Boer war. As recently as in 1966, a report titled "*Accidental Death and Disability: The Neglected Disease of Modern Society"* initiated organized EMS in the USA.

In India, Centralized Accident and Trauma Services (CATS), an autonomous body of the National Capital Territory of Delhi, has started ambulances services in 1991. The Hyderabad-based GVK Emergency Management and Research Institute was pioneered in technology-driven state-level "108" ambulance-based prehospital care services in public–private partnership framework in 2005. Apollo Hospitals in Hyderabad have started hospital-based ambulance services with a four-digit number 1066.

CURRENT CONTEXT

The 72nd World Health Assembly resolution (May, 2019) highlighted that timely care for the acutely ill and injured will save more than half of the deaths in lower- and middle-income countries. It emphasized the need for treatment with prehospital care and emergency care interventions. No one should die because of lack of access to emergency care as it is now an integral part of universal health care (UHC). The provision of emergency services is enshrined in India's Constitution. Failure on the part of any hospital to provide timely medical treatment to a person results in violation of the person's "right to life," as guaranteed under Article 21 of India's Constitution. Therefore, a big picture of the role of ground medical transfers should be at the forefront of the frontline healthcare providers and medical professionals involved with emergency care.

Ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), and stroke are the top three causes of death in India (2017). Noncommunicable diseases (NCD) cause 55%, communicable diseases cause 33%, and injuries cause 12% of disease burden in India, measured in the units of disability-adjusted life years (DALYs) (2016). Road traffic accident-related deaths are highest in India (150,000 per year). About 40% of the deaths are due to hemorrhage. Maternal deaths and neonatal deaths are also important concerned areas. Tertiary-level institutional care can only increase survival chances during the obstetric and neonatal emergencies. Early recognition, early referral, and early interventions save lives, emphasizing the importance of ground medical transfers.

KEY PRINCIPLES GUIDING THE GROUND MEDICAL TRANSFERS

If ground medical transfers are assumed as a significant component of EMS, about one third of lives can be saved. A response time of 8 minutes or less in an ambulance and prehospital care has proven to increase survival rates among

cardiac arrest patients. In case of road crashes, if the victim can be transferred to a definite care facility in the first 60 minutes *(golden hour)* after the incident, a good proportion of lives can be saved, limbs can be saved, complications can be reduced, and the duration of the hospital stay can be reduced. The same analogy can also be applied in case of postpartum hemorrhage (PPH), ST-elevation myocardial infarction, stroke, traumatic brain injuries, high-risk newborns, snakebite victims, etc. The first 10 minutes, otherwise named *"platinum 10 minutes,"* after a trained professional reaches the emergency patient in the field are very critical for favorable outcomes. The principle being followed is *3As—assessment, analysis, and action*. If a paramedic is attending the patient, he/she is expected to obtain medical direction in all critical cases. Emergency care in ground medical transfers should always follow the *principle of "Do No Harm and Do Not Add Insult to the Injury,"* this being more applicable in the context of road accidents. Immobilization with a split, if not done in a fractured lower limb, and trying to transport the victim which is likely to result in vascular or neurological injury is a typical example. This can be grounded by ensuring quality of care using an evidence-based approach and scrutiny of documentation of transit patient care. These documents are often called *prehospital care records*. In multicasualty incidents, the practice of field triage and categorization of victims into red, yellow, and green (using triage tag) will confirm the most critical patient, who needs to be given the highest priority and immediate transport.

In most of the lower- and middle-income countries, the *"scoop and run model"* of out-of-hospital care is adopted, unlike the developed world where the *"stay and stabilize"* principle is often attempted. If basic life support competencies are within the scope of practice of an emergency medical technician (EMT), it is advisable to adopt "scoop and run" but if a highly trained advanced EMT is available or a trained physician is available in the ambulance, "stay and stabilize" can be followed. About 28% of the emergencies require advanced life support skills in out-of-hospital care scenarios. Before the transfer, make *sure that the "ACCEPT approach" (Assessment-Control-Communication-Evaluation-Preparation-Transportation)* is in place. Thus, the key principles universally applicable in ground medical transfers are as follows:

- Do No Harm and Do Not Add Insult to Injury
- What is not documented is not done
- Evidence-based, planned, logical, and critical actions
- Stabilization of the patient before transport
- Consent and counseling of family
- Triage
- If you do not control the situation, the situation will control you
- Rapid response and minimal delay
- 24 hours × 7 days in a week
- Near real-time communication between ambulance staff and hospital
- Estimated time of arrival (ETA) communicated in advance for preparedness
- Adopt "scoop and run" and "stay and stabilize" based on the competencies of the ambulance-based professional.

MODELS OF GROUND MEDICAL TRANSFERS

The major models of the ambulance services offered based on the ownership observed in the country at present are:

- Government-owned
- Private run ground medical services
- Public-private partnership (PPP)
- Private hospital-based
- Trust hospital/organization based

In the *government-owned model*, staff and ambulances are owned by the state government and the transfers happen between government institutions. The services are provided free of cost.

Private-owned ground medical services either own ambulances/employee, staff, or lease vehicles. Patient transfers happen from incident location as well as between hospitals of choice. It is a chargeable model.

Private hospitals with one or more centers keep a dedicated helpline number and required number of ambulances for ground medical transfers with EMTs/paramedics as per standards. In critical care transfers, use the services of emergency department (ED) residents/physicians. All the transfers are destined to their own private hospitals. Services are charged.

In the PPP model, the government awards services to the private organization through a fixed cost model by tendering process of per month per ambulance (PMPA) and signs a memorandum of understanding (MoU) mentioning the service levels. This model has become very popular in India in the last 10-year period. Staff and maintenance of vehicles are by the agency while the government monitors the services. Services are rendered free of cost to the citizens. Most of the transfers happen to government hospitals. Trust hospitals run few vehicles and enable services to the locals in a limited fashion.

Independent of the type of ownership, ground medical transfers attend to primary transfer from the field as well as secondary transfer between lower and higher level hospitals. The second cited services are also termed *interfacility transfers (IFT)*. Besides, *intrahospital transport* of emergency patient for diagnostics or special units is also an area which requires special attention.

While most of the public-accessed ground medical transfers, sometimes referred to as EMS or emergency medical services, are manned by a basic life support skilled EMT, it is preferred to have an advanced life support skilled EMT in the IFT ambulances. Private hospital-based ambulances involved with ground medical transfers are often manned by physicians or advanced life support skilled EMTs. In ambulances manned by either basic or advanced EMTs, medical oversight is mandatory. Use of drugs, advanced airway [endotracheal (ET) intubation], etc., requires guidance from qualified physicians.

BASIC TASKS AND TENANTS

In order to provide end-to-end ground medical transfer, *functional and critical* prerequisites are essential.

Functional prerequisites are:

- Telecommunication system for responding to calls in a timely manner
- Ability in delivering qualified providers to the scene
- Providing emergency care
- Transporting ill or injured to the appropriate hospital in ambulances

Critical elements needed are:

- Road ambulance
- Personnel—physicians or EMTs

- Equipment—basic or advanced life support
- Communication network in the form of mobile or radiofrequency handsets/internet

TYPES OF ROAD AMBULANCES

Based on the level of care, road ambulances in India as per the *National Ambulance Code* (AIS 125) are grouped into four types (**Table 1**).

TABLE 1: Types of road ambulance.

Type of ambulance	*Purpose*
Medical first responder	Will not have the capability to transport patients in a supine state or provide them medical care inside the vehicle
Patient transport vehicle	For the transport of patients who are not expected to become emergency patients
Basic life support ambulance	For the transport and treatment of patients requiring noninvasive airway management/basic monitoring
Advanced life support ambulance	For the transport and treatment of emergency patients requiring invasive airway management/intensive monitoring

Medical Equipment and Drugs

To assess, stabilize, and monitor the patient, appropriate medical equipment is a must. A list of medical equipment and expected tasks need to be a part of learning to optimize the usage in emergency care. The National Health Mission, Ministry of Health and Family Welfare, Government of India, has standardized the medical equipment for ambulances in India (**Box 1**).

- Patient transport equipment such as semiautomatic collapsible stretcher, spine board, scoop stretcher, and wheelchair are meant to be used in fixing, moving, and lifting the patient.
- Suction apparatus, manual/electrical as well as handheld, are needed to clear airway.
- Immobilization equipment in the form of splints, cervical collar.
- Vitals assessment equipment such as blood pressure (BP) apparatus, stethoscope, and pulse oximeter
- Diagnostic equipment such as glucometer
- Monitor
- Oxygen delivery system
- Wound care and nursing equipment
- Life support drugs
- Intravenous (IV) fluids
- Basic and advanced airway equipment
- Assisted breathing equipment such as bag-valve-mask (BVM) (adult/pediatric)
- Biomedical waste management
- Extrication equipment
- Telecommunication equipment

BOX 1: Standard list of essential equipment for ambulances.

Medical equipment

- Suction pump, portable electric
- Suction pump, foot-operated
- Suction pump, hand-operated
- Laryngoscope
- Flowmeter with humidifier bottle
- Oxygen cylinder "B" type
- Oxygen cylinder "D" type
- Bag and mask ventilation device (Adult)
- Bag and mask ventilation device (Child and neonatal)
- Trolley stretcher with back tilt facility and collapsible wheels
- Canvas stretcher, folding
- Stretcher scoop
- BP instrument aneroid
- Stethoscope
- Pneumatic splints
- Cervical collar
- First aid box
- Spinal board
- Double head immobilizers
- Fetal Doppler
- Portable hand-held glucometer
- Nebulizer (Electric)
- Automated external defibrillator
- Monitor
- Syringe pump
- Transport ventilator (Adult and pediatrics)
- Transport ventilator (Neonatal and pediatrics)
- (A) Intravenous, (B) Cutdown set, (C) Suture kit
- Pulse oximeter

(BP: blood pressure)

Drugs

- Adrenergic drugs
- Antiarrhythmic drugs
- Antihypertensive drugs
- Antiepileptics
- Antidotes
- Elements/Electrolytes
- IV fluids
- Miscellaneous

PLANNING AND COORDINATION

In order to plan and implement ground medical transfer services, a well-laid process needs to be established and adhered to. Globally, the "star of life" highlights the various phases of out-of-hospital medical transfer, namely early detection, early reporting, early response, on-scene care, transit care, and transfer to definite care. In the *Indian context unified emergency number 112 (108/102/104)* and state-level command and control centers (CCC) locate the emergency (SENSE), strategically placed ambulance reaches the emergency location quickly (REACH) and provides emergency care (CARE). A follow-up call after the transfer will document the status and satisfaction of services.

Planning for Patient Transfer

Transfer of patients is an important aspect of medical care. Transfer decision should balance risks and benefits. Staff, support equipment, standard treatment guidelines, and standardized communication are success factors. Out-of-hospital care protocols, applied during ground medical transfers, highlight initial assessment and immediate interventions. In addition, the role of direct medical oversight is also crisply documented for common emergencies. Protocols need revision based on the advances in medical technology. Expected complications during transfer are as follows:

- Pulmonary (hypoxia, pneumothorax, atelectasis, embolism)
- Cardiovascular (arrest, hypotension, hypertension, rhythm changes)
- Acid–base disorders (metabolic or respiratory alkalosis or acidosis)
- Endocrine (hypoglycemia)
- Infectious (risk for provider or patient)

Response Officers from the Command Center obtain the location, chief complaint, and communication details. "*On scene care"* focuses on scene size up, scene safety, triage, patient assessment, life support interventions such as CPR, use of AED, arrest of active bleeding depending on the need, fixing, moving, and lifting. "*Transit care"* focuses on stabilization of airway, breathing, circulation, monitoring, medical direction, documentation, use of drugs, reassurance, etc.

Prearrival information (PAI) to the receiving hospital is an important task of ground medical transfers with proven favorable outcomes. Destination determination (hospital selection) is conceptually dependent on the condition of the patient, facilities at the receiving hospital, and patient's choice. Good ground medical transfers or EMS system practice evidence-based protocols.

Patient handover or handoff activity at ED or a hospital follows the *acronym of SBAR (situation, background, assessment, and recommendation) or alternatively I-PASS (Illness severity, Patient summary, Action list, Situation awareness & contingency planning; and Synthesis by receiver).* Patient handover should include both *clinical handover and administrative handover* in the form of prehospital care record (manual or electronic).

TRAINING SCHEDULE FOR EMERGENCY MEDICAL TECHNICIAN

Hence, public access EMS system should have trained EMTs in the ambulance and qualified doctors in the state-level center for online medical direction. EMTs are trained for nearly 400 hours for basic life support skills and over 1,000 hours for advanced life support skills. Training of EMTs encompasses knowledge, skills, and attitude. Generally, EMTs are trained in institutional, hospital, and ambulance phases. Simulation education is extensively used in skill training. Simulation education using manikins ensures patient safety concerns and is considered as experiential learning. Even for assessment of skills, the Objectively Structured Skills Evaluation (OSCE) method is used for EMTs. In addition to the not-for-profit organization involved with EMS services, paramedical education and mainstream universities are also offering bachelor and postgraduate degrees and diplomas to EMS professionals (**Fig. 1**).

QUALITY ASSURANCE

The National Accreditation of Board of Healthcare Organizations and Hospitals (NABH) amply echoed the need for availability of ground medical transfers in all hospitals. Equipment, competencies, processes, communication, and care practices are also highlighted. Alignment of ground medical transfers, either public access or hospital-based, will not only save lives but also reduce cost barriers to institutional care. First aid at the incident by a trained bystander, prehospital care by ground medical transfers, and care continuum at the hospital are not only a concept of chain of survival but an opportunity to prove the fact that "a system saves lives."

SUMMARY

The medical team performing road transfer of patients should be highly qualified and competent within their respective field. A mix of medical teams exists, but is usually made up of doctors, paramedics, nurses, and driver. The medical team should ideally be made up of clinical specialists who have undergone extra training in the transfer of patients including postgraduate study. It may prove beneficial to have some heterogeneity within the medical team by mixing doctor/nurse or doctor/paramedic teams where each team member can bring his/her own specialist skills to the transfer and work together to provide optimal patient care. The skillset of the medical team should always match the potential needs of the patient. Road transfer of patients can be high risk for errors to occur such as airway problems, detached intravenous lines, equipment failure, etc., so the medical team should be competent in skills/treatment for problems, which may arise during transfer. Irrespective of the type of transfer, e.g., primary, tertiary or type of vehicle used, the medical approach to the

FIG. 1: Paramedic education schedule.

patient should be similar. Standard operating procedures are an excellent tool in the transfer of patients by road as it gives an objective guide and provides "checklists" to ensure essential tasks have been completed. Ambulance transport team is incomplete without a transport physician, just as an intensive care unit (ICU) would be incomplete without an intensivist. The advantage of a specialized transfer team is that it is more familiar with transport-specific procedures and equipment. Establishment of a specialized transfer team associated with a decline adverse events. Specialized teams are better able to stabilize the patient prior to the transfer. A specialized team better deals with logistic problems. "ACCEPT" approach should be adopted by the team before start: A-Assessment, C-Control, C-Communication, E-Evaluation, P-Preparation, and T-Transfer. Team must remember "6 R" for the safe transfer of the patient: The Right patient, at the Right time, by the Right people, to the Right place, by the Right transport, with Right care throughout.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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26
CHAPTER

Air Medical Transfer

Saleh Fares, Michael J Nolan

INTRODUCTION

The use of rotary-wing and fixed-wing aircraft in the transfer of patients has increased in popularity in recent years. The utilization of helicopters as air ambulances is beneficial due to the speed of transfer of a specialist medical team to the scene of the patient and subsequent transport to a specialist hospital. This is especially important in urban areas where traffic congestion may hamper necessary resources. The use of a fixed-wing aircraft to transfer patients is required where the distance is greater and is advantageous due to the ability of longer distance and speed; however, disadvantages include secondary transfers from airport/landing strip to hospital. The air transfer of patients can generally be described in *three phases*:

1. *Primary transfer*: An air ambulance is used to transport a medical team to the scene of an accident or location of a patient. The patient is then transferred to an appropriate facility dependent on the specific patient requirement and local specialist centers. This air transfer is usually undertaken by a helicopter and flight times are usually short.
2. *Secondary transfer*: A fixed-wing or rotary-wing aircraft is used to transfer patients who require an advanced level of care. This transfer is usually from a clinic/hospital where medical treatment has been started but the patient requires treatment/intervention at a specialist facility. A fixed-wing or rotary-wing aircraft can undertake this.
3. *Tertiary transfer*: A patient is transferred by air from one facility to another, usually for definitive care. This includes international transfer of patients who require repatriation to their home country after illness/injury. This is usually undertaken on a fixed-wing aircraft including commercial jets.

DECISION FOR AIR MEDICAL TRANSFER

The decision to transfer a patient by air has several factors, including the current pathophysiology of the patient/intervention requirements, the training and expertise of the medical transport team, the location of the aircraft, and the distance to the patient and hospitals or facilities. Patients who have time-critical injury/illness and require life-saving interventions can benefit most from air transfer. These include conditions such as polytrauma, myocardial infarction, severe burns, surgery, premature neonates, intra-aortic balloon pump, extracorporeal membrane oxygenation, and many more. A "*doughnut model*" (**Fig. 1**) has been created to display the benefits of using different modes of transport for air transfer over variant distances. The area marked A will provide minimal assistance using air transfer (ground transfer is quicker), whereas area B is superior when using rotary-wing air transfer to transport an advanced medical team to the patient, where treatment/intervention can be initiated at the scene and en route to a specialist facility. Area C shows the distance that a rotary-wing aircraft will be time beneficial over other forms of transport. Area D is the distance where fixed-wing transfer would be the most beneficial regardless of necessary secondary transfers.

FLIGHT PHYSIOLOGY

The air transfer of patients creates many considerations for the medical team including the effects of altitude on the

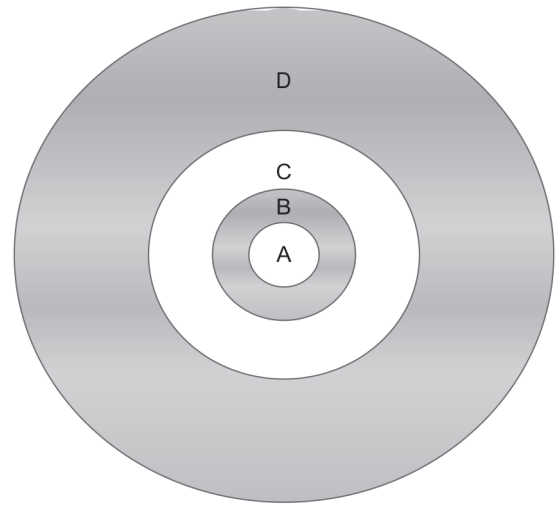

FIG. 1: Doughnut model of air transfer distances.

TABLE 1: Physiological impact of air transfer.

Effects of hypothermia	*Increase in oxygen demand and consumption*
Effects of hypoxic hypoxia	Oxygen saturation and ABG preflight may change at altitude
Effects of noise	• The patient may become panicked/distressed/combative • Monitoring audible alarms may not be heard • Communication with the awake patient may be difficult
Effects of vibration	• Increase in pain at fracture sites • May exacerbate nausea and vomiting • Higher amounts of analgesia and sedation are required • Inaccurate electrical artifacts on monitoring machines

(ABG: arterial blood gases)

TABLE 2: Comparison of ground and air medical transfer.

Ground medical transfer	*Air medical transfer*
Advantages	***Advantages***
• Door-to-door transfer • Rapid mobilization time • No landing zone required • Very few weather restrictions • Overall cost low and mostly affordable • Less physiological impact • More familiar environment for staff	• Rapid transfer • Consider where difficult road access • Can add few more medical personnel
Disadvantages	***Disadvantages***
• Motion sickness is a common problem • Traffic—major common problem	• Physiologic effect of high altitude • Assistance required for safe loading and unloading of patient • Runway is required sometimes • No night facility • Higher cost

physiology of the patient. Any medical crew involved in air transfer should have advanced knowledge of flight physiology in order to be aware and, subsequently, deal with any situations that may arise due to the stressors of flight. This is especially pertinent when transferring critically ill patients who may already be at the upper end of their physiological reserve as physiological deterioration may occur more rapidly from the stresses of flight (**Table 1**). These stressors would mainly be associated with fixed-wing transfer due to the higher altitude; however, patients transferred in helicopters may also suffer from the stresses of flight. It is important to note that these stressors are not limited to the patient but may also affect the medical crew. Some air transfer physiological considerations include the following:

- From sea level to 5,000 ft represents a significant change in barometric pressure and temperature for the patient
- Trapped air will increase 20% in size.
- The temperature will decrease by approximately 10°C.
- Ambient oxygen pressure will decrease by almost 17%.
- Arterial oxygen pressure will decrease by 23%.
- Alveolar oxygen pressure will decrease by 21%.
- Alveolar CO_2 pressure will decrease by 6.5%.

This will have a direct impact on air transfer patient care, and thus the medical crew must preempt these physiological changes that may occur and be prepared to treat accordingly.

STANDARDS OF CARE: AIR MEDICAL TRANSFER

It is important to discuss the advantages and disadvantages of the air and ground medical transfer in due course of planning (**Table 2**) to ascertain if air medical transfer would be beneficial in a particular case. The standards of care of the medical team will differ vastly across the globe. The medical team performing air transfer of patients should be highly qualified and competent within their respective fields. A mix of medical teams exists which is usually made up of doctors, paramedics, nurses, and respiratory therapists. There is no ideal medical team; however, it should ideally be made up of clinical specialists who have undergone extra training in the air transfer of patients including postgraduate study. It may prove beneficial to have some heterogeneity within the medical team by mixing doctor/nurse or doctor/paramedic teams where each team member can bring his/her own specialist skills to the transfer and work together to provide optimal patient care. The skillset of the medical team should always match the potential needs of the patient. Air transfer of patients can be high risk for errors to occur such as airway problems, detached intravenous lines, and equipment failure, so the medical team should be competent in skills/treatment for problems, which may arise during transfer. The patient should be examined thoroughly (airway, breathing, circulation); systemic examination before transfer and checklist can be used to confirm the availability of essential equipment for transfer according to the need (**Table 3**).

Irrespective of the type of transfer, e.g., primary, tertiary, or type of aircraft used, the medical approach to the patient should be similar. Standard operating procedures are an excellent tool in the transfer of patients by air as it gives an objective guide and provides "checklists" to ensure that essential tasks have been completed. This mitigates potential problems that may occur during flight where these tasks are difficult and sometimes impossible to carry out in a moving and sometimes cramped aircraft (**Fig. 2**). An example of this would be a patient who has suffered burns including facial/airway burns. During the assessment, it may be obvious that the patient has facial/airway burns but not displaying any symptoms of airway swelling or obstruction. However, problems arise during air transfer where the patient becomes distressed with respiratory difficulty, and impeding airway obstruction ensues due to swelling of the airway. It would prove beneficial to ensure that this potential complication is treated on the ground by identifying possible issues in flight and securing the airway beforehand with anesthesia and mechanical ventilation. This

TABLE 3: Checklist for air medical transfer.

Airway	*Safe/Secured by intubation*	*Yes/No*
Ventilation	• ETT confirmed (by X-ray) in right position	Yes/No
	• Paralyzed, sedated, ventilated	Yes/No
	• Comfortable on a transport ventilator	Yes/No
	• Confirmed by arterial blood gases	Yes/No
Circulation	• HR and blood pressure stable	Yes/No
	• Tissue perfusion adequate	Yes/No
	• Any obvious blood loss controlled	Yes/No
	• Have you checked hemoglobin?	Yes/No
	• Two types of venous access present?	Yes/No
	• Central and arterial line secured	Yes/No
Neurology	• Seizures controlled	Yes/No
	• Raised ICT managed	Yes/No
Trauma	• Protect cervical spine	Yes/No
	• Secure drain if pneumothorax	Yes/No
	• No intrathoracic/intra-abdominal bleed	Yes/No
	• All thoracic/abdominal/long bone/pelvic fractures are stabilized?	Yes/No
Metabolic	• Temperature adequately controlled	Yes/No
	• Acceptable acid–base balance	Yes/No
	• Acceptable range of blood glucose	Yes/No
	• Serum potassium, calcium	Yes/No
Monitoring device	• ECG	Yes/No
	• Blood pressure	Yes/No
	• Oxygen saturation	Yes/No
	• $ETCO_2$	Yes/No
	• Temperature	Yes/No

Make sure the following equipment are available on board:

Airway • Goeddel airways (assorted sizes) • Laryngeal masks (assorted sizes) • Tracheal tubes (assorted sizes) • Laryngoscopes (spare bulbs and battery) • Intubating stylet • Lubricating gel • Magill's forceps • Tape for securing tracheal tube • Sterile scissors • Stethoscope

Suction • Yankauer sucker • Suction catheters • Nasogastric tubes and drainage bag

Ventilation • Self-inflating bag and mask with oxygen reservoir and tubing • High-flow breathing circuit • Spare valves for portable ventilator • Chest drains (assorted sizes) • Heimlich flutter valves

Circulation • Syringes (assorted sizes) • Needles (assorted sizes) • Alcohol wipes • IV cannula (assorted sizes) • Arterial cannula (assorted sizes) • Central venous cannula • Intravenous fluids • Infusion sets/extensions • Three-way taps • Dressings • Tape • Minor instrument/cut-down set

(ECG: electrocardiogram; $ETCO_2$: end-tidal carbon dioxide; ETT: endotracheal tube; ICT: intracranial tension)

ensures a more comfortable environment to carry out this procedure and not in the back of an aircraft where conditions and space are limited.

The air transfer of patients is often most beneficial for critical care patients requiring specialist treatment/intervention. Whilst it is necessary to stabilize certain types of patients, it may also be required to expedite patient transfer to definitive intervention. This is the case in patients with noncompressible hemorrhage where the definitive treatment is surgery (penetrating/blunt injury). Minimal delay on the scene should be advocated and solutions for any issues that arise en route to definitive care should be instigated. The air transfer of patients in cardiac arrest should not be advocated due to several potential issues. The ability to perform cardiopulmonary resuscitation in the back of an aircraft is impractical due to limited space, crew restraint in the aircraft, and safety issues. Advanced life support treatment should be instigated according to standard operating procedures at the scene of the patient where space and resources may not be limited.

SPECIAL CONSIDERATIONS

During the air transfer of patients, there are some special considerations that clinicians must be aware of to mitigate problems due to altitude. Any patient who may have trapped air in pathological airspaces can have a possible catastrophic reaction to altitude. The conservative management of any condition with trapped air such as pneumothorax, intraocular air, and pneumocephalus must be handled with extreme caution. The insertion of chest drains in the restricted space of an aircraft if a patient deteriorates is impractical due to patient accessibility and limited space/resources. During the air transfer of psychiatric patients, special considerations are mandatory before placing the patient in the aircraft. The preferential use of ground transport is always advocated, but certain instances may arise where air transfer is the only option. Patients experiencing psychiatric illness may appear docile on the ground but become agitated due to the stressors of flight and the claustrophobic environment. This can have the potential to jeopardize the safety of the crew and the flight. All efforts must be made to carefully plan and adhere to local standard operating procedures (SOPs) whilst maintaining legal and ethical consideration in respect of pharmacological sedation of psychiatric patients.

RECENT ADVANCES

The most recent advance in the air transfer of patients is the increasing number of rotary-wing air ambulances. In the United Kingdom (UK), there are approximately 20 civilian air ambulances providing life-saving care to the public. Most of these air ambulances are funded by charity and rely on public donations. With the introduction of major trauma centers, injured patients may have to travel further to access this specialist facility. Air ambulance helicopters are the fastest way to deliver patients to life-saving specialist intervention

FIGS. 2A AND B: (A) Fixed-wing and (B) rotary-wing air transfer (limited space and access to the patient).

and play a key part in an increase in patient survival. Air ambulance faces few fatal crashes also, so regulations are required to increase the safety of air ambulance missions by implementing the latest technology and flight data monitoring systems to assist flying in challenging weather, at night, and in remote locations.

SUMMARY

The air transfer of patients poses risks for the patient, medical, and flight crew due to several reasons including altitude, environment, and severity of the patient's condition. Most situations that arise can be mitigated by careful planning and utilizing SOPs, which ensure that medical crews develop motor programs so that working in a changing environment can be completed safely and successfully. Below are some helpful rules for the air transfer of patients:

- Most complications that occur were not anticipated by the air medical crew. Large problems are usually small ones that were not planned for.
- The ability to competently deal with any situation that arises is mandatory. No one can run for help whilst in the sky!
- Make sure to spend extra time securing all tubes and infusion lines. These extra few minutes will pay off as loading/unloading patients can be haphazard for accidental removal.
- Treat the patient as well as the monitor. The environment of air transfer can be noisy and distracting. Ensure good clinical observation.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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27 CHAPTER

Basic Concepts of Disaster Management

Venkat Changavalli, Devendra Richhariya

INTRODUCTION

The term disaster consists of two Latin words (dis—bad and aster—star/fortune). As the word itself suggests, it was considered as misfortune or punishment given by God and also considered the fact that these are not under human control. With time, these theories changed and now understood that these are not beyond the control of human and can be managed with appropriate planning.

In India, about 60% of land is vulnerable to earthquakes, 16% of land is vulnerable to drought, 12% of land is vulnerable to floods, and 8% of land is vulnerable to cyclones. These calamities result in injuries, deaths, and property damage and these cannot be managed by individual capacity through the routine measures. Preparedness is an integral part of a control program and is important for effective management of an incident to minimize losses to people and property, both in and around the facility. A comprehensive *disaster preparedness strategy* is required and components are as follows:

- Hazard, risk, and vulnerability assessments
- Response mechanisms and strategies
- Preparedness plans
- Coordination
- Information management
- Early warning systems (EWSs)
- Resource mobilization
- Public education, training, and rehearsals
- Community-based disaster preparedness

DEFINITIONS

Disaster, as per the Disaster Management Act, 2005, is defined as "A catastrophe, mishap, calamity, or grave occurrence in any area, arising from natural or man-made causes, or by accident or negligence which results in substantial loss of life or human suffering or damage to, and destruction of property, or damage to, or degradation of environment and is of such a nature or magnitude as to be beyond the coping capacity of the community of the affected area."

Any occurrence that causes damage, economic disruption, loss of human life, and deterioration in health and health services on a scale sufficient to warrant an extraordinary response from outside the affected area or community can be termed disaster. The United Nations International Strategy for Disaster Reduction (UNISDR) defines disaster as a serious disruption of the functioning of a community or a society causing widespread human, material, or environmental losses which exceed the ability of the affected community or society to cope using its own resources.

Examples of disaster:

- Road traffic accidents, air crash
- Bullet and blast injuries
- Collapse of a building
- Fire
- Communal riots
- Terrorist attacks
- Floods
- Earthquakes, tsunami
- Epidemics
- Nuclear/biological/chemical warfare

CLASSIFICATION OF DISASTERS

Disasters are classified into two major categories: (1) Natural and (2) Manmade (**Table 1**). Classification helps us in risk assessment of the disaster vulnerability and in building sufficient capacity to manage the disaster.

Risk factors for disaster: If the scale of hazard is too big, vulnerabilities are too high and capacity is insufficient to deal with it, the risk is too high, so emergencies cannot be managed locally, and the communities may not be able to handle the situation.

(Hazard + Vulnerability = Increase in disaster risk) and
(Increase in capacity = Decrease in disaster risk)

Hazard: A potentially damaging physical event, phenomenon, and/or human activity, which may cause loss of life or injury, property damage, social and economic disruption, or environmental degradation

Vulnerability: A condition or sets of conditions that reduce people's ability to prepare for, withstand, or respond to a hazard.

TABLE 1: Classification of disaster.

Manmade disaster	*Natural disaster*
• *Civil disturbances*: Riots, explosion, and demonstrations • *Warfare*: Conventional warfare (bombardment, blockage, and siege) • *Nonconventional warfare*: Nuclear, biological, and chemical warfare (NBC) • *Terrorism refugees*: Forced movement of a large number of people usually across frontiers • *Accidents*: Transportation calamities (land, air, and sea), collapse of building, dams, and other structures, mine disasters, fire, poison gas panic • *Technological failures*: Nuclear power station, leak at a chemical plant, breakdown of a public sanitation system	• *Meteorological*: Storms (cyclones, hailstorms, hurricanes, typhoons, and snowstorms) • Cold spells, heat, waves, droughts • *Topographical disasters*: Avalanches, landslides, and floods • *Geological disasters*: Earthquakes, tsunamis, volcanic eruptions • *Biological disasters*: Insects, swarms (locust) and epidemics of communicable diseases

Capacity: Those positive conditions or abilities which increase a community's ability to deal with hazards.

Risk: The probability that a community's structure or geographic area is to be damaged or disrupted by the impact of a particular hazard, on account of its nature, construction, and proximity to a hazardous area.

Features of disaster: Disaster disrupts a large number of people of a normal functioning society. It causes damage to property and loss of human life. Disaster management requires external help to manage the disaster. The following steps are important to minimize the losses:

- Reliable and early detection of an emergency and careful planning
- Coordination along with efficient trained personnel
- Resources for handling emergencies
- Appropriate emergency response actions
- Effective notification and communication facilities
- Proper training of concerned personnel
- Regular mock drill/rehearsal
- Regular review and updating plan

DISASTER MANAGEMENT CYCLE

Emergencies and disasters can strike without warning. Each individual with a disability has unique circumstances and needs. There will likely be problems with drinking water, electricity, and other utilities. When large-scale disasters strike, most assistance is provided by one citizen to another. Police, fire, or emergency medical service (EMS) resources will not be able to reach everyone right away. In the last few years, we have seen that disasters also simultaneously destroy health facilities, besides other infrastructures. *Disaster management* is a collective term encompassing all aspects of planning for preparing and responding to disasters. It refers to the management of the consequences of disasters. The fundamental of disaster management is to do the greatest possible good for possibly the greatest number of affected people. The disaster management cycle broadly has six phases covering predisaster [(1) prevention, (2) mitigation, (3) preparedness] and postdisaster [(4) rescue, (5) relief, (6) rehabilitation and reconstruction] responses (**Fig. 1**).

Response: Actions are taken immediately following the impact of a disaster when exceptional measures are required to meet the basic needs of the survivors.

Relief: Measures that are required in search and rescue of survivors as well to meet the basic needs for shelter, water, food and healthcare.

FIG. 1: Disaster management cycle.

Recovery: The process undertaken by a disaster-affected community to fully restore itself to the predisaster level of functioning.

Rehabilitation: Actions taken in the aftermath of a disaster to:

- Assist victims to repair their dwellings
- Re-establish essential services
- Revive key economic and social activities

Reconstruction: Permanent measures to repair or replace damaged dwellings and infrastructure and to set the economy back on course.

Development: Sustained efforts intended to improve or maintain the social and economic well-being of a community.

Prevention: Measures taken to avert a disaster from occurring, if possible (to impede a hazard so that it does not have any harmful effects).

Mitigation: Measures taken prior to the impact of a disaster to minimize its effects (sometimes referred to as structural and nonstructural measures). Structural and nonstructural measures undertaken to limit the adverse impact of natural hazards, environmental degradation, and technological hazards are as follows:

- Structural measures refer to any physical construction to reduce or avoid possible impacts of hazards, which include engineering measures and construction of hazard-resistant and protective structures and infrastructure, such as construction, hazard-resistant house construction, planting mangroves, drainage channels, and water conservation measures.
- Nonstructural measures refer to policies, awareness, knowledge development, public commitment, and methods and operating practices, including participatory

mechanisms and the provision of information, which can reduce risk and related impacts.

Preparedness: Measures taken in anticipation of a disaster to ensure that appropriate and effective actions are taken in the aftermath.

DISASTER RESPONSE MANAGEMENT

Disaster response is the immediate intervention or provision during the disaster or just after the disaster to preserve human life and provide basic needs to affected people. In view of the complexity of the disaster, response would vary and depend on the sudden/slow-onset disaster, place of disaster (rural, urban, mountain, coastal, marine), and magnitude of disaster (managed with local authority or need central government assistance).

Disaster responders: Responders can be divided into various categories such as immediate responders (community which includes family members, friends, and neighbors), core responders [police, fire services, EMS, district collector and National Disaster Response Forces (NDRF)]. Secondary responders are the civil defense special team, nongovernmental organizations, engineers, food and supply department.

Major response activities: Major activities for responders are search and rescue, which require especially trained persons who can rescue trapped people from the disaster area and collapsed structures, e.g., mountain rescue, air rescue, and sea mining rescue. Evacuation is an important activity which can be started before disaster in the form of early warning and moving the people to a safe area. Fire fighters are trained and well equipped to rescue people from car accidents, collapsed buildings, and other difficult situations.

Emergency medical treatment: Nearest hospitals are the first place where disaster casualties are received. A proper triage scheme, core medical emergency team with pediatric care units, is necessary to deal with mass casualties. Setting up mobile and field hospitals, placing first-aid equipment at community-level hospitals, etc., are important activities.

Ambulance services: Boat, ships, vans, etc., can be used for transporting injured and sick people. Ambulances can be used as mobile medical units outside the hospital to treat the people.

Restoration of important infrastructure: Water, sanitation, electricity, communication, repair of roads and bridges that connect the rural area to the urban areas, restoration of the functionality of healthcare centers and hospitals.

Tools for professionalizing disaster response: Various measures are implemented for streamlining the response such as setting up an *incident command system* (ICS), simulation and scenario analysis, exercise (tabletop and functional), mock drill, implementation of new innovations, and research.

INCIDENT COMMAND SYSTEM

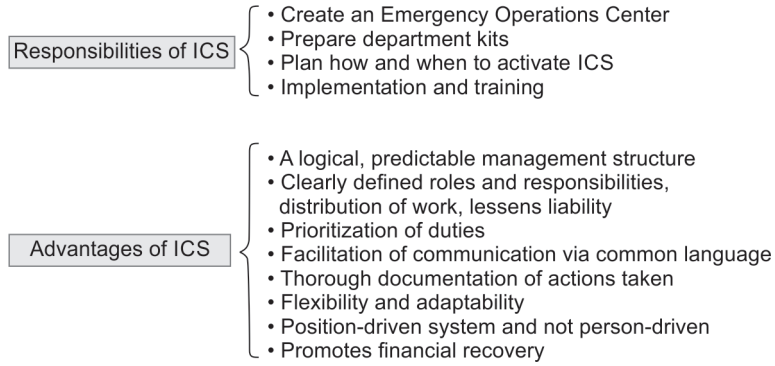
Incident command system (ICS) is an emergency management system that helps the primary responders, responding agencies, and personnel to unify services. Medical disaster can quickly lead to chaos and confusion and ICS provides medical facilities with an organized management structure that promotes immediate, focused direction of activities during a disaster and allows for prompt resumption of normal operations. Incident Command Center is headed by an Incident Commander whose responsibilities are administration, planning, finance, and arranging logistics (**Table 2**). Incident command is helpful in defining the role and responsibilities, prioritizing duties, and providing a predictable management structure (**Fig. 2**). The public information officer, safety officer, and liaison officer are the other important members of the ICS and their roles are clearly defined. An incident command organization chart is shown in **Flowchart 1**.

MULTIAGENCY COORDINATION DURING RESPONSE

Disaster is a complex situation, and a single-point contact mechanism is required for coordinated comprehensive relief operation.

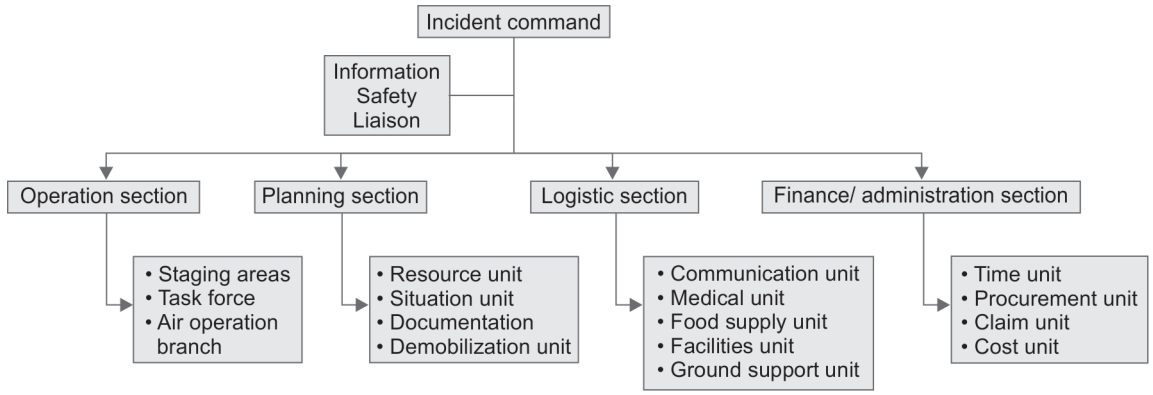
TABLE 2: Overall responsibilities of the head of the incident command center.

Logistic (provide support)	***Planning (prepare action plan)***	***Finance (cost accounting and procurement)***	***Operations (direct tactical action)***
Responsible for acquisition and maintenance of facilities, services, and personnel equipment materials	• Collect, analyze, and display information • Prepare an incident action plan • Maintain situation and resource status • Maintain incident documentation • Prepare demobilization • Promote continuity of operations	• Monitor incident costs • Maintain financial records • Administer procurement contracts	Carry out the medical objective to the best of their ability
Other important command staff			
Public Information Officer	***Safety Officer***	***Liaison Officer***	
Provide information to the news media; serves as the one central point for information dissemination	Monitors the facility and anticipates, detects, and corrects unsafe situations	Functions as an incident contact person for representatives from other assisting and cooperating agencies	


Responsibilities of ICS
• Create an Emergency Operations Center
• Prepare department kits
• Plan how and when to activate ICS
• Implementation and training
Advantages of ICS
• A logical, predictable management structure
• Clearly defined roles and responsibilities, distribution of work, lessens liability
• Prioritization of duties
• Facilitation of communication via common language
• Thorough documentation of actions taken
• Flexibility and adaptability
• Position-driven system and not person-driven
• Promotes financial recovery

(ICS: incident command system)

FIG. 2: Advantages of the incident command system.



FLOWCHART 1: Incident command organization chart.

Coordination is important: For prioritization of work, deploying resources in high-need areas, monitoring, evaluating population at risk.

Coordination facilitates assessment of roles, resource capabilities and also identifies gaps, overlaps and bottleneck. Coordination facilitates communication between various agencies.

Coordination barriers: Involvement of too many organizations and decision-makers which work for different priorities, expectations, and beliefs. Most of the time lack of resources and not possible to devote a person only for coordination, thus leading to ineffective coordination and leadership.

Coordination technique: Increase linkage and understanding between all responding agencies by promoting transparencies, involving right people or agencies, and allocating them appropriate role with written proceedings of coordination meetings. Have a rapid reporting system in place, know each other's strengths, respect each other, and acknowledge each other's contribution.

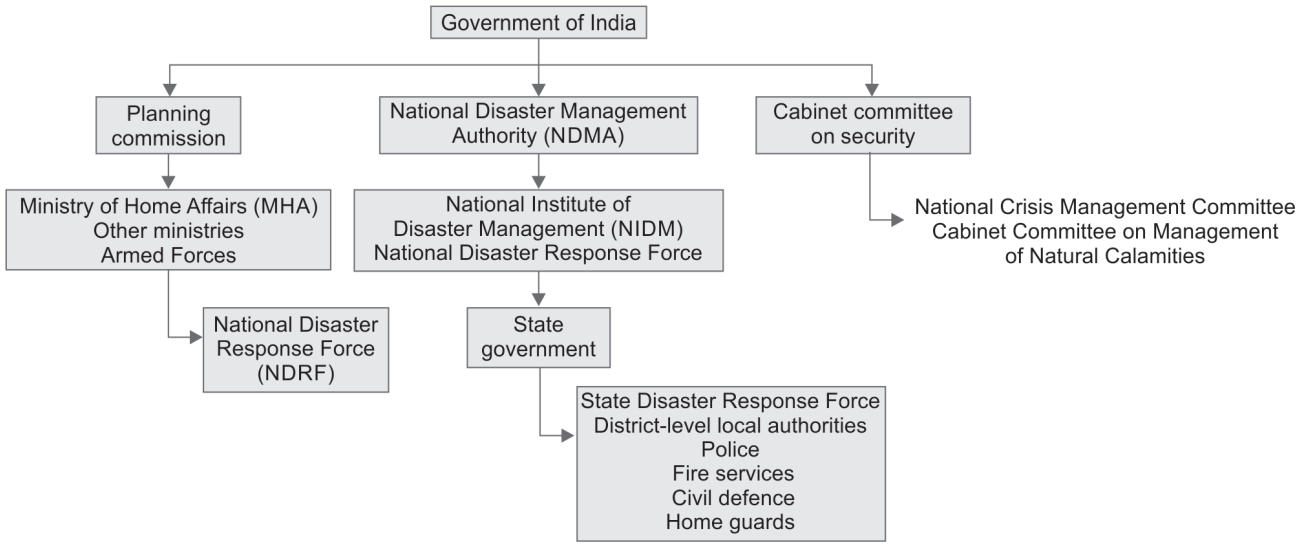
Role of Armed Forces, Paramilitary, and NDRF: The Indian armed forces are generally expected to call to intervene in specific tasks when any situation is beyond the capabilities of civil administration. Armed forces are positioned in various locations in the country and are always in readiness to respond to any situation. The armed forces and NDRF are disciplined manpower, show a high degree of professionalism, and are equipped with various machinery for restoration of immediate services and relief work. Armed forces, paramilitary forces, and national disaster relief forces provide various types of relief operations such as search, rescue and evacuation, medical aid, aerial dropping of food, setting up the relief camp, restoring damaged road and bridges, and restoration of essential services such as water and electricity.

The role of Indian armed forces in providing assistance to civil authorities in a disaster situation is well known. Armed forces provide assistance in disaster relief not only within the country but also in neighboring countries. The roles of police in disaster management are maintaining law and order, evacuation of the population, first-aid, record of lost and found people, identification and disposal of the dead, and guidance to other agencies. A specialist force that has been created to respond to disaster and a disaster-like situation in India is the *NDRF*. NDRF is equipped to assist state and local authorities in managing natural as well as manmade disasters. During nondisaster situations, NDRF provides community awareness education and disaster preparedness. Multiple agencies' coordination for disaster response in India is summarized in **Flowchart 2**.

EARLY WARNING SYSTEM FOR DISASTER

The role of any warning system is to inform vulnerable people about the possible threat of an impending natural hazard so that timely and appropriate action can be taken for the safety of life and property (**Table 3**). There are four elements of EWS:

1. Detection or risk knowledge
2. Monitoring and prediction



FLOWCHART 2: Multiple agencies' coordination during disaster response.

TABLE 3: Early warning system in India.

Hazard	*Nodal agency*
Cyclone	Indian Meteorological Department
Flood	Central Water Commission
Landslides	Geological Survey of India
Tsunami	Department of Ocean Development
Avalanches	Defence Research and Development Organization

3. Dissemination and communication
4. Response capabilities

An effective EWS for all hazards needs to be established which can give information about the more frequent hazard in that region as well as rare but most destructive hazard such as tsunami. Monitoring and warning service is an important part of EWS. Local warning procedures such as siren, drums, and bells are most effective at the time of emergencies.

Various technological advances to communicate early warnings need to be taken into account while designing the dissemination mechanism so that we can reach out to the last person and avoid failure.

ROLE OF TECHNOLOGY AS DECISION SUPPORT TOOLS

During critical hours of a disaster, quick and authentic information is required regarding the population likely to be affected, resource availability, critical infrastructure available, evacuation routes, and communication channels for effective decision-making. The National Informatics Centre officials support the administrators in managing the information.

Geographic Information System Role in Disaster Response

Geographic Information System (GIS) is a computer-based tool helpful in mapping and analyzing activities on earth, and GIS-based solution includes flood and earthquake damage assessment, emergency response planning, hazard mapping, and resource mapping. GIS integrates five key components: (1) Hardware, (2) software, (3) data, (4) procedure, and (5) people who manage the system. GIS is capable of capturing, storing, querying, analyzing, and displaying data. GIS is a powerful tool helpful in decision-making in all phases of the disaster management cycle.

Global Positioning System Role in Disaster Response

Global Positioning System (GPS) is a satellite-based navigation system helpful in locating the position anywhere on the earth. GPS is helpful in mapping of soil, vegetation type, endangered species, and wildlife habitat. It is helpful in the assessment of the damage after natural disasters such as fires, floods, and earthquakes.

HUMANITARIAN CONSIDERATION IN DISASTER RESPONSE

The most important part of disaster management is that all agencies taking part in rescue and relief work should respect all human beings and should not be looked down upon as helpless recipients of assistance. The responding agencies should ensure that assistance is given without any discrimination of nationality, race, religious belief, class, or political favor. The main issues during the response phase of a disaster are related to the evacuation of pregnant women, lactating mothers, elderly, and physically and mentally challenged.

CONDUCTING EXERCISE FOR DISASTER MANAGEMENT

"Practice makes a man perfect." Practice is an important aspect of the preparation process for disaster and a practical and cost-effective way to prepare for response and recovery. Exercise enables us to know the areas that need improvement and the operation plan that can be revised and training improves proficiency in executing these plans. Participants are placed in a simulated situation and required to function like a real

event. Preparedness and operational plan are tested by doing the exercise. The main reasons for conducting the exercise are as follows:

- To test and evaluate plans, policies, and procedures
- To detect planning and procedural weakness
- To detect gaps in resources
- To improve coordination and communication within the organization
- To clarify and train the individuals in their role and responsibilities
- To improve individual performance

Four types of exercise are helpful:

1. Drill
2. Tabletop exercise
3. Functional exercise
4. Full-scale exercise

Drill: Drill is a coordinated supervised activity to test a single specific function. In this, there is no need to activate the whole machinery and the role is to practice and perfect one small part of the response plan and put tight focus on the potential problem area. Drill activities may range from simple operational procedures to more elaborate communication and command post drill. Four components of the drill are as follows:

1. Preparation for drill
2. General briefing to participants
3. Use of audiovisual aids
4. Monitoring of exercise

Tabletop exercise: This is an analysis of an emergency situation in an informal and stress-free environment. A group of participants examine and resolve the problem through constructive discussion. The exercise starts with reading out a small hypothetical emergency and then the facilitator leads the tabletop discussion. The discussion-generated problems focus on how participants would respond in real emergencies. Participants are allowed to take their time in arriving at a conclusion. Tabletop exercise usually lasts for 1–4 hours or more. The advantages of tabletop exercises are as follows:

- Provide a low-stress discussion of coordination
- Provide a good environment for problem-solving
- Provide opportunities to various agencies to know each other and coordinate well
- Provide good preparation for functional exercise

Full-scale exercise: A full-scale exercise coordinates the several activities of the disaster management cycle, tests several emergency functions, and activates an incident command system or emergency operation command; thus, a scale exercise simulates a real event as closely as possible.

The following measures are taken for realism:

- On-scene action and decision
- Simulated victim
- Search and rescue requirements
- Communication devices
- Equipment deployment
- Actual resource and personnel allocation

The exercise begins with a description of events in the form of mock emergencies such as a collapsed or a burning building, a simulated chemical spill on a highway, or a terrorist attack. The incident command center or emergency operation center (EOC) is activated. The responder has to take action and one or more controllers manage the exercise. All the stakeholders such as policy personnel, coordination personnel, operational personnel, and field personnel take part in the full-scale exercise. At the end of the exercise, debriefing and evaluation are conducted.

PREPARING THE EMERGENCY DEPARTMENT FOR MASS CASUALTIES

Hospital Disaster Management Committee:

- Medical Director
- Medical Superintendent
- Additional Superintendent/DMS
- Heads of departments such as Emergency, Surgery, Orthopedics, Medicine, and Laboratory Radiology
- Heads of operation theater (OT), Security, Store/logistics in-charge
- Blood Bank Officer
- Nursing Superintendent
- Ambulance

In-hospital challenges during disaster management:

- Additional bed space
- Biological warfare/Chemical warfare
- Temporary isolation ward
- Barrier nursing, universal precaution
- Additional OT tables
- Cancel routine/Elective surgery
- Monitor consumption of essential drugs and supplies
- Ensure adequate supply
- Documentation including medicolegal record (MLR)
- Crowd management
- Media management
- Proper identification, tagging documentation of dead
- Creating temporary morgue
- Maintaining the essential services, water power supply, emergency lights, and waiting area

Creating the additional capacity for disaster:

- Utilize all available beds
- Additional bed capacity: Vacant beds, daycare beds, preoperative beds, trolley beds, folding beds, floor beds
- The patient whose elective surgery is planned can be discharged, patients requiring domiciliary/outpatient department (OPD) care.
- Utility areas (side rooms, galleries, seminar rooms, etc.) can also be used.

Logistic support system for EOC: There should be separate stock for routine day-to-day emergencies and for disaster. Inventory should include:

- All essential medicines
- Dressing materials
- Splints
- Disinfectants
- Vaccines
- Emergency trays
- Surgical supplies
- Resuscitation room
- Resuscitation kit

- Electrocardiogram (ECG), defibrillator
- Ventilators
- Suction machine
- Oxygen
- Endotracheal (ET) tubes
- Stretchers
- Wheelchairs
- Linen, blankets, etc.

MASS CASUALTY MANAGEMENT

Establishing the Emergency Operation Center

It serves as a central command post during a disaster, generally established outside the emergency department (ED), should be large enough for key people and support staff, and should be located in a safe area (**Table 4**).

How to activate and when to activate ICS:
- Determine who will activate the ICS
- Notification to hospital personnel
- Briefing all core members regarding assignments and clear immediate direction
- Activation of ICS should be announced using standardized codes, such as "disaster code"

Mass casualty: When an unexpectedly large number of injured/ill persons need emergency medical care at the same time, it is referred to as mass casualty. The aim in a mass casualty situation is to "do the best for the most, not everything for everyone" and "doing the best for the most."

Goal: To apply trauma triage principles in multiple patient scenarios

The grading of the mass casualty is done as follows:
Grade I: 10–15 victims
Grade II: 16–30 victims
Grade III: >30 victims

TABLE 4: Sequence of activities in the emergency department during mass casualty management.

Assignments	*Strategies*	*Coordination*
• Assembly of team • Roles and responsibilities • Personal protection equipment distribution	• Patient identifications • Triage tagging • Documentation	• With command center • Use of mobile
Mass casualty—triaging and treatment		
• Victim identification • Rapid vitals assessment and physical examination • Tagging according to triage categories • Care priorities • Documentation • Disposition • Regular communication with the emergency command center		
Debriefing		
• Evaluation of triaging decisions and evaluation of strategies • Assessment of medical and diagnostic performance • Discussion about communication and management skills		

Disaster triage: The objective of disaster triaging is focused on the critically ill patients and saving the maximum number of lives with limited medical resources and doctors.

Simple Triage and Rapid Transport System Principle: *Tag—Treat—Transfer….*

The objective is to locate, identify, and tag priority-1 patients who require immediate care and transportation. "Triage tags," applied to patients, make one's task of sorting much easier. It is of four different colors: red, yellow, green, and black. Fold the triage tag to show appropriate color on the outside. Priority patients are those with a good chance of survival.

Simple Triage and Rapid Transport System (START) focuses on three areas:
1. Respiration
2. Pulse rate and quality
3. Mental status

Goal: Correction of life-threatening condition: Airway or breathing problem and profuse bleeding

How to identify so many unknowns:
- Name
- Mass Unique Health Identification (UHID)
- Marks of identification—tattoo, scar
- Belongings—purse, clothes, DL, ID
- Typical injuries—amputation

Mass casualty incident: Situation may be one or combination of biological, nuclear, fire chemical, explosion, or natural event and natural disaster with mass casualty incident.

Chemical and Radiological Disaster

Disasters such as earthquake, landslide, road traffic accidents, and hurricane are more common than chemical and radiological disasters but it is essential to have planning for chemical and radiological events because they have the potential for major disruption to clinical care and create hazardous consequences such as chaos and confusion. Hospitals should have a trained emergency team to deal with chemical and radiological exposure (**Table 5**). A decontamination area with shower and place for stocking of antidotes for toxicants should be within the ED (**Table 6**). The components for chemical and radiological management (disaster management cycle) are the same as any other disaster (already discussed earlier). Decontamination of radiological activity is to be dealt in the same way as chemical activity. Clothes should be removed and after showering, the patient should be scanned by radiation detector equipment.

Common challenges in a chemical event:
- Failure to identify the offending agents for hours or days
- Medical team gives only supportive care (act blindly initially)
- Mistaken diagnosis
- Inadequate resources in the ED for effective management of large number of chemical exposure victims
- Medication errors
- Chaotic and confusion in society

Offending chemical agents can be identified with the help of the following observations:
- Vital signs
- Mental status

TABLE 5: Common clinical features of chemical and radiological exposures.		
Toxins	***Common features***	***Examples***
Irritant gases	Irritation of eye, ear, nose, throat, wheezing, breathlessness, chest pain, and tightness	Ammonia, chlorine, nitrogen dioxide, phosgene
Chemical burns	Painful skin, mucous membrane irritation	Hydrochloric acid
Organophosphate	Pinpoint pupil, eye pain, breathlessness, wheeze, sweating, drooling of saliva, vomiting, diarrhea, seizure, coma	Organophosphate, carbamates insecticides
Solvent	Headache, nausea, confusion, syncope	Paint thinners, lubricants, methylene chloride
Metabolic poisoning	Unconsciousness, hypotension, cardiac arrest	Cyanide, hydrogen sulfide
Radioactive material	Vomiting, delayed onset of skin manifestations	

TABLE 6: Recommended stock of antidotes in the emergency department.	
Atropine 1 mg/mL	16 mg
Dextrose 50%	100 mL
Diazepam 5 mg/mL	40 mg
Hydroxocobalamin plus sodium thiosulfate	4 kits
Methylene blue	8 units
Naloxone 1 mg/mL	16 mg
Pralidoxime 1 g vial	10 mg
Prussian blue 500-mg capsules	12 capsules

- Pupil size
- Involvement of mucous membranes
- Lung findings
- Skin examination where the skin has to be looked for burn, moisture, color

SUMMARY

Return to normal activity as soon as possible is the important goal for effective disaster management. A detailed after-action report is helpful in the improvement of a disaster management plan. Revision of disaster management plan and regular mock drills should be conducted.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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28
CHAPTER

Mass Casualty Management

Saurabh Dalal

INTRODUCTION

Mass casualty management (MCM) is the exercise of saving "maximum number of people in minimum time, with minimum resources"; therefore, this chapter is dedicated to save lives on a mass scale. The MCM comes into play "when a mass casualty incident (MCI) has occurred during any mass gathering."

"What is exactly a mass gathering?" "It is the influx of large number of people to any mass gathering events that may give rise to specific public health risks" as defined by the World Health Organization (WHO). Further, when we come to breaking up the jargon, we need to understand what exactly does an "MCI means." "MCI basically creates stress, even in those hospitals which have adequate resources, because by definition 'mass casualty' is an occurrence which is beyond the resource capacity of the health facility at the given time."

Mass casualty incident could lead to an event resulting in illness and/or injuries that disrupt the routine functioning of the nearby hospital/health facility/locality/jurisdiction and/or of the whole region. As per the WHO, MCI is "any event resulting in a number of victims large enough to disrupt the root cause of emergency of health-care services." As observed in the past few decades, MCIs have been characterized by quantity, severity, and diversity of patients who can rapidly overwhelm the ability of local medical resources to deliver comprehensive and definitive medical care. These MCIs have been occurring more frequently in recent decades and can affect countries of all socioeconomic backgrounds. So, therefore, preparedness toward MCM needs to be well in place, in the community as well as by the authorities, because the community is, in any case, the first responder; therefore, they need to be confident in any given situation.

BACKGROUND

In order to understand the history of MCM, we need to understand the kind of MCIs that have been taking place in the history. During the last century, events creating a large number of casualties have been infrequent but with depressing repetition, which has absorbed the attention of the world community. In these years, nations have increased to sufficient population densities and have developed technologies of sufficient power to create the conditions for sudden catastrophe, whereby in a relatively brief time span an enormous number of people may be killed or injured.

When discussing nuclear war, reference to precedent may admit sources of serious error, since in terms of the scale of effects, this disaster would depart fundamentally from anything the world has yet experienced. Yet people still struggle to comprehend what nuclear war might mean, if only to give better warning now. As part of this attempt to make real the unimaginable, it is instructive to inquire into how massive numbers of casualties have been managed in the past. The perspective taken here is the organization of medical response. Wars and major civilian disasters provide the context and the time frame dates from the US Civil War.

The current theory of MCM rests on the concept of triage, according to which casualties are sorted into categories by severity of injury and treatment plans assigned to each based on an assessment of transport availability and resources. The word is said to derive from the French *triage*, meaning the process of sorting by quality, and its use in the wool and coffee trades during the eighteenth and nineteenth centuries carried the distinct connotation of separating higher from lower quality.

Although the process of prioritizing military casualties on the basis of wound severity has been traced to Baron Dominique Jean Larrey, surgeon-in-chief of Napoleon's Russian Campaign, the term *triage* was first applied in this context during the World War I. The British Expeditionary Force used *triage* to mean *division into three*: (1) Those who could withstand travel back from the front, (2) those who required immediate surgery, and (3) those whose injuries were so severe that they would be left to die. The US military command currently prefers the term *sorting*, but in all other respects it relies on the concept of triage in its protocols for MCM. The main causes apart from natural disasters are manmade disasters such as terrorist bombings and accidents:

- Planned events such as sporting and mass gathering events
- Conventional, which usually have some level of recurring frequency (transportation incidents, burn, and severe weather events)
- Chemical, biological, radiological incidences

- Nuclear agents from an unintentional or accidental release or act of terrorism
- Catastrophic health events (nuclear detonation, major explosion, major hurricane, pandemic influenza, or others)

In India, the National Disaster Management Authority guidelines on medical preparedness and MCM serve as a basic framework for managing mass casualties; several capacity-building activities and mock drills have been carried out across the country in accordance with the guidance.

CASE STUDIES

Mass gathering events pose critical health challenges, especially for the control of diseases. The rising population, better connectivity, and scope of travel have increased the frequency and magnitude of mass gatherings and underscored the need to shift the discourse from reacting to the public health issues they throw up to taking active steps in preventing them based on evidence through research.

Kumbh Mela: The Largest Human Gathering on the Planet

One of the largest human gatherings in India, the *Kumbh Mela*, is a religious event in India that constitutes the largest number of people gathered at a specific place and at a specific time. Understanding the *Kumbh Mela* can highlight the health challenges faced and provide crucial lessons for the management of mass gatherings. The investigations undertaken at the recent *Kumbh Mela* in the city of Allahabad have showcased what kind of mammoth efforts are undertaken to manage such big events without any accidents. Many in-depth studies on the *Kumbh Mela* have generated evidence for context-specific measures to address the complex health challenges of mass gatherings.

Kanpur Rail Accident Tragedy

One of the recent examples of efficient MCM was the accident of the Patna–Indore Express, in which as many as 142 people were killed and >200 injured when 14 coaches of the train were derailed in the Kanpur Dehat district of Uttar Pradesh on a Sunday; this was one of India's worst train accidents of the decade. The derailment happened at 3.10 AM near Pukhrayan, about 100 km from Kanpur. Most of the 500 passengers on board were sleeping and some of the shocked survivors recalled how they got jolted out of their slumber by a violent thud.

- Army initiated the rescue operations throughout the night and recovery vehicles were deployed to clear the wreckage. A team of doctors and paramedics were also deployed at the spot to help in rescue operations.
- Two NDRF teams from Varanasi and another from Lucknow were also rushed to the accident spot.
- Medical assistance of all kinds was offered. Rail mobile medical units were also rushed to the site. All the injured were rushed to hospitals; immediate medical help and hospitals like King George's Medical University in Lucknow were kept on standby.
- The primary care on-site and first aid were carried out after extrication from the coaches. This was a classic case of a mixture of multiple mortalities and morbidities in the rural Indian context and reiterated need of pan-nation preparedness for all hazards, both natural and manmade.

Tughlakabad Hazardous Gas Leak Tragedy, New Delhi

Hazardous material is commonly referred to as HAZMAT or dangerous goods by the industry and these are chemicals that can constitute a health hazard or physical hazard. In the early hours on May 6, 2017, the driver of a truck carrying a container with 80 drums of an agrochemical pesticide powder observed leakage from some containers. A total of six drums had sprung leaks and, at 7:30 AM, local laborers spread soil over the ground spill and poured water to wash the crystals away. This triggered a chemical reaction that caused the release of toxic fumes. The chemical cloud was carried by winds into a local school where students inhaled the gas and developed burning sensations in the eyes, breathlessness, pain in the abdomen, and nausea.

The school principal alerted local authorities at 7:43 AM and evacuated all the students. The NDRF, Police, Fire, and medical services responded and evacuated the affected children to nearby hospitals. A total of 578 symptomatic girl students and 37 teachers were shifted to local hospitals and treated. Scrutiny of the Material Safety Data Sheet (MSDS) identified that the HAZCHEM was 2-chloro-5-(chloromethyl) pyridine (60%) ($C_6H_5Cl_2N$, commonly known as CCMP), an organic corrosive, an acidic compound, and a pesticide intermediate.

The key aspect in such a massive accident was on-time and on-site triage. A total of 578 symptomatic girl students and 37 teachers were shifted to local hospitals. About 310 were sent to the Hakim Abdul Hamid Zamia (Majeediya) Centenary, 66 to the Apollo Hospital, 171 to Okhla ESI, 65 to the Batra Hospital, and 3 to the AIIMS Trauma Hospital where they were given first aid and discharged after 6–7 hours of observation. Of those affected, 378 had burning sensation of the eyes, 164 had spasmodic cough and breathing difficulty, 51 had abdominal cramps and nausea/vomiting, and 22 developed a mild skin rash. The symptoms were mild and responded to symptomatic treatment. No specific antidotes were necessary, and all the school children were discharged in the same evening. This event reemphasized the focused capacity building within the communities and health systems to deal mass casualties effectively.

INNOVATION AND BEST PRACTICES

The MCM is an innovation from the war-room science to civilian science. It is being developed as a structured tool globally to recognize the effort of preparedness and thus provide the right thrust or mix of all the elements of authority/science/response mechanisms and equipment and to save maximum lives, with a minimum number of resources in minimum time. This has emerged as a management tool for emergency medicine practice. Most recently, post-Sendai framework, the mass casualty and public health events are addressed under a combined Health Emergencies and Disaster Risk Management Framework and Public Health Emergency Preparedness and Planning initiative.

It is important to look at how the concepts of first responders, triage, prehospital care, and MCM have linked together in the hospital disaster management planning, particularly look at the surge capacity in times of need and activate the incident response system (IRS) to prevent anarchy. This customized approach to trauma and injury whether in the case of bomb blast, CBRN (chemical, biological, radiology, and nuclear) or a simple chaos caused by stampede all are MCIs

but have different approaches to deal with in case of school bombings; similarly, there is a very specific response to be tailored. Therefore, in the dearth of basic MCM training, we find it difficult to work in sync with emergency room physicians; this absence of skills leads to increased casualties. There are very few examples where the amalgamation of "lessons learned" have been brought into future use.

The counter-strategy to MCIs will be to develop MCM tools like trauma systems based on data-intensive models integrated with a decision support system, to make sure that victims of mass casualty get on-site care, and also replicated at each level of the healthcare system, i.e., from a smaller to a larger setup and even during transport. The most recent initiatives such as the World Health Emergency programs and WHO Emergency Medical Teams (EMT) should be widely endorsed and training to different cadres should be provided. The EMTs are an important part of the global health workforce and have a specific role. Any doctor, nurse, or paramedic team coming from another country to practice healthcare in an emergency needs to come as a member of a team. This team has quality, training, and equipment/supplies so it can respond with success rather than impose a burden on the national system. The EMTs strive for self-sufficiency, a quality of care that is appropriate for the context, with credentials that meet the minimum acceptable standard of the WHO.

BRIDGING THE GAP

In our country, till date spiritual festivals/gatherings were treated as "confusion" and nonfocused or rather random steps were being taken to provide health security, but lately these events, whether road-shows by Kavadiyas, which is visible on state/national highways in north-India, or the *Kumbh Melas* organized every 3 years, have been treated in a cautious manner with government agencies working along with global security agencies/disaster management planning agencies to draw up plans to respond to any mishaps. New innovative approaches such as two-seater fire extinguisher bikes were introduced for easier access.

The mantra/process of *"triage, treat, and transfer"* is being followed for MCM, but in order to sustain any process we need to have a framework. The framework on which the MCM rests is the IRS certified by the National Institute of Disaster Management (NIDM) in India. This framework outlines the role and responsibility of each of the components in the response chain right from administration, community, healthcare professionals to organizers of the event.

INCIDENT RESPONSE SYSTEM

The IRS (**Flowchart 1**) is an effective mechanism for reducing adhoc measures in *response*. It envisages a composite team with various sections to attend to all the possible *response* requirements. The IRS designates officers to perform various duties and get them trained in their respective roles. No matter what forms government and public administration take, the National Emergency Management Systems should include:

- Identification of lines of authority, from the national to the local level
- Financial arrangements for funding emergency work
- Arrangements to ensure that government and community activities are maintained (e.g., creation of parallel or "hardened" communication systems to take over if normal voice or data transfer systems are affected)
- National stockpiling of appropriate resources (including provincial or state and local prepositioning of stockpiles)
- Database of national experts for advice on specific problems
- Protocols and formal arrangements for coordinated efforts with other countries or between provincial/state governments within the country.

NATIONAL EMERGENCY OPERATIONAL AND PREPAREDNESS STRUCTURE

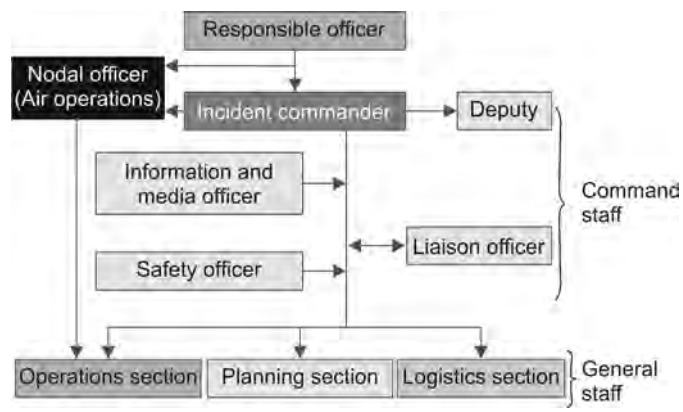
The MCM concept has travelled a long way, from being an ad hoc understanding to an integral part of any medium to large event. The three core issues in terms of managing any mass gathering would be (1) surveillance, (2) response, and (3) the system's ability to rapidly detect and implement appropriate and commensurate measures to contain/minimize the impact on the health system (**Flowchart 2**).

The system is helpful in maintaining the state of alertness for prolonged periods of time throughout the mass gathering. The local medical services and hospital system are able to manage large number of patients in case of emergency. Ultimately, food and water safety, i.e., the ability of the local infrastructure to ensure safe preparation of food and its delivery including safe water to attendees of mass gatherings, is also a key aspect that needs to be looked at from a preparedness and public health perspective to prevent any adverse events of mass poisoning.

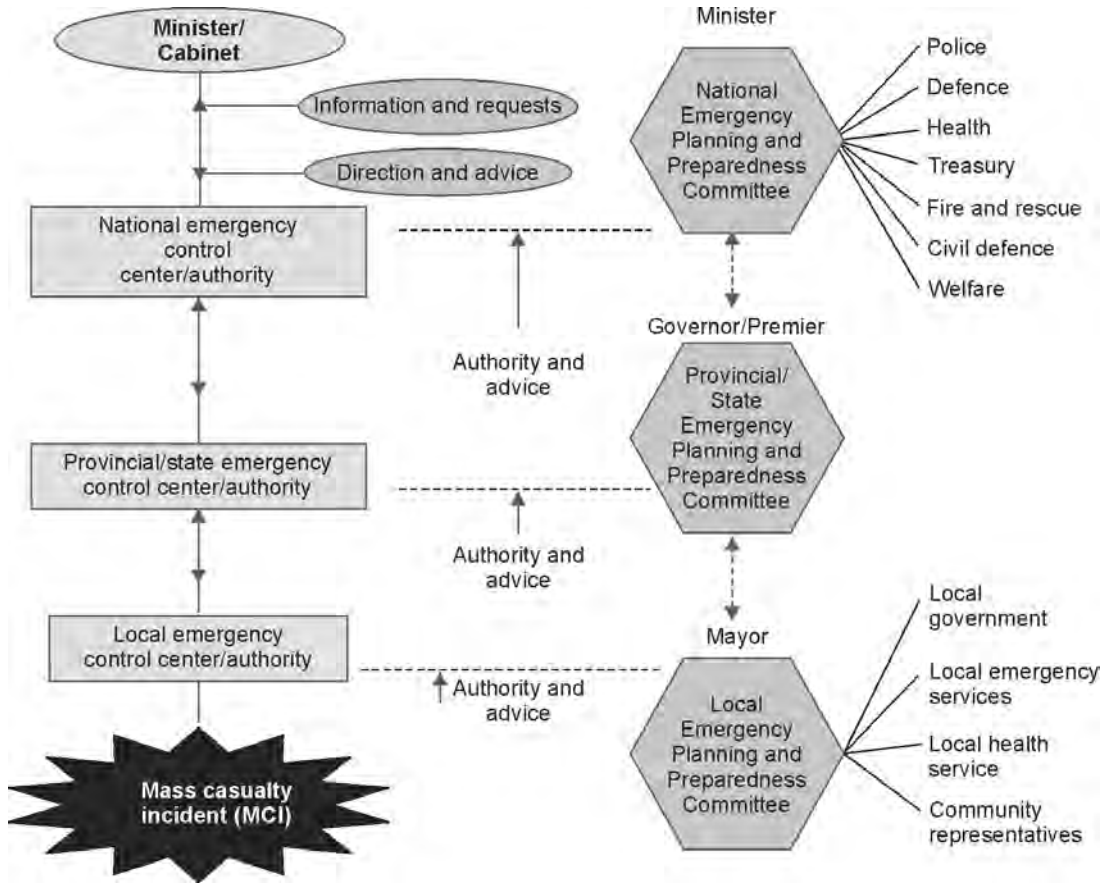
Bridging the gap between the healthcare system and the hospital and from policy to patients'/mass gathering perspective is key for safer future. Till date, random preparedness was being undertaken globally on mass gatherings, but formal steps have been initiated by public institutions such as WHO and other global bodies to come up with structured response mechanisms to develop a culture of focused response.

WAY FORWARD

The way forward on MCM would necessarily include sustainability element in the system. Therefore, specific MCM



FLOWCHART 1: Incident response system.



FLOWCHART 2: National emergency operational and preparedness structure.

response plans for each of the genres should be created/planned. Further, creation is not the "key to success"; rather practicing those plans in the form of drills at regular intervals is the approved way forward, to bring in the concept in the form of "a natural response" among the community.

Sensitive response plans such as radiation emergencies should be regularly rehearsed and documented and well exhibited in the designated area. Another sensitive area for preparation is terrorism; globally, this form of human casualty has presently become a part of our daily lives in many countries. Therefore, a district-/state- and national-level plan should be created and disseminated among the teams so that during the activation phase, everyone is clear about his/her roles and responsibilities. In the public services of our country such as airlines, railways, roadways, and general traffic, the partnership of trauma with MCM is key to success, especially in metros. We need to localize the global perspectives and carry forward the management implications of this partnership, so that resources are directed where they are required to essentially save lives in times of chaos.

SUMMARY

When an unexpectedly large number of injured/ill persons needs emergency medical care, at the same time it can be termed as "mass casualty situation". The aim in a mass casualty situation is to "Do the best for the most, not everything for everyone" and "doing the best for the most". Main goal of mass casualty management is to apply triage principles in multiple patient scenarios.

In other term exercise of saving "maximum number of people in minimum time, with minimum resources", is "MCM". The MCM comes in to play "when a MCI has occurred during any mass gathering". The MCM is transformed from the war-room science to civilian science. Over the time MCM developed as a structured concepts internationally to recognize the effort of preparedness, and thus provide the right guidelines of all the elements of authority/science/response mechanisms and equipment to save maximum lives with minimum number of resources in minimum time. Mass casualty management has emerged as a management tool for emergency medicine practice.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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Preparedness for Chemical, Biological, Radiological, and Nuclear/Energetics Disasters

29
CHAPTER

Shaza Karrar, Mohammad Anzal Rehman, Saleh Fares

INTRODUCTION

As far back as ancient times, the capacity for offensive agents and vectors to precipitate massive, population-wide losses to human life has been evident. One of the earliest accounts of an infectious epidemic describes the plague of Athens in 430 BC, where an unknown disease characterized by fever, pustular rash, and diarrhea resulted in the death of up to 100,000 people under siege in the city of Athens. Over the years, a multitude of mediums capable of producing mass casualty have been discovered, classified as chemical, biological, radiological, nuclear/energetics, and commonly grouped under the acronym CBRN/CBRNE. CBRN emergencies can present as natural phenomena or accidents that arise secondary to nonadherence to contaminant guidelines or negligence, such as the coolant system failure that resulted in a reactor explosion at the Chernobyl Nuclear Power Plant in 1986. However, during the past 100 years, the world has seen an unprecedented increase in chemical, biological, and nuclear agents being implicated in acts of terrorism, leading to the realization of their potential as weapons of mass destruction (WMD). There is no doubt that CBRN threats are a clear and present danger in modern civilization. In the year 2020, the global pandemic caused by the novel coronavirus, SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2), also known as "Coronavirus disease 19 (COVID-19)," showcased the unprecedented breadth and devastation that can be associated with these events. Therefore, all healthcare providers must equip themselves with the tools needed to recognize, prevent, and manage these low-probability, high-impact occurrences and their catastrophic consequences.

CBRN PREPAREDNESS AMONG EMERGENCY PROVIDERS

Healthcare providers in the prehospital and emergency department settings are uniquely integral to CBRN incidents, representing the frontlines of defense in disaster management. However, several studies evaluating preparedness among emergency workers around the world found that a large number of providers were not confident in their ability to adequately manage CBRN incidents, with various training simulations highlighting significant gaps in awareness and proficiency in these scenarios.

One proposed explanation for the prevalent gaps in knowledge and preparedness is the general lack of prior staff experience with these events as well as a relatively low integration of formalized training in CBRN preparedness in most healthcare institutions. An online survey assessing training among 1,028 Emergency Medical Services staff in Canada revealed that only 63% of providers received some form of training to work in a contaminated environment.

Fortunately, over the past decade, several training tools, exercises, and guidelines have been proposed and successfully implemented by hospitals to improve staff awareness and optimize institutional response to CBRN events. Furthermore, international societies such as the World Association for Disaster and Emergency Medicine (WADEM) have made significant progress in promoting high-impact disaster awareness and preparedness at a global scale.

All emergency healthcare providers should strive to update individual and institutional awareness of CBRN incidents. The integration and practice of regular, standardized training exercises in the acute care setting are useful in optimizing the local emergency response against potential high-impact threats.

APPROACH TO A CBRNE INCIDENT

The potential threat of a CBRNE incident holds a frightening risk of infrastructure and environmental destruction, large-scale mortality and morbidity, and a devastating economic impact. A CBRNE incident occurring would have severe implications on a broad national level. These include, but are not limited to, loss of life, a threat to public health safety, political and psychosocial repercussions, and burdens to the healthcare systems. Additionally, these agents may cause extensive contamination prolonging their associated harm. Hence, it

is necessary to establish a strategic response and develop effective countermeasures and protocols to help mitigate risk, minimize the potential loss of life, and collaboratively manage a CBRNE incident if it ever materializes.

CBRNE weapons and warfare have urged international efforts to enforce laws and treaties to monitor and regulate the existing CBRNE risks. Covering international treaties would go beyond this chapter's scope; therefore, the aim of this chapter will be on the approach and preparedness for a CBRNE incident and later on converge to each weapon preparedness, risk stratification, and management depending on its nature. The primary purpose of a CBRNE disaster preparedness approach and possible associated mass casualty training is to take all the necessary measures of mitigating the potential risk of an incident in order to prevent it and, in case it occurs, to have a strategic, controlled, and effective response to minimize its implications.

Before we go further into CBRNE preparedness, we must understand the value of disaster risk stratification and management as an initial approach to better identify opportunities for hazard reduction and mitigating losses. Disaster Risk Management, henceforth, should be a structured and systematic approach to enable any organization or healthcare system to consolidate efforts, allocate resources, and aim for minimal losses. Disaster management at a larger scale aims to diminish potential losses, ensure a rapid medical response to victims, achieve effective recovery, decontaminate, and minimize further harm from the incident. The disaster management cycle demonstrates the ongoing process to reduce the impact of a disaster incident, react during and immediately following a disaster, and take steps to recover after a disaster has occurred (**Fig. 1**). All four phases of the disaster management cycle do not always occur in this particular order; often these phases overlap in the cycle and the length of each can differ significantly depending on the severity of the incident. Each CBRN threat differs substantially concerning its weapon nature and potential risk and associated damage. Hence, the disaster management approach would address each weapon's nature to encounter its specific potential risk and response. A brief overview of each phase definition is given in the following text, and later, we will review each specific weapon disaster management approach.

FIG. 1: Disaster management cycle.

MITIGATION

Mitigation represents measures taken to prevent and reduce the impact of the disaster. For example, it may include building codes and zoning, vulnerability analysis, public education, and prevention.

PREPAREDNESS

Preparedness constitutes response planning, training, and educational activities. For example, formulating preparedness plans, disaster response drills, mock codes, and developing warning systems set up before a disaster could occur. Preparedness training theoretically and practically, as well as research, is an integral component of combating the evolving threat of a disaster and CBRN incidents.

The abruptness of such incidents may prohibit response activation, which poses a serious challenge. Therefore, training through mock drills and exercises needs to be conducted to hone the responder's skills and reflexes to decontaminate and remove victims from the agent's source promptly.

Part of preparedness would consist of efforts taken to recognize a potential event via identifying indicators and triggers. Indicators are measures or predictors of changes in demand and resource availability, while triggers are decision points to respond to these indicators that require adaptations in terms of contingencies, crises, and return toward the conventional system.

Mitigation and preparedness phases are usually developed and enhanced in anticipation of a disaster incident. Developmental efforts would play a key role in involving a contribution from the community, healthcare systems, humanitarian organizations, prehospital, and police or military authorities, encompassing all relevant parties to be involved in the immediate response and long-term recovery phase.

Appropriate preparedness in these two phases significantly enhances response and recovery phases in the cycle, better warnings, and reduced vulnerability or prevention of disasters during the next cycle. It may include reshaping public policies, plans, and modifications in causes of such incidents or mitigating potential live risks.

RESPONSE

CBRN Scene Management

Response encompasses the efforts utilized to minimize the hazards created by a disaster. Effective scene isolation mitigates consequences by restricting access to and from the incident scene and controls the movement of contaminated victims, providing a safe parameter for responders to manage and contain the incident, and prevent any further release of the contaminant substance.

In the view of an incident, an emergency response or incident response team would be the first to respond to the incident scene. The first person on-scene would typically serve as an incident commander until relieved by a senior. He/she would take appropriate measures of equipping personal protective measures, report to supervisory personnel

on the nature of the incident and potential threats, initiate decontamination measures, and set up evacuation procedures and triage of victims. A defined Incident Commander would activate emergency response teams and mobilize all response efforts and local recourses to the scene, further restricting access to the surrounding areas of risk and evaluating the severity and impact of an incident and its required safety measures.

The first emergency response team at the scene usually approaches the scene with caution parallel to wind directions, assesses the scenes, establishes incident command, recognizes indicators of the nature of CBRN weapon used and hazardous materials of harm. Furthermore, they would estimate the number of casualties, carry out primary triage and decontamination procedures, and approximate needed resource requirement and allocations.

In a mass casualty due to a CBRN incident, before detecting and analyzing the weapon/agent utilized, incident zoning, triage, decontamination, and treatment of victims take priority. Several triage systems can be applied to CBRN casualties, none of which are standardized globally. It is essential to utilize a triage and decontamination system that is simple, direct, easy to follow, and available to medical recourses. More on triage systems is delved into in the mass casualty section of this chapter.

CBRN incidents can occur due to industrial disasters, occupational exposure, natural catastrophe, warfare, or acts of terrorism. These incidents present different challenges for all responders, necessitating the rapid decontamination and treatment of a significant number of casualties while taking critical measures to ensure the well-being of the personnel managing the incident.

The detection following a CBRN incident is part of a triad of actions consisting of detection, identification, and monitoring. Specific devices designed to detect gas, nuclear agents, and radiation are available for detection utilization. The ability of devices to detect all CBRN agents does not exist. Therefore, it is essential to identify incident variables that should be detected and organized according to the devices and personal protective equipment (PPE) required.

Personal Protective Equipment

All scene responders must take appropriate measures to protect themselves before entering the contaminated area. The use of PPE to protect the airway, skin, and eyes is an indispensable component of emergency response. Limitations to the use of PPE are restriction of physical activity, dehydration, heat-related illness, and psychological effect. These limitations can be avoided by training emergency personnel to use PPE appropriately (**Fig. 2**).

Level A PPE should be used when the highest level of respiratory, skin, eye, and mucous membranes protection is needed. A typical Level A conveys a chemical-resistant fully encapsulated suit, overgloves, and boots integrated into the suit. Respiratory protection is a self-contained breathing apparatus. Level A protection is required for entry into an unknown hazardous environment.

Level B PPE is used when the highest level of respiratory protection is needed, but lesser protection to skin and eyes is needed. It represents a chemical-resistant hooded suit, double gloves, overboots, and a self-contained breathing apparatus and may be used for decontamination procedures for an unknown substance and for entry into hot zones where the agent is not caustic.

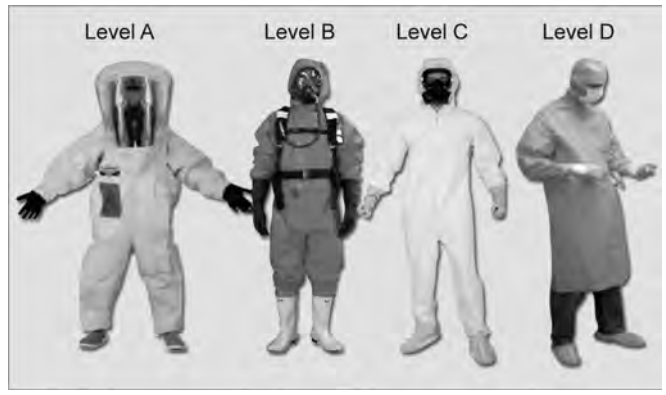

FIG. 2: Personal protective equipment levels. ***(For color version, see plate 1)***

Level C PPE is utilized when the type of airborne substance is known and identified, similar to Level B, but uses an air-purifying respirator instead of a self-contained breathing apparatus. Level C PPE can be used only after the hazardous substance has been identified and upon verification of adequate oxygen in the environment.

Level D PPE is used for droplet precautions and consists of a gown, head cover, mask, gloves, and shoe covers. A more enhanced mask with a higher filtration rate can be utilized in the case of a known airborne substance.

CBRN SCENE MANAGEMENT ZONES

When it comes to a CBRN incident site zoning, a clean treatment zone needs to be set up, at least 300 yards upwind of the contaminated scene; this is referred to as the cold zone. The contaminated area is referred to as the hot zone. What separates the cold and hot zones is a warm zone, utilized for decontamination. A warm zone is usually set up several 100 yards away from the hot zone and 50 yards from the cold zone. All responders must leave the hot zone via specially designated pathways into the warm zone where they will be decontaminated.

No medical care is provided within the warm zone awaiting the decontamination process. Therefore, before leaving the emergency care area, the patient must be stabilized to the extent that his/her condition will not deteriorate during the decontamination process. After receiving emergency care, a casualty must go through the decontamination station before receiving more definitive care in a clean environment. Decontamination takes 10–20 minutes.

Decontamination Considerations

Each CBRN incident type necessitates a distinctive triage system and decontamination principles that naturally go along with each other. These principles consider command control, planning resources, task forces, decontamination operational sites, and allocations. Decontamination decreases the risk of incident-related contaminants to victims and health providers and personnel. Generally speaking, delaying the stabilization of critical victims for decontamination should not put a victim at additional risk. Qualified triage personnel would determine the priority of stabilization efforts and decontamination. Hence, these two processes are designed along and parallel to

each other to reduce the risk of contaminants while ensuring safety and safe treatment or stabilization of causalities. General principles of decontamination would include promptness of initiation and priority and necessity when it comes to victims or location.

Chain of Custody and Evidence Documentation

Maintaining a documented chain of custody is of high importance to stratify future risk and perpetrators. It would include process and procedures and digital fingerprints. In principle, the chain of custody does not interfere with the response efforts, triage, treatment, or decontamination procedures.

RECOVERY

Recovery constitutes the restoration efforts and allocated resources utilized in returning the community to normal. Recovery may include temporary housing of affected victims and involved personnel, expanding medical care capacity and services, rehabilitation, reconstruction, and restarting regular services.

CHEMICAL AGENTS

Chemical agents are described as toxic compounds that were designed to cause injury or death. Their appeal as easily synthesized substances that, once disseminated, carry with them the potential to generate large-scale casualties made them a popular agent of warfare in the First World War, being responsible for over 1.3 million casualties and approximately 90,000 deaths over a 4-year period.

In the years that followed, the devastating loss of life attributable to chemical warfare, as well as rising frequencies in their use for acts of terrorism, culminated in the enforcement of the Chemical Weapons Convention (CWC) in 1997 which effectively prohibited the use, development, acquisition, stockpiling, or transport of chemical weapons and/or their precursors. However, despite this, the threat of attacks using these agents looms ever larger, and emergency providers must be prepared to combat their potentially hazardous effects.

Chemical warfare agents usually exist in solid or liquid form. However, these substances are oftentimes very volatile and allow for extensive dispersal through aerosolization and conversion to gaseous forms. Key features responsible for determining the potential harm from these agents include their inherent toxic capacity, route of entry in humans, mechanism of action, stability, and miscibility (ability to mix with solvents or thickeners). The various types of chemical agents can be classified based on their physiological effects on humans. **Table 1** outlines some of the more prominent chemical agents identified over the years with their relevant mechanisms of toxicity, route of exposure, and clinical characteristics.

Chemicals are usually introduced into the body by inhalation, absorption, ingestion, or inoculation, rapidly acting or with delayed effects. The principles of management after exposure to chemical agents center around the removal of the patient from further exposure to the toxin; attention to airway, breathing and circulation (ABCs); prior to evacuation; and during decontamination. Rapid identification of the offending agent based on history and/or examination can allow for the initiation of specific antidotes for reversal of symptoms as outlined above. Therapeutic measures are otherwise largely supportive, depending on the organ system affected, and include antibiotic coverage to prevent secondary bacterial infection where appropriate.

Once again, it should be emphasized that triage be performed at every echelon of medical care, preferably several times, because the health status of some chemical casualties categorized as "delayed" may change within a short time and develop unanticipated life-threatening conditions such as severe bleeding.

BIOLOGIC AGENTS

Microorganisms are abundant in nature worldwide, and the vast majority of species present no risk of harm to humans. However, various pathogenic strains do exist and have been known to cause illness or even death. Biological agents represent a subgroup of these disease-causing microorganisms unique for properties such as enhanced toxicity, environmental stability, transmissibility, and host susceptibility to the exposure that enables their implication in population-level morbidity and mortality.

The characteristics that allow biological agents to induce mass casualty may be a consequence of their natural propensity for disease and transmission. An example of this was the emergence of the novel strain of *SARS-CoV-2* in Wuhan, China, in 2020. An alarmingly high rate of transmission and uncertainties surrounding effective management strategies contributed to the rapid evolution of COVID-19 from a localized outbreak to a worldwide pandemic.

Unfortunately, biological agents can also be intentionally manipulated to target specific individuals and populations, with emerging techniques, to synthesize easily and artificially augment agents to permit improved infectivity and survivability raising concerns for their use as agents of bioterrorism and warfare in the future.

Biological agents can be grouped into four main categories, namely (1) bacteria, (2) viruses, (3) fungi, and (4) toxins, as outlined in **Table 2**. Several attempts have been made to classify these agents based on the burden of their disease. The US Centers for Disease Control and Prevention (CDC) categorizes biological agents as A, B, or C based on their relative risk to national security as well as ease of production and/or dissemination. Other guidelines, such as the European Directive 2000/54/CE, classify pathogens from groups 1 to 4 in increasing order of risk or hazard to humans, with decreasing order of availability of effective preventive or management strategies. Although most national guidelines may prove useful when developing local defense strategies against biological agents, several inconsistencies among different risk classifications reveal opportunities for improved collaboration and global consensus on standardized methods of evaluating biological agents.

As evidenced in **Table 2**, many biological agents, while reserving their high transmission rates, may not produce symptoms until several days, making it especially difficult to respond to incidents of disease spread. Therefore, some of the key factors contributing to an effective defense strategy against biological events center around establishing techniques to detect and diagnose the presence of disease rapidly.

TABLE 1: Classification and characteristics of chemical agents.

Agent class	*Examples of agents*	*Mechanism of action*	*Route of exposure*	*Clinical characteristics*
Nerve agents	• *G-agents*—Sarin, cyclosarin, tabun, and soman • *V-agents*—VE, VG, VM, VR, and VX	Inhibition of acetylcholinesterase leads to the accumulation of acetylcholine in the body	Inhalation or skin	• *Symptoms*: Miosis, hypersalivation, runny nose, diaphoresis, bronchospasm, muscle excitation, arrhythmias, seizures, respiratory paralysis • *Management*: Supportive ± seizure control. Atropine + pralidoxime
Vesicants (blister agents)	• *Mustards*—mustard gas, nitrogen mustard • *Arsenicals*—Lewisite *Phosgene oxime*	• *Mustards*—DNA alkylation leads to cell death • *Arsenicals*—enzyme inhibition causes NADPH and glutathione oxidation, resulting in disruption of metabolism and cell death • *Phosgene oxime*—unknown	Inhalation or skin	• *Onset*: Hallmark of mustards is postexposure latency (symptom-free period) for several hours. Arsenical exposure—immediate pain • *Symptoms*: Corneal irritation/erosion, skin erythema/blistering, rhinorrhea, hoarseness of voice, cough. Phosgene oxime causes wheals followed by eschars (no blisters) • *Management*: Mainly supportive. No antidote for mustards or phosgene • *Antidote for arsenicals (Lewisite)*: Dimercaprol/British Anti-Lewisite (BAL)
Blood agents (cyanogenic agents)	Hydrogen cyanide, cyanogen chloride	Inhibition of cytochrome oxidase in cells, preventing oxygen utilization	Skin, inhalation, or ingestion	• *Symptoms*: Confusion, nausea, weakness, cyanosis, CNS excitation followed rapidly by depression, convulsions, coma, and cardiorespiratory arrest • *Antidotes for cyanide toxicity*: Hydroxocobalamin, sodium nitrite followed by sodium thiosulfate
Choking agents (pulmonary agents)	Phosgene, diphosgene, chloropicrin, chlorine	• Chlorine—acidification of gas causes irritation/necrosis of respiratory tract mucosa/lung tissue→pulmonary edema/ARDS • Phosgene/diphosgene—disruption of alveolar surface tension→pulmonary edema	Inhalation	• *Symptoms*: Nose and throat irritation, dyspnea, wheezing, cough with increased secretions, hypoxia on room air is a sign of ARDS-such as lung injury • *Management*: Mainly supportive with high-flow oxygen/mechanical ventilation as needed. Possible role of corticosteroids, bronchodilators and/or inhaled sodium bicarbonate
Incapacitating agents (tear gases)	Chloroacetophenone (CN), O-chlorobenzylidene malononitrile (CS), oleoresin of capsicum (OC), and dibenz [b, f]1: 4-oxazepine (CR)	Direct toxicity, possibly through NADH-dependent receptors of skin and mucosa	Inhalation or skin	• *Symptoms*: Lachrymators—conjunctivitis, tearing of the eye, blepharospasm • *Sternutators*: Sneezing, upper respiratory tract irritation • *Vomiting agents*: Nausea/vomiting • *Management*: Immediate decontamination + supportive treatment

(ARDS: acute respiratory distress syndrome; CNS: central nervous system; DNA: deoxyribonucleic acid; NADH: nicotinamide adenine dinucleotide hydrogenase; NADPH: nicotinamide adenine dinucleotide phosphate hydrogen)

Various tactics are used to decrease the spread of infection from potential secondary aerosolization. Three basic methods of decontamination are (1) physical removal, (2) chemical deactivation, and (3) biological deactivation of the agent. Biological deactivation has not been developed to the point of being practical.

Effective management policies will undoubtedly address triage, workflow, medical supplies, equipment delivery, and manpower. Public health education and safety programs should be incorporated to raise awareness of the extent of disease and risk of transmission. Disease-prevention techniques should focus not only on reducing exposure and

TABLE 2: List of major biological agents with clinical characteristics of their associated diseases.

Agent/Disease	*Route of exposure*	*Clinical characteristics*
Bacteria		
Bacillus anthracis/ Anthrax	Inhalation, direct contact, and ingestion	• Symptoms begin in 2–5 days • *Cutaneous*: Vesicular ring→ulceration→black eschar, lymphadenitis, edema • *Inhalation*: Initial flu-like illness, followed by fever, dyspnea, respiratory distress, cyanosis • *Gastrointestinal*: Fever, nausea/vomiting, hematemesis, bloody diarrhea, dysphagia • All forms can also lead to meningitis and death • *Antibiotics*: Ciprofloxacin, doxycycline, amoxicillin • *Prophylaxis*: Ciprofloxacin licensed vaccine available
Francisella tularensis/ Tularemia	Bite from arthropod vector, direct contact, ingestion, and inhalation	• Symptoms begin in 3–6 days • Fever, chills, headache, malaise, ulcer at the site of infection can lead to lymphatic infiltration • *Antibiotics*: Aminoglycosides (streptomycin, gentamicin) • *Prophylaxis*: No fully licensed vaccine available
Yersinia pestis/Plague	Bite from arthropod vector, inhalation, and ingestion	• Symptoms begin in 2–6 days • Fever, chills, headache, pain at the bite site, lymphadenopathy, cough, bloody sputum • *Antibiotics*: Streptomycin, gentamicin, doxycycline, ciprofloxacin, chloramphenicol • *Prophylaxis*: Tetracycline, streptomycin, chloramphenicol. No effective vaccine available
Burkholderia mallei/ Glanders	Direct contact and inhalation	• Symptoms usually begin in 1–14 days • Fever, headache, lymphadenopathy, chest pain, mucosal inflammation and/or necrosis, cutaneous ulcers, dyspnea, cough, mucopurulent sputum • *Antibiotics*: Limited efficacy. No FDA approved treatment regimen available • *Prophylaxis*: No effective vaccine available
Brucella/Brucellosis	Inhalation, direct contact, and ingestion	• Symptoms begin in a few weeks up to several months • Fever, arthralgia, headache, malaise, night sweats, and cough • *Antibiotics*: Rifampicin, doxycycline, streptomycin • *Prophylaxis*: No vaccine available
Viruses		
Ebola/Marburg virus, arenaviruses, flaviviruses, tick-borne viruses/hemorrhagic fever	Direct contact, various vectors, inhalation	• Symptoms begin in 2–19 days • Fever, myalgias, fatigue, headache, nausea, vomiting, encephalopathy, thrombocytopenia, bleeding, DIC, shock • *Treatment*: Mainly supportive. Ribavirin useful in some cases • *Prophylaxis*: General lack of available effective vaccines (except in cases of tick-borne virus, yellow fever, and/or chemoprophylaxis
Variola major virus/ smallpox	Direct contact	• Symptoms usually begin after 10–14 days • Fever, rash (macules→papules→vesicles→pustules→scab/scarring), sepsis • *Treatment*: supportive • *Prophylaxis*: Vaccine available
Venezuelan equine encephalitis virus (VEEV)/Encephalitis	Mosquito vector, inhalation	• Symptoms begin in 1–5 days • Fever, vomiting, diarrhea, encephalitis, convulsions, coma • *Treatment*: Supportive • *Prophylaxis*: No FDA-approved vaccine available
Nipah virus/ Encephalomyelitis	Direct contact, animal reservoir	• Symptoms begin in 4–21 days • Fever, headache, myalgia, cough, encephalitis, coma • *Treatment*: Mainly supportive. Ribavirin useful in some cases • *Prophylaxis*: No vaccine or chemoprophylaxis available

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Continued

Agent/Disease	*Route of exposure*	*Clinical characteristics*
Toxins		
Clostridial toxins	Ingestion	• *Clostridium botulinum*: Blurred vision, paralysis, dry mouth, mydriasis. Treatment: Antitoxin • *Clostridium perfringens*: Abdominal pain, diarrhea. Treatment: Supportive
Staphylococcus enterotoxin B (SEB)	Ingestion	• Abdominal pain, nausea, vomiting, diarrhea • *Treatment*: Mainly supportive
Abrin/Ricin	Ingestion, inhalation	• *Abrin*: Abdominal pain, vomiting, diarrhea, pulmonary edema, hemolysis • *Ricin*: Vomiting, diarrhea, gastrointestinal bleeding, hypotension, pulmonary edema • *Treatment*: Supportive, no effective treatment available
Fungi		
Coccidioidomycosis/ Valley fever	Inhalation of spores	• Symptoms begin in 7–21 days • Fever, night sweats, fatigue, cough • Immunocompromised individuals at greater risk of infection • *Treatment options*: Fluconazole, itraconazole, amphotericin B • No vaccine available

(FDA: Food and Drug Administration; DIC: disseminated intravascular coagulation)

transmission but also on exploring options for vaccines and prophylactic treatment.

RADIATION/ENERGETICS

Events associated with the exposure of humans and the environment to dangerous levels of radiation are rare. However, their destructive potential for harm to exposed humans and the environment, coupled with their long-term implications in exposed populations and infrastructures, make them genuinely formidable threats. In 1998, the International Atomic Energy Agency (IAEA) and World Health Organization (WHO) recognized important concepts in managing radiation accidents and published guidelines in their Safety Reports Series.

Radioactive material exposure health risks to responders depend on several factors, such as the amount of radiation received, known as the dose, and the length of time over which the dose is received.

To best respond to radiation threats, it is essential to assess the severity of the inciting event as well as the risks associated with exposure. The International Nuclear and Radiological Event Scale (INES), outlined in **Figure 3**, is a tool used to categorize radiation events into one of seven levels based on radiation dose, radiological barriers, and controls, consequences to affected people and the environment, including *potential* repercussions covered under "degradation of defense in depth."

Individuals may be exposed to a radiological dispersion device (RDD), also known as a "dirty bomb," which would produce injuries from heat, force of the explosion, debris, and radiological dust. Radiation that was dispersed with or without an associated explosive component results in either direct (blast injury) or indirect trauma (projectiles), flash, and/or thermal burns, with subsequent radiation sickness. Upon confirming the initial fatalities after an explosion, the future radiation can be determined. This will be dependent upon the grade of radioactive material and the amount that has been released.

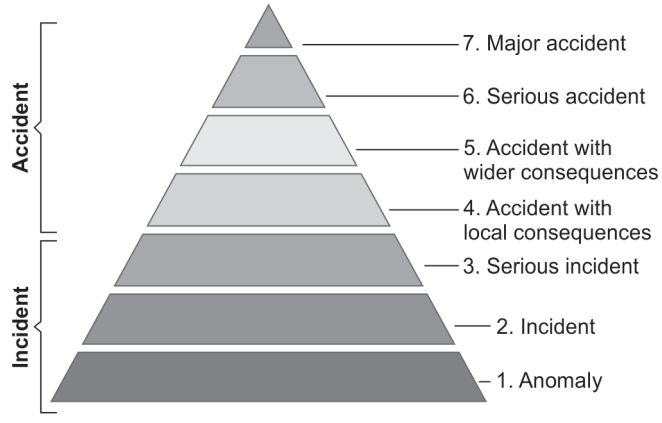


FIG. 3: International Nuclear and Radiological Event Scale (INES).

First responders to the scene are prompted to utilize time, distance, and shielding (TDS) to reduce or eliminate radiation exposure. A further threat to first scene responders to a dirty bomb incident is the possibility of a secondary explosive device planned against the first responders.

The initial triage of patients should attempt to ascertain the extent of exposure, associated injuries, and the degree of internal and external contamination. An RTR system consists of Radiation-specific TRiage, Treatment, and TRansport sites, designed to support medical care following a nuclear incident. Its goal is to characterize, organize, and efficiently deploy appropriate material and personnel assets as close as physically possible to various categories of victims while preserving the safety of responders. After an incident is characterized and safe perimeters are established, RTR sites should be determined in real time, based on the extent of the destruction, environmental factors, residual radiation, available infrastructure, and transportation routes. Such RTR

sites are divided into three types depending on their physical/situational relationship to the incident: (1) RTR1 sites are near the epicenter with residual radiation and include victims with blast injuries and other major traumatic injuries, including radiation exposure; (2) RTR2 sites are situated in relationship to the plume with varying amounts of residual radiation present, with most victims being ambulatory; (3) RTR3 sites are collection and transport sites with minimal or no radiation present or exposure risk and a victim population with a potential variety of injuries or radiation exposures.

Symptoms of exposure are influenced by factors such as the type of radiation, total dose amount and rate, individual susceptibility, and surface area irradiated. Clinical signs may include nausea, vomiting, and erythema within the first 48 hours of exposure, a latent phase with no apparent symptoms, followed by the manifestation of disease days to weeks postexposure in the form of various hematopoietic, gastrointestinal, cutaneous, and neurovascular syndromes. Management involves decontamination measures such as removal of contaminated debris, washing of skin and nasal passage, wound debridement and irrigation, internal decontamination with chelating agents, antibiotic coverage as well as appropriate surveillance, testing, and supportive therapy as needed.

MASS CASUALTY TRAINING

Mass casualty incident (MCI) is defined as an incident that could potentially overwhelm, exceed, or threaten the local capacity of response available due to the severity of the incident and the number of casualties. In an MCI, multiple organizations are augmented by protocols and measures to maintain an effective emergency response.

Decontamination, triage, and rescue of casualties are considered the cornerstone of the initial assessment of a CBRN incident, followed by appropriate evacuation of the public at risk and warning systems, which further contribute to saving lives and mitigating exposure risks.

The management of casualties resulting from exposure to a CBRN incident requires appropriate triage assessment and categorization. Separating minor injuries significantly reduces the burden on the healthcare system and prioritizes life or limb-threatening casualties in need of rapid medical care. Furthermore, it rationally distributes these casualty burdens to an appropriate complexity level of care hospitals and healthcare facilities.

During a suspected radiation hazard, responders should be provided ionizing radiation dose estimating devices for use in medical triage and diagnosis of potentially exposed casualties. When it comes to biological incidents, the first indication of exposure may be immediate as in biological toxins or delayed, making it difficult for responders to evaluate possible exposure with victims who may present with delayed onset of symptoms. Some potential biological agents are transmissible among humans and may spread fast after the initial attack; this may become a vital triage planning consideration.

In addition to hot, warm, and cold zones mentioned previously in the chapter, in a CBRN MCI, the incident field triage site should be divided into zones that are conducted at three levels. These consist of (1) on-site triage, (2) medical triage, and (3) evacuation triage. A triage officer would be appointed to each level/zone.

Onsite Triage Hot Zone—Level 1

At this zone, the first responders carry out a rapid categorization of victims with potential life- or limb-threatening injuries needing immediate medical care. First responders can utilize the Simple Triage And rapid treatment (START) protocol for the primary triage during the initial response phase (**Flowchart 1**). Emergency care administered by START teams is restricted to positioning airways, controlling hemorrhage, and elevating the patient's feet. All casualties will be tagged according to the severity of their conditions and placed into one of the following four categories:

1. *Immediate—red tag color*: Victims with spontaneous breathing upon airway positioning, or respiratory rate over 30 per minute, or a capillary refill >2 seconds, or absent radial pulse, or cannot obey the command. These victims can be helped by immediate intervention and transport.
2. *Delayed—yellow tag color*: Victims who are not in immediate or minor category. These are generally nonambulatory; their transport can be delayed, as, despite possible life-threatening injuries, they are not expected to deteriorate significantly over several hours.
3. *Minor—green tag color*: Walking wounded who can assist in their own care. These victims are ambulatory with relatively minor injuries and are unlikely to deteriorate over several days.
4. *Expectant—black triage color*: No ventilation despite airway positioning. These victims have either expired or are unlikely to survive the severity of their injuries. Pain and palliative care should be provided to them.

It is also essential to move casualties triaged as black triage color, who are deceased or unsalvageable, to a site that is easily seen by the public or other casualties. The deceased has to be kept there until law enforcement authorities have acquired a chain of custody evidence, and the living casualties have been evacuated from the scene after decontamination. Deceased casualties require thorough decontamination before they are moved to the morgue or are deemed ready for release.

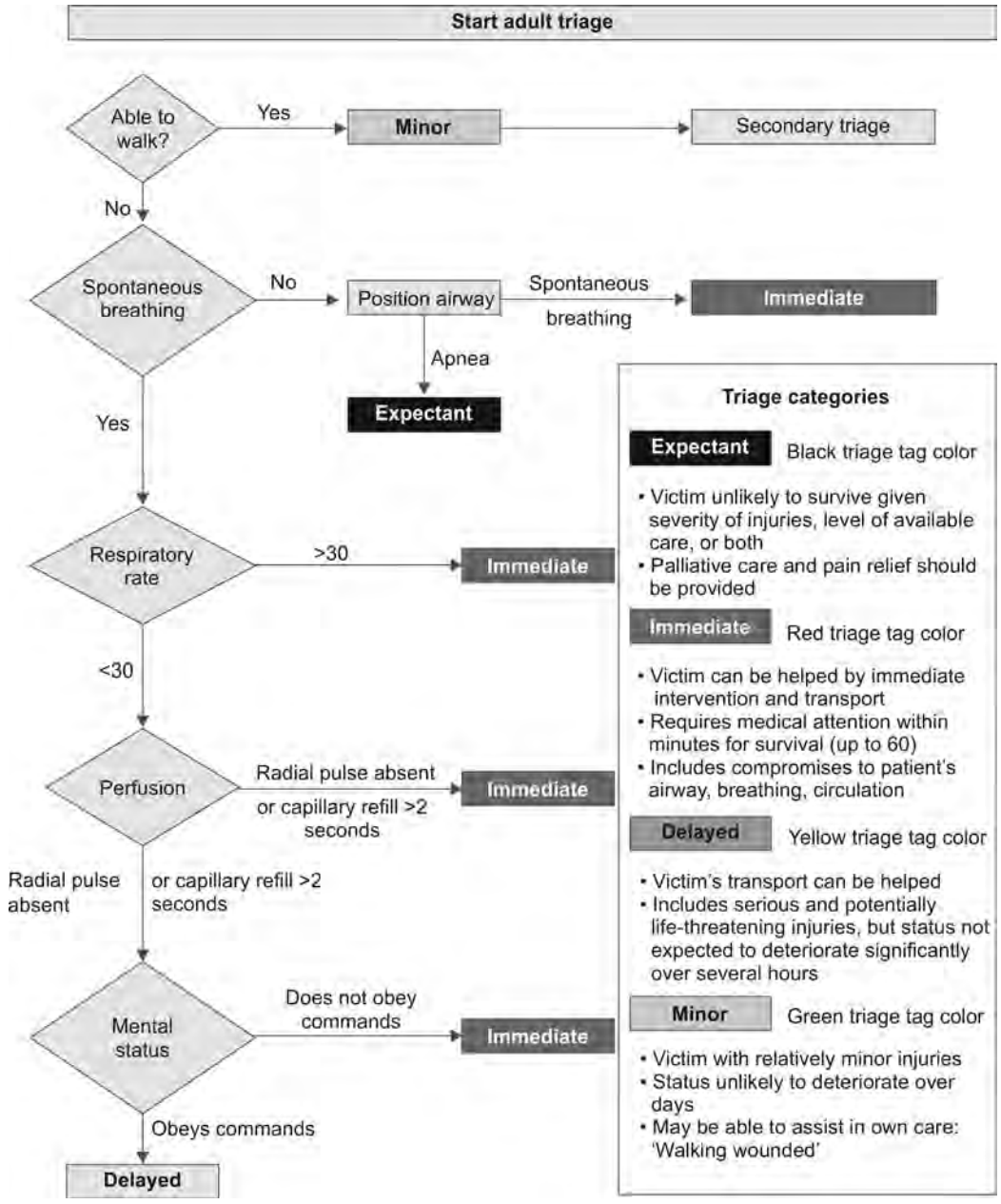
Several triage tools have been developed, including START, Jump START (pediatrics), care flight triage, SALT (Sort, Assess, Lifesaving Interventions, Treatment/Transport), MASS (Move, Assess, Sort, Send), and STM (Sacco Triage Method) models. Supportive evidence for the use of one triage algorithm over another is limited, and the development of effective triage protocols is a vital research priority. Currently, the presence of a standardized MCI triage system that is well validated, reliable, and uniformly accepted remains a significant gap.

Medical Triage Cold Zone—Level 2

This zone carries on a rapid categorization of victims by the most experienced medical personnel available to identify the medical care level needed. Responders assigned to the medical triage zone will perform a *secondary assessment* and complete any required information on the triage tag. Emergency personnel is not required to follow the START protocol during secondary and subsequent triage.

Evacuation Triage Zone—Level 3

This zone assigns priorities to disaster victims requiring urgent transfer to hospitals by air or land according to the severity of the injury and available resources.



(START: simple triage and rapid treatment)

FLOWCHART 1: START adult triage algorithm. ***(For color version, see plate 1)***

Evacuation can help decompress the disaster area and provide further care to critical casualties to off-site medical facilities. On the other hand, there could be several reasons that may delay the evacuation of some casualties; these may include contaminated victims, casualties with transmissible disease, and unstable patients.

SUMMARY

Over the last few decades, more and more sources capable of inducing mass casualty have been identified, grouped under common acronym CBRN/CBRNe (chemical, biological, radiological, nuclear/energetics). CBRN emergencies can be present as natural phenomena or can occur due to negligence and nonadherence to guidelines. The world has witnessed an unprecedented rise in chemical, biological, and nuclear agents being used as an act of terrorism. Undoubtably in modern civilization, CBRN threats are a clear and present danger. Meanwhile various studies evaluated preparedness for disaster among healthcare facilities and found that a large number of providers were not confident in their ability to adequately manage CBRN incidents. In various mock drills and training simulations, significant gaps in awareness and proficiency in these scenarios were also highlighted. Thus, all healthcare providers must take steps to update themselves with the tools needed to identify, prevent, and manage these low-probabilities, high-impact disasters, and their catastrophic consequences. Over the last few years, various hospitals successfully implemented several training tools, exercises, and guidelines to improve staff awareness and optimize institutional response to CBRN events.In the acute care setting integration and practice of regular and standardized training exercises are useful in optimizing the local "Emergency Response" against potential high-impact of CBRN.

MULTIPLE CHOICE QUESTIONS

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30
CHAPTER

Military Medicine

Ahmed Humaid, Saleh Fares, Abdulla Alhmoudi

INTRODUCTION

Military medicine is a broad branch of medicine which encompasses many aims, from treating traumatic injuries of those in active battle to caring for the mental health of service personnel and their families. Historically, military medicine has been more focused on ensuring good health amongst soldiers. Many died from communicable diseases rather than injuries sustained on the battlefield. For example, during the American Revolution in the 1700s, approximately 90% of soldier deaths were attributable to poor sanitation.

Improvements in general public health and modern medicine have rendered this less of an issue. Contrastingly amongst active-duty American personnel between the years 2006 and 2018, only 17.5% of deaths were from illness. Within this group, the highest cause of death was accident (31.9%), followed by self-inflicted injury (23.2%). Only 21.6% died of wounds sustained in active combat. As public health has improved through time, so have modern methods of warfare. The treatment of the injured soldier will very much depend upon the injuries he has sustained.

We are no longer seeing a majority of penetrating injuries. The rise of the roadside improvised explosive devices in both the Afghanistan and Iraq wars has led to increased blast injuries and blunt trauma. Given the stressful nature of these situations, a standardized approach by which to structure initial care is beneficial and has been shown to improve outcomes. This standardized approach has not only improved outcomes within military medicine, but also improved care in civilian trauma. A good example of this is the use of the tourniquet for a major hemorrhage from a limb. This was first researched and applied in combat situations before being implemented more widely in general trauma care.

TACTICAL COMBAT CASUALTY CARE PRINCIPLES

Tactical combat casualty care (TCCC) was the first set of battlefield trauma care guidelines. It was the result of the Naval Special Warfare biomedical research program that it was realized that the most common cause of preventable death amongst injured service personnel was external hemorrhage; however, the use of tourniquets was actively discouraged. The resulting set of guidance was put together comprising a phased approach to care on the battlefield as laid out in **Table 1**.

TABLE 1: Phases of tactical combat casualty care.

Phase	*Tactical situation*	*Aims*
Care under fire	Personnel engaged in combat with the ongoing threat	• Return fire and take cover—superior firepower prevents further wounds/casualties • Direct casualty to self-aid and continue combat or take cover as able • If able, stop life-threatening hemorrhage or place in the recovery position if airway or consciousness impaired
Tactical field care	No longer engaged in a hostile situation	• Field triage (see **Fig. 1**) • Disarm casualty with altered mental status—preventing further injury/casualties • Structured assessment using the acronym MARCH as outlined in *approach to injured soldier* • Perform secondary survey and treat other wounds if able
Tactical evacuation	Transportation available to a higher level of medical care	As per tactical field care, however, increased resources may mean better ability to treat and monitor certain conditions, e.g., traumatic brain injury

(MARCH: massive hemorrhage, airway assessment, respiratory assessment, circulatory assessment, and hypothermia)

FIELD TRIAGE

Field triage is used to identify the priority for the treatment of mass casualties. **Figure 1** shows how they are sorted to ensure that those who need immediate life-saving intervention receive this promptly, whilst identifying those less severely injured who can wait. Traumatic arrest in the context of the battlefield is unlikely to be survivable. Diverting resources when under fire, or in the context of mass casualties to the arrested patient, is likely to result in further deaths. If resources permit during tactical evacuation, it may be that more specialist interventions, such as resuscitative thoracotomy (RT), could be considered.

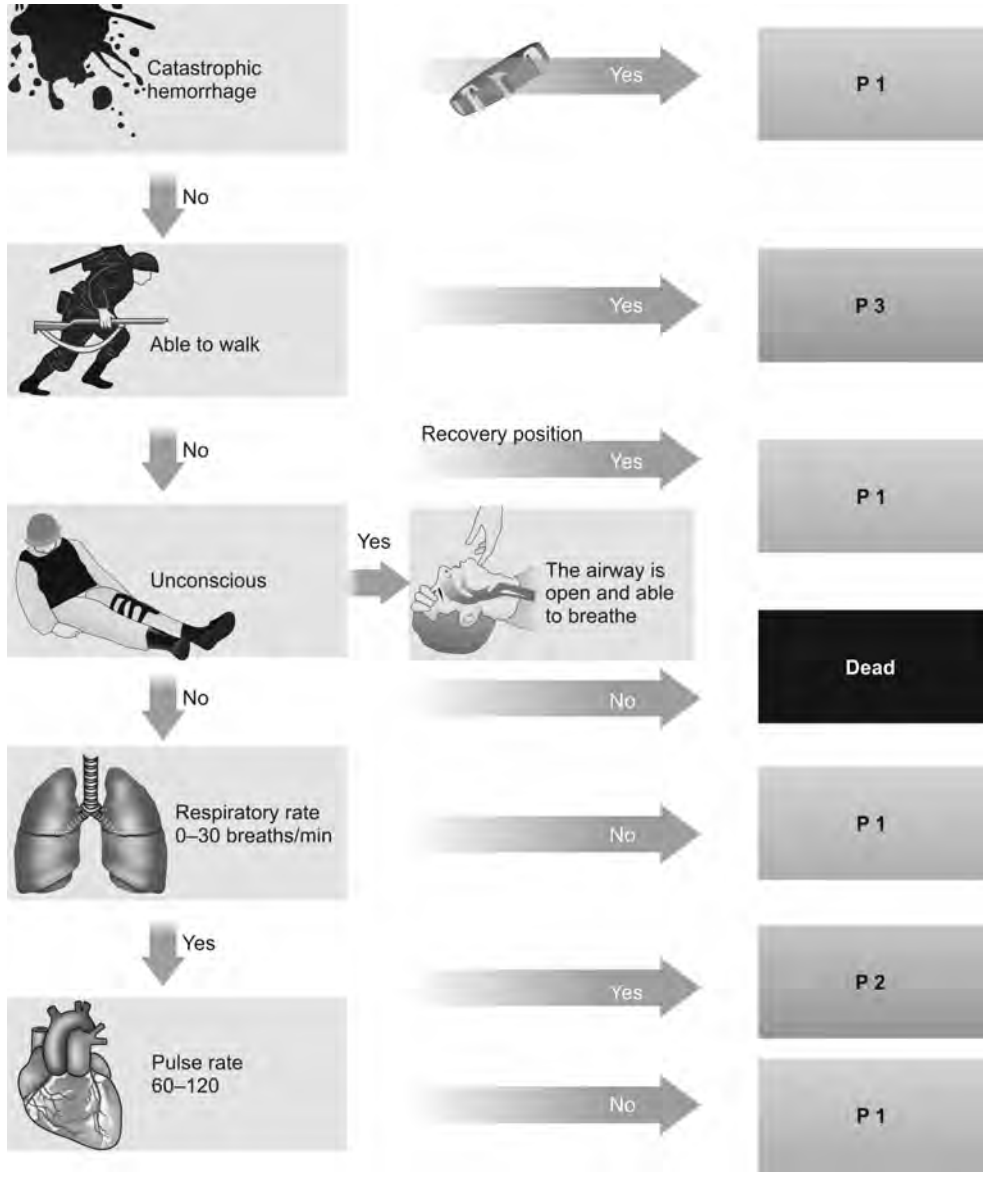
APPROACH TO THE INJURED SOLDIER

During the tactical field care phase of TCCC, a primary survey can be conducted of the patient. Help provided will be limited by resources available to attending medics, though the standard kit carried by forward surgical teams is extensive. **Table 2** is an example of the kit you would expect one of these teams to carry. Though this may vary it gives an indication as to the capabilities of these prehospital responders.

The primary survey has been modified for military medicine to prioritize the treatment of massive hemorrhage—by far the leading cause of preventable death. The acronym MARCH (Massive hemorrhage, Airway assessment, Respiratory assessment, Circulatory assessment, and Hypothermia) is used as a hierarchical structure to approach, with each section having to be corrected before moving on to the next. This is outlined below:

Massive hemorrhage (M): Control any bleeding. This can be done in a number of ways based on anatomical location:

- If from an extremity, apply a tourniquet or direct pressure.
- Bleeding from a junctional anatomic area, i.e., the junction between limb and torso may be better managed by specialized junctional tourniquets as hemorrhage



[P1 (Priority 1): immediate life-saving interventions required; P2 (Priority 2): interventions can be delayed but urgent care required within 2 hours; P3 (Priority 3): requires medical intervention that can be delayed without risk to patient]

FIG. 1: Field triage of mass casualties.

TABLE 2: Example kit carried by forward surgical teams.

Combat application tourniquet	*Method for securing tube (e.g., tape)*	*Adhesive on way flutter valve/seal*	*Wound antibiotics of choice (multiple doses)*
Gloves (multiple, sterile, and nonsterile)	Surgical airway kit	Hemostatic bandage	CNS wound prophylactic antibiotics of choice
Protective eyewear	Cleaning swabs	Large dressings	Morphine
Headlamp	Stylets	Skin stapler	Lidocaine with epinephrine
Stethoscope	CO_2 monitoring (colorimetric indicator sufficient)	Benzoin swabs to aid adherence of dressings	Acetaminophen
Red, green, blue, and yellow safety light sticks	Finger pulse oximeter	Hypothermia prevention kit	SAM/Traction splints
Cervical spine immobilization collar	Suction device	IV fluid administration kit	Needled (multiple gauges)
Nasopharyngeal airways	Thoracotomy kit	IV/IO access kits	Sharps bin
Multiple endotracheal tubes including intubation kit	Thoracostomy tube and kit	IV fluids of choice	Indelible marker
Laryngeal scopes (×2) with replacement	Scalpel	Fluid warmer	Mass casualty patient cards
Bag valve mask	Forceps	Pressure bag	Burns dressings
Suction device	Trauma shears	Syringes (multiple sizes)	Sterile water

(CNS: central nervous system; IO: intraosseous; IV: intravenous; SAM: structural aluminum malleable)

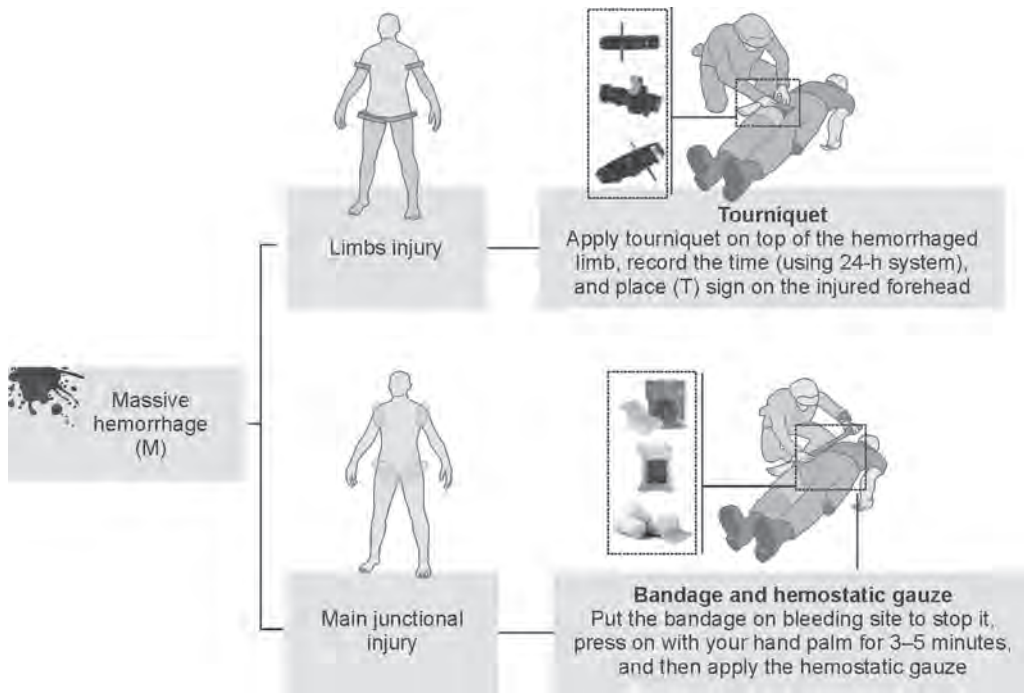

Massive hemorrhage (M)
Limbs injury
Tourniquet
Apply tourniquet on top of the hemorrhaged limb, record the time (using 24-h system), and place (T) sign on the injured forehead
Main junctional injury
Bandage and hemostatic gauze
Put the bandage on bleeding site to stop it, press on with your hand palm for 3–5 minutes, and then apply the hemostatic gauze

FIG. 2: Methods of achieving hemostasis depending upon the anatomical site of injury.

is unlikely to be amenable to standard tourniquets or hemostatic agents.

- For torso injuries, hemostatic agents can be used for the direct packing of wounds. If pelvic fractures are suspected, application of a pelvic binder may be helpful in stemming internal blood loss.

Figure 2 illustrates some of the ways in which hemostasis can be achieved through adjuncts, as described above.

Airway assessment (A): Ensure a patent airway. Airway adjuncts can be used; however, in the context of mass casualties, a secure airway is preferable. Cricothyroidotomy is used with greater frequency than in civilian medicine. This has the benefit of greater certainty of correct placement of the tube within the trachea when compared to endotracheal intubation. C-spine immobilization can be considered; however, in the context of care under fire, it is likely to take time which could result in

further casualties. Consideration should be given to a tactical situation when considering immobilization.

Figure 3 illustrates basic airway maneuvers and adjuncts which can be used to secure the airway, and the order in which they should be employed.

Respiratory assessment (R): In the context of trauma, impaired breathing is likely due to hemothorax, pneumothorax, or tension pneumothorax. Ensure that any open chest wounds are sealed with a vented dressing and have a low threshold for needle thoracostomy.

Circulatory assessment (C): Hemorrhagic shock should be treated with permissive hypotension. Casualties are likely to be suffering from acute traumatic coagulopathy and guidance is aimed at preserving the initial clots formed. Aggressive resuscitation may lead to increased bleeding by disrupting these clots. As such, systolic blood pressure should be maintained at around 90 mm Hg.

Tranexamic acid is widely used outside of military medicine in the context of trauma. Its administration within the 1st hour has been shown to significantly improve outcomes in this context. Intraosseous (IO) access is an effective method by which to gain access in patients with poor perfusion quickly.

Hypothermia (H): Prevention of hypothermia is essential. This contributes to traumatic coagulopathy and greater mortality.

Following this, a secondary survey can be performed. If safe to do so, the patient should be exposed and all other injuries identified and tended to. Ensure constant reassessment of the situation and flexibility to move back to the *MARCH algorithm* if there is deterioration.

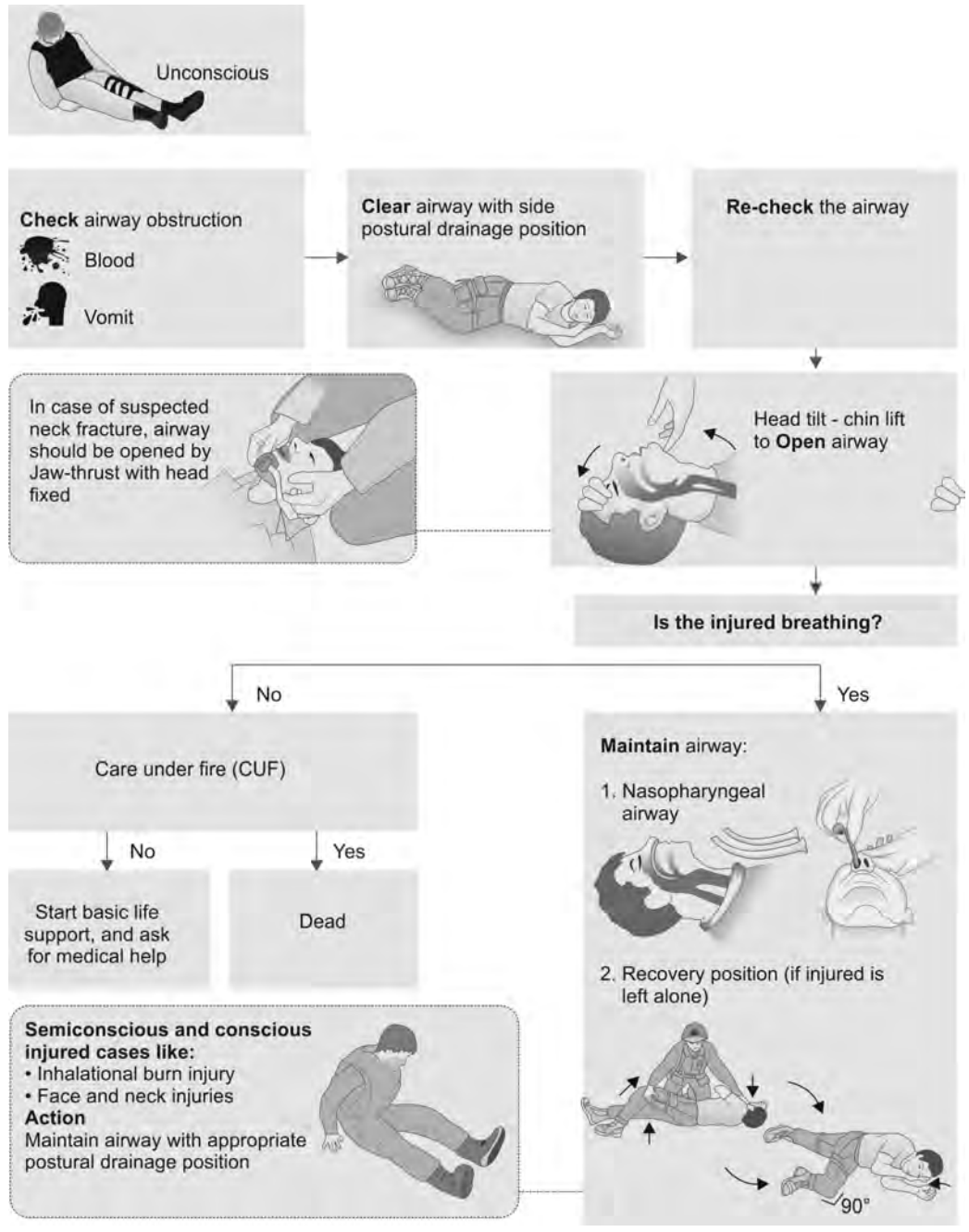


FIG. 3: Methods of positioning and use of airway adjuncts.

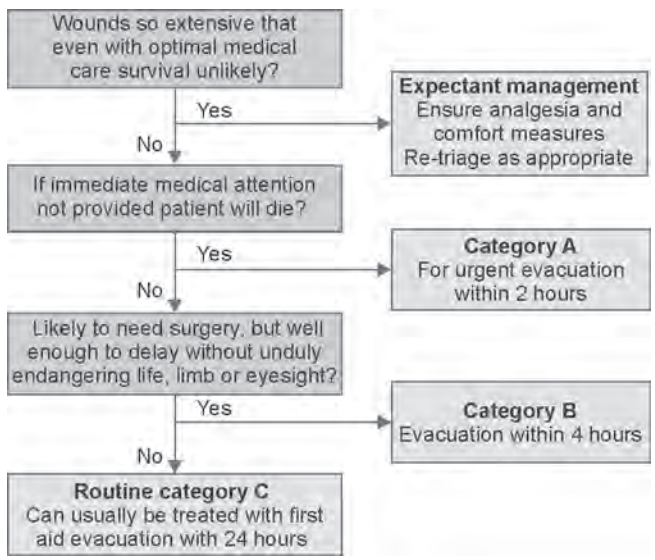
MEDICAL EVACUATION

Medical evacuation (MEDEVAC) is considered a crucial step in the care of any injured patient. It refers to the medical care provided during the movement of injured patients from the point-of-injury (POI) to a higher level of care. The purpose of the MEDEVAC is to take the right injured patient, at the right time, to the right medical facility, using the right transportation method, and providing the right en-route care (**Flowchart 1**).

Ensuring timely evacuation of the patient has been shown to vastly decrease patient mortality. The introduction of "the golden hour," meaning ensuring the transport of a patient for more definitive care, has been incorporated into both battlefield care and civilian trauma medicine, generally improving outcomes.

MEDEVACs are integral to ensuring the safe transport of the patient to each level of care. When it is being conducted to transfer specific patients, who are more likely to survive transport, it is referred to as tactical MEDEVAC. When MEDEVAC is performed to move patients out of operation theatres, thereby decreasing workload in these areas, it is referred to as strategic MEDEVAC.

The evacuation process is most successful when it is taken as a system-wide approach with integrated levels of care. This includes having trained prehospital care providers, well-equipped transportation methods and medical facilities, organized policies and procedures, and robust governance with clear command and control structures, to mention but a few. Several models exist utilizing different resources. There are numerous ambulance types with different capacities and capabilities. Similarly, helicopters (such as the Black Hawk) and fixed-wing aircraft (such as the C-130 or C-17) play a vital role in transporting casualties within the operation theatres as well as strategically.


Wounds so extensive that even with optimal medical care survival unlikely?
Yes
No
Expectant management
Ensure analgesia and comfort measures
Re-triage as appropriate
If immediate medical attention not provided patient will die?
Yes
No
Category A
For urgent evacuation within 2 hours
Likely to need surgery, but well enough to delay without unduly endangering life, limb or eyesight?
Yes
No
Category B
Evacuation within 4 hours
Routine category C
Can usually be treated with first aid evacuation with 24 hours

FLOWCHART 1: Prioritization of evacuation of casualties.

During any MEDEVAC, necessary equipment must be available to ensure the delivery of the best care possible. Every member of the evacuation team must be familiar with everything, well trained on when and how to use it, and know the location to find it.

Medical care during evacuation requires special education and training. There are different levels of providers, ranging from basic to advanced, or even subspecialized. Similarly, special teams are usually tasked with evacuating critically ill patients. Those teams are usually formed by emergency or critical care physicians, nurses, respiratory therapists, and occasionally paramedics. Examples of this include the Critical Care Air Transport Teams (CCATT) in the United States or the Medical Emergency Response Team (MERT) in the United Kingdom.

Survival of the casualty does not only depend on medical care at POI but also on the intermediate and longer term care, including rehabilitation. The surgical teams responding are traditionally split into four "roles," each having their own priorities for management based on the resources available to them. They are outlined in **Table 3**.

Working in austere environments (including safety issues, limited resources, and unfamiliar surroundings) poses several challenges to care providers. Other challenges include dealing with injured patients in contaminated areas or managing a large number of casualties.

When the transportation is made by nonmedical vehicles with no en-route medical care, with a purpose of rapidly evacuating the casualties to a medical facility, it is known as casualty evacuation (CASEVAC). There are numerous types of MEDEVAC and CASEVAC options, with several advantages and disadvantages. This is beyond the scope of this chapter.

CHALLENGES AND INNOVATIONS

Long gone are the days where soldiers could expect to die from minor wounds which become infected. Military medicine has moved on with rapidly administered broad-spectrum antibiotics.

More modern innovations largely target improving survival in battlefield trauma care. The widespread adaptation of the TCCC guidelines reduced battlefield-preventable deaths significantly. Interventions such as extremity and junctional hemorrhage largely contributed to this.

A widely recognized ongoing challenge is reducing death from *noncompressible torso hemorrhage (NCTH).* NCTH is defined by high-grade injury present in one or more of the

TABLE 3: Four roles in the care of casualties.

Role	*Location*	*Time from injury*	*Aims*
1	Point of injury/aid station	Within the 1st hour	Basic first aid, immediate life-saving measures, and triage
2	Forward surgical teams	Within the 1st hour	Ability to provide triage and damage control resuscitation (DCR), with some capability for damage control surgery (DCS)
3	Combat support hospital	24–72 h	Capability for more advanced diagnostics and treatment, including DCS
4	Usually, country of origin or designated hospital	>72 h	Definitive medical care for those whose needs outstrip role 3. Highly specialized input of care

following anatomic domains: pulmonary, solid abdominal organ, major vascular or pelvic trauma plus hemodynamic instability. It carries the highest mortality rate of potentially preventable death in military trauma.

In patients with hemorrhagic shock, the goal is to enable casualties to survive long enough to reach the care of a surgeon capable of performing damage control surgery (DCS). Fluid resuscitation using nonblood products is known for its detrimental effects of dilutional coagulopathy and hence must be avoided. Whole-blood transfusion, or packed red blood cells (pRBC) and plasma in a 1:1 ratio are the best options but most often not logistically possible. *Freeze-dried plasma (FDP)* as a resuscitative fluid has re-emerged as the fluid of choice for hemorrhagic shock at the POI, in both prehospital civilian and military trauma. Studies on the use of FDP showed positive effects on volume expansion and coagulation profiles. It was also shown to reduce the use of pRBC units required when used early during the evacuation of traumatic hemorrhagic shock patients in prehospital settings. FDP has logistical benefits as it can be stored at ambient temperatures for 2 years with preserved efficacy. Each bottle of powdered plasma is easily reconstituted with 200 mL of sterile water before transfusion. These advantages make it an ideal choice for role-1 and role-2 levels and also during helicopter evacuation.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a less-invasive option for mechanical homeostatic control of NCTH compared to RT with aortic cross-clamping. Studies have shown mortality benefits with REBOA compared to RT for the control of NCTH. However, it is important to note that REBOA does not serve to replace RT in the setting of thoracic injury, but is currently only generally used for infradiaphragmatic injuries. REBOA has been used in military medicine with success by trained personnel; it should be considered when the casualty presents in a periarrest state, if surgery is likely to be delayed, or where the single operating table is occupied by another case. The placement of REBOA can be done by emergency physicians who are trained and able to maintain their skills as long as a surgeon is immediately available for DCS.

Another area of innovation in battlefield trauma care is optimal analgesia with minimal risks. In an attempt to simplify the battlefield analgesia options, pioneered initially by TCCC, the protocol shown in **Table 4** was devised.

TABLE 4: Triple analgesia option for battlefield pain relief.

Injury severity	*Pain relief*
Minor pain, able to engage in ongoing combat	Oral *acetaminophen* 1,000 mg and *meloxicam* 15 mg
Moderate-to-severe pain, but neither shocked or with respiratory difficulty and unlikely to develop either condition	Transmucosal *fentanyl citrate* 800 µg
Severe pain with either shock or respiratory distress	*Ketamine* 100 mg intramuscularly, 50 mg intranasally, or 20–50 mg intravenously

It is worth noting that nonsteroidal anti-inflammatory drugs (NSAIDs) are not recommended in trauma settings due to their significant cyclooxygenase-1 (COX-1) inhibition causing inhibition of platelet function. However, meloxicam is a selective NSAID that works 90% on COX-2 inhibition; hence, it is preferable in this context.

SUMMARY

Ongoing research in military medicine has a number of challenges to address, this being one small part. However, owing to its very nature, research in military medicine can be difficult. Documentation is likely to be inaccurate in the heat of battle and conducting high-quality randomized control trials poses its own difficulties. The use of large trauma registries has sought to minimize some of these challenges as well as the use of telecommunications. There continue to be high-quality research driving improvements not only in battlefield care but also in general trauma management. Off of the battlefield, there has been greater awareness placed on the psychological impact of trauma in service personnel. This has led to public support groups and funding for psychotherapy. This is likely to continue to pose a future challenge, with the survival rates of trauma patients improving.

MULTIPLE CHOICE QUESTIONS

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31
CHAPTER

Basic and Nondefinitive Airways

Advait Thakor

INTRODUCTION

The human body requires a continuous supply of oxygen (air) and a continuous removal of carbon dioxide to properly function. This is accomplished by a patent airway and adequate ventilation. The airway consists of the upper airway and the lower airway. The upper airway extends from the mouth and nose to the laryngeal inlet. The lower airway extends from the laryngeal inlet to the bronchioles in the lungs. The most common causes of airway obstruction in patients presenting to the emergency department include—infections of the oral cavity, trauma, and burns (**Table 1**).Emergency physician should be able to recognize the features of airway obstruction. The management of airway and ventilation is necessary to provide adequate oxygenation to the patient and is an essential skill to be mastered by emergency physicians. The gold standard for a definitive airway is endotracheal intubation. However, there are basic skills required to be learnt for achieving proper airway management viz.

TABLE 1: Causes of airway obstruction.

Congenital	• *Obstruction above the larynx*—choanal atresia, micrognathia, and Treacher Collins syndrome • *Obstruction at the level of larynx*—atresia and webs • *Tracheal level*—web and tracheomalacia
Infections	*Nose*—septal abscess rhinosporidiosis *Oral cavity*—peritonsillar abscess, infection of floor of mouth *Pharynx*—adenoids retropharyngeal abscess *Larynx*—epiglottis laryngeotracheobronchitis diphtheria *Neck*—Ludwig's angina
Trauma	Maxillofacial trauma, neck trauma, laryngeal trauma, and burn scaring
Tumors	Papilloma, cysts, hygroma, benign tumors (may cause both internal or external narrowing)
Others	• Radiation—edema of surrounding tissue • Pregnancy, obtunded patient, obese individuals

- Basic airway positioning maneuvers
- Suctioning
- Supplemental oxygenation
- Use of airway adjuvants such as oropharyngeal airway (OPA) and nasopharyngeal airway (NPA)
- Bag-valve-mask (BVM) ventilation
- Supraglottic airway devices (SADs)

HOW TO RECOGNIZE AIRWAY OBSTRUCTION IN AN EMERGENCY DEPARTMENT?

Recognition of an *"obstructed airway"* is the first step toward successful airway management. Unobstructed respiration is always "quiet," it is never silent or noisy. Total respiratory obstruction may usually have a "silent" (due to absence of breath sounds and movement of air) presentation. Partial respiratory obstruction is noisy, snoring which may be due to tongue fall. Gurgling sounds due to collection of fluids/secretions in the pharynx. Stridor manifests due to glottic or supraglottic obstruction. Tachypnea may be an early sign of airways and ventilatory compromise. Severely compromised airways may lead to the use of accessory muscles of respiration, sternal retraction, cyanosis, anxiety, sweating, tachycardia, etc. The presentation may be (1) sudden in onset with complete obstruction, (2) gradual onset with partial obstruction, and (3) progressive and recurrent.

AIRWAY POSITIONING MANEUVERS

The principle behind airway maneuvers is that a patient should have an airway as open as possible. This is most efficient when the head of the bed is elevated to at least 30°, if possible. In order to maximize the patency of the upper airway, the external auditory meatus of the patient should be aligned at or above the sternal notch. The maneuvers are:

Head tilt-chin lift: This is done by tilting the head back by giving pressure on the forehead and lifting the chin with the other hand so as to open the airway ***(Fig. 1A)***. *Caution: It should not be done in patients with suspected cervical spine injury.*

Jaw thrust: The aim of this maneuver is to open the airway with minimum movement of cervical spine. The clinician stands behind the patient and places his hands on each side of the face such that the fingertips are at the angle of the jaw on the mandible. The jaw is lifted without tilting the neck causing forward displacement of the jaw which moves the tongue forward (**Fig. 1B**).

AIRWAY ADJUNCTS

Oropharyngeal Airway

The OPA (oral airways) helps to maintain or open the airway by preventing the tongue from covering the epiglottis. This happens when a person becomes unconscious which causes the jaw to relax and the tongue falls back obstructing the airway. It also helps to make BVM ventilation more effective especially in cardiopulmonary resuscitation. OPA is made up of rigid material and can be divided in various parts to facilitate airway as shown in **Figure 2**. Various sizes of OPA are available (**Fig. 3**) and a proper-sized OPA estimated by the method shown in should be used. Sizing of the OPA—the flange should be approximated, externally, to where it is abutting the lips, and the tip should be able to reach the angle of the mandible (**Fig. 4**).

There are two techniques to use the OPA: (1) open the mouth and with a tongue depressor, push down the tongue toward the floor of the mouth, and insert the OPA directly into

FIGS. 1A AND B: Head tilt-chin lift and jaw thrust maneuvers.
Courtesy: Dr Amit B Nabar.

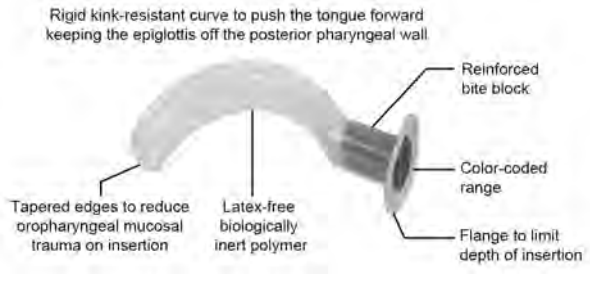

Rigid kink-resistant curve to push the tongue forward keeping the epiglottis off the posterior pharyngeal wall
Reinforced bite block
Color-coded range
Flange to limit depth of insertion
Tapered edges to reduce oropharyngeal mucosal trauma on insertion
Latex-free biologically inert polymer

FIG. 2: Oral pharyngeal airway (OPA).

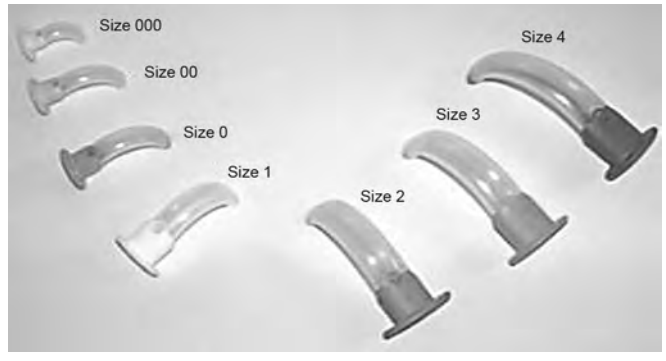


FIG. 3: Various sizes of oropharyngeal airway.

FIGS. 4A TO C: Estimation of (A) correct size; (B and C) Correct technique of placement of oropharyngeal airway.

the mouth over the tongue; and (2) open the mouth and with the tip pointing cephalad toward the roof of the mouth, and insert the OPA in such a way that the concave part of the OPA faces the palate. Advance the OPA and rotate it 180°. *Caution: A proper-sized OPA should be used as a small airway would cause obstruction by pushing the tongue back and a larger airway may induce laryngeal spasm. OPA use is contraindicated* in the presence of gag reflex and if foreign body in the airway.

Nasopharyngeal Airway (Also Called Nasal Airway or Nasal Trumpet)

It is a hollow noncuffed tube which is soft, flexible, and available for various sizes (**Fig. 5**). It is inserted nasally along the floor of the nasopharynx going beyond the base of the tongue to maintain a patent airway. *Sizing the NPA and placement*—the proper size of the tube is measured from the tragus to the tip of nostril. The diameter of the NPA should be less than that of the nostril. A well-lubricated NPA is inserted with the bevel facing the septum of the nose. The NPA is advanced gently along the floor of the nose. The flange should rest on the nostril and may be secured (**Figs. 6A** and **B**). *Caution: If resistance is felt, no force should be used.*

Advantages of NPA:

- It can be used in semiconscious patients with intact gag reflex and cough reflex.
- It can be used in patients with trismus.
- It can be used with patients with wiring of the jaw.

FIG. 5: Nasopharyngeal airway.

Contraindications to use of NPA:

- Patients with central facial trauma
- Patients with suspected skull fracture
- Patients with coagulopathies
- Patients on anticoagulants
- Patients with history of recent transsphenoidal surgery, recent rhinoplasty, or septoplasty

SUCTIONING

The upper airway may be obstructed by material in the airway such as blood, blood clots, vomitus, foreign bodies, etc. In such situations, it is imperative to remove the material from the oropharynx. This requires a properly functioning suction usually with a Yankauer cannula (**Fig. 7**). In case the material is very thick and viscid, it may have to be removed by detaching the tip of the suction cannula and using the tubing directly. Alternatively, a gauze piece held in a Magill's forceps can be used to remove the thick material in the oral cavity. Magill forceps are also useful for removing solid foreign bodies especially in children. *Caution: Keep a watch on the oxygen saturation while suctioning.*

BAG-VALVE-MASK VENTILATION

Once the airway is clear and maintained by maneuvers or airway adjuncts, check the breathing. If the breathing is inadequate or absent, pulse oximetry shows a falling reading, the patient needs to be assisted by BVM ventilation. A BVM is a system comprises a self-inflatable bag with a face mask with a one-way valve, a reservoir bag and an inlet to connect to a source of oxygen.

Parts of the Bag-valve-mask System

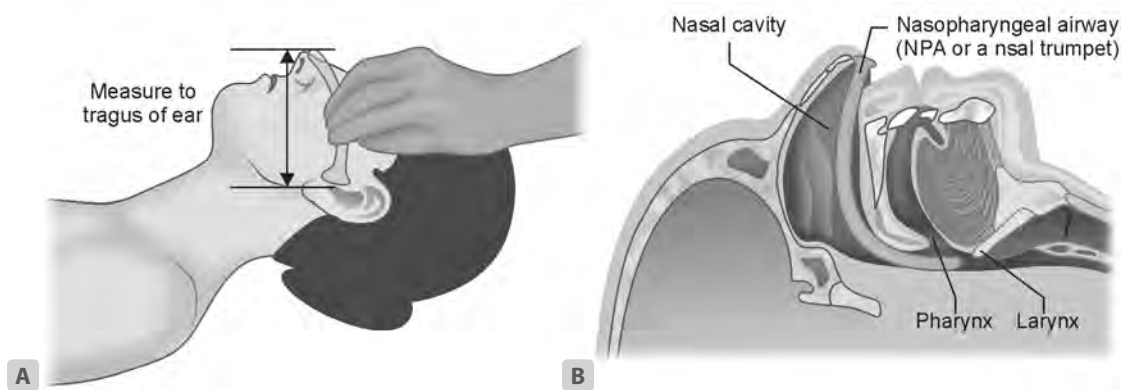
Various parts of the BVM system are shown in **Figures 8A** and **B**.

Face Mask

It is usually transparent and has a cushion at the face end which can be inflated to ensure a proper seal. It is molded so as to minimize dead space.

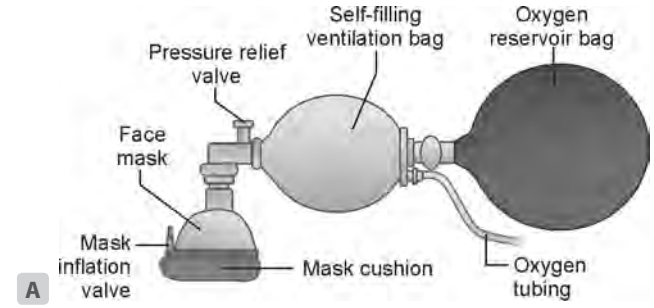
Valve

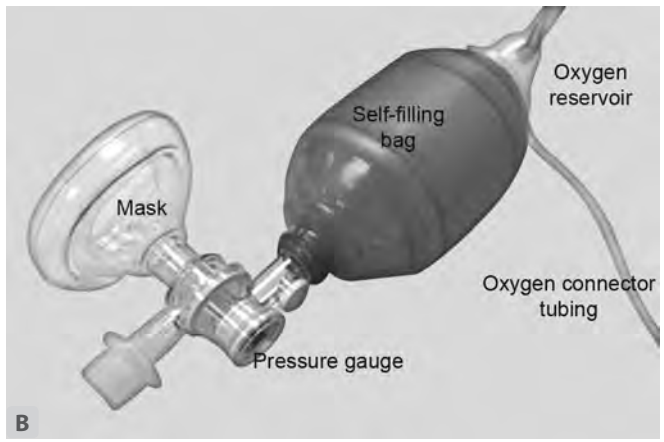
It is a nonrebreathing valve which prevents the exhaled air to go back into the bag. Some valves have a built-in pressure gauge



FIGS. 6A AND B: (A) Estimation of correct size; (B) Placement of nasopharyngeal airway.

FIG. 7: Yankauer suction cannula.





FIGS. 8A AND B: (A) Parts of bag-valve-mask system (BVM); (B) BVM with pressure gauge.

(**Figs. 9A** and **B**). A positive end-expiratory pressure (PEEP) valve can be attached to the exhalation port in some systems.

Bag

It is a self-inflating bag which reinflates after compression. It is usually available in various sizes (e.g., Laerdal™ 240 mL for infants, 500 mL for children, and 1600 mL bag for adults).

Reservoir Bag

It is almost equal to or more than the self-inflating bag so as to give 100% oxygen if required.

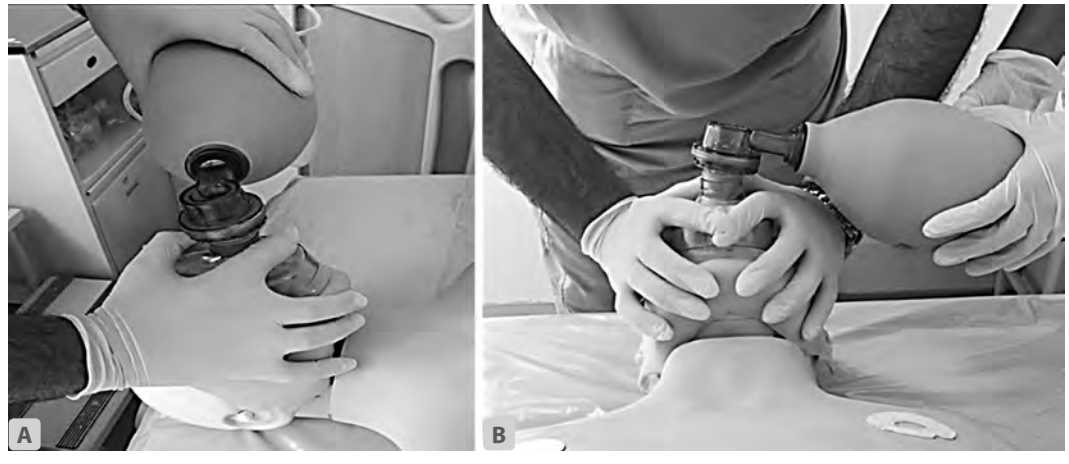
Use of Bag-valve-mask System

It is very important to properly use the BVM system so that adequate ventilation of the patient can be done. The mask has to fit properly to the face of the patient.

The C-E technique of holding the mask achieves this. Herein, the user makes a C with his thumb and first finger and grasps the body of the mask whereas his middle, ring, and little finger form an E to grasp the ramus of the mandible and lift it onto the mask.

Caution: The thumb and index finger forming the C should not push down the body of the mask on the face else there is a chance of the tongue falling back. The three other fingers forming an E should be on the bony part of the mandible and not on the soft tissue.

A single person can follow the above method; however, if there are two persons available, the BVM can be held by one person using both hands for a proper mask fit and the second person compresses the bag. If the ventilation is not proper, use of oropharyngeal or NPAs can be done. There are certain patients who are *difficult to ventilate with a BVM*. They can be identified by the mnemonics *MOANS* [mask seal, obesity, age (elderly), no teeth, stiffness stiffness] *BONES* (beard, obesity, no teeth, elderly, snoring, or sleep apnea). These patients can be managed by shaving off the beard with the patient's consent, keeping a denture in edentulous patients, giving reverse Trendelenburg position in the obese, etc. The compression of the self-inflating bag should be slow and not very forceful so as to prevent the air or oxygen to enter the stomach causing distension, vomiting, aspiration, and barotrauma.



FIGS. 9A AND B: (A) Use of bag-valve-mask (BVM) by one person C-E technique; (B) Use of BVM by two persons.

SUPRAGLOTTIC AIRWAY DEVICES

Supraglottic airway device(s) (SAD) (periglottic airway devices and extraglottic airway devices) are designed to provide a means for oxygenation, ventilation, and delivery of anesthetic gases. They are used as an alternative to BVM ventilation and endotracheal intubation. They are used as rescue airways when intubation is difficult or when experienced personnel are not present for intubation. They are also referred to as periglottic airway devices, extraglottic airway devices, or extralaryngeal airway devices. All of them are inserted via the mouth and do not go beyond the laryngeal inlet (**Fig. 10**).

The first SAD was laryngeal mask airway (LMA) developed by Dr Archie Brain in 1981 and put to clinical use in 1988. They are available in various sizes.

Characteristics

The LMA has *three main components, viz., a mask, an airway tube and an inflation line.* The small mask is designed to sit in the hypopharynx with its anterior surface opening lying over the laryngeal inlet. The mask has a rim which can be inflated by a line with a pilot balloon. This rim when inflated creates a seal which allows a positive pressure ventilation of up to 20 cm of H_2O.The adequacy of the seal depends on the proper size of the LMA and correct placement. The airway tube is connected to the posterior surface of the mask and opens into the aperture having two bands which prevent the epiglottis from obstructing the aperture.

Classification of Supraglottic Airway Devices

There are a variety of SADs available and are classified as (**Table 2**):

- *Cook's classification (2011)*: First-generation SAD—simple airway tube with no specific design for safety or performance. Second-generation SAD—have a gastric drain tube, improved pharyngeal seal and bite block.
- *Miller's classification (2014)*: It consists of three generations of SAD depending on sealing mechanism and location of the seal.

FIG. 10: Supraglottic airway devices [laryngeal mask airway (LMA)] different sizes picture showing three main parts of LMA mask tube and inflation line.

Other Supraglottic Airway Devices

Some of the SADs are in use, apart from classical LMA are:

- *Laryngeal mask airway unique*: It is similar to the classical LMA but is meant for single use. It is useful in patients with infections.
- *Proseal LMA*: It is an improvement on the classic LMA and has an esophageal drain tube. It also has a posterior cuff. It forms a high-pressure seal in the pharynx. It can be inserted directly or railroaded on a bougie (**Fig. 11**).
- *Laryngeal mask airway supreme*: It has a drain tube and a large inflatable cuff but no posterior cuff. It is meant for single use. There are fins in the mask bowl to prevent epiglottic obstruction (**Fig. 12**).

TABLE 2: Miller's classification of supraglottic airway devices.

	Location of sealing	
Sealing mechanism	***Perilaryngeal***	***Base of tongue***
First-generation—inflatable cuff	cLMA; pLMA	Combitube
Second-generation—preshaped	i-gel	SLIPA
Third-generation—self energizing	Baska mask	

(cLMA: classic laryngeal mask airway; pLMA: proseal LMA; SLIPA: streamlined liner of the pharynx airway)

FIG. 11: Proseal laryngeal mask airway.

FIG. 12: Laryngeal mask airway supreme.

- *King laryngeal tube (LT)*: It consists of an airway tube and two cuffs, a proximal large balloon cuff and a distal small balloon cuff. The tube is angulated in the middle. Both cuffs are inflated by a single pilot tube and balloon. The proximal cuff provides a seal in the pharynx and the distal cuff seals the esophagus. There are openings between the two cuffs for ventilation. There are six sizes available. There is a modification called LTS-II which has a lumen beyond the esophageal cuff for suctioning. King LT and LTS II are available in single use disposable models also (**Fig. 13**).
- *I-gel*: This is a preshaped cuff-less SAD, made of a gel-like material which adapts to the anatomy of the pharynx after insertion. It also has a channel for suctioning. It is very easy to use and has a fast insertion time (**Fig. 14**).
- *Esophageal tracheal tube (Combitube)*: It consists of two lumens and two cuffs. It is a double lumen-double balloon supraglottic device (**Fig. 15**). It is introduced blindly and can work with either tracheal or esophageal placement. It is easy to learn, easy to use especially in the emergency department. The disadvantages are increased chances of vomiting and aspiration: Oral, tracheal, pharyngeal trauma: difficulty in using with cervical immobilization.
- *Cobra perilaryngeal airway (PLA)*: It is a PLA device with larger pharyngeal cuff when inflated. It has better airway sealing pressure (**Fig. 16**).
- *Intubating LMA (Fastrach)*: It is a rigid anatomically curved airway tube wide enough to pass an 8.0 mm endotracheal tube. It is short enough to ensure passage of the endotracheal tube beyond the vocal cords (**Fig. 17**).

Method of Laryngeal Mask Airway Use

Check the patency of the LMA and the cuff integrity. Lubricate the dorsal surface of the mask of LMA and after deflating the cuff, introduce it in such a manner that the tip goes in the mouth first and the dorsal surface of the mask of the LMA is against the palate. Check for proper ventilation after passing the LMA and fix it (**Fig. 18**).

Advantages of Laryngeal Mask Airway

- It is easier to insert as compared to endotracheal intubation especially by inexperienced personnel.
- It causes less sore throat as compared to endotracheal intubation.
- It gives better oxygen saturation than BVM.
- It causes less hand fatigue as compared to BVM.

Disadvantages of Laryngeal Mask Airway

- There are more chances of gastric distension and it has to be used with caution in persons with full stomach.
- It is not a definitive airway and has to be replaced by endotracheal intubation subsequently.

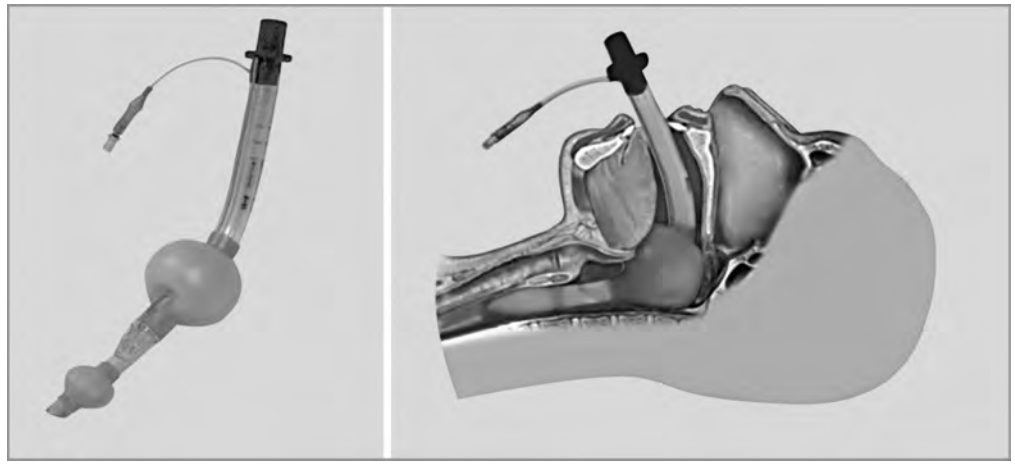


FIG. 13: King laryngeal tube.

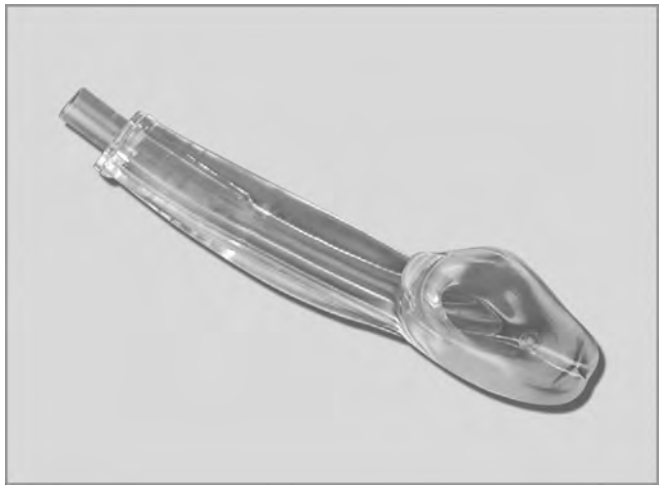
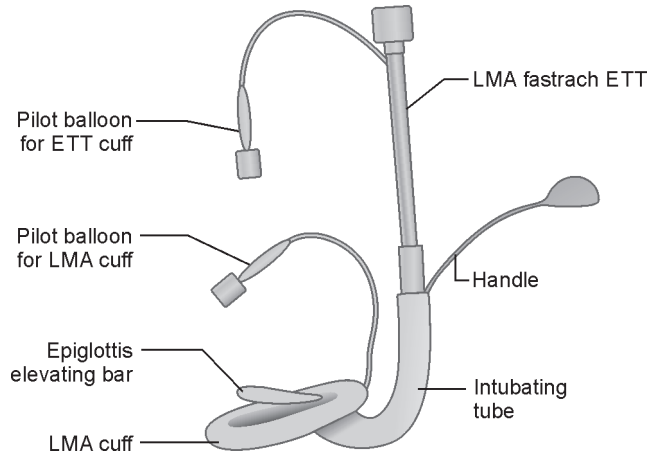


FIG. 14: I-gel laryngeal mask airway.

FIG. 15: Combitube.

FIG. 16: Cobra perilaryngeal airway.



(ETT: endotracheal tube; LMA: laryngeal mask airway)

FIG. 17: Intubating LMA (Fastrach).

FIG. 18: Use of supraglottic airway [position of laryngeal mask airway (LMA)].

SUMMARY

Airway management is an essential skill and is fundamental to the practice of emergency medicine. Hypoxia and airway compromise, contribute significantly to prehospital deaths. Hypoxemia prevention needs an unobstructed and protected airway with adequate ventilation that takes precedence over management of all other clinical conditions. The challenges facing an emergency physician are augmented in acute settings and respiratory management demands higher level of competency and composure. There has been a significant progress in effective airway management in emergencies and a lot of efforts are going into training and auditing these core skills. Airway management in emergency department is a challenging procedure. Every emergency physician should be competent to perform it. Airway management is vital procedure and this is not a "one size fit to all" procedure. Emergency physician should be trained and expertise in managing the difficult airway. Patient with respiratory distress often needs airway management. Systematic approach is needed for airway management.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Advanced Airway Management

Venugopalan Poovathumparambil

INTRODUCTION

Airway management is essential skill for all emergency physicians. Timely and effective airway interventions are a critical procedure for optimal resuscitation of medical and trauma patients. Airway management in operation theatre is being done in a highly controlled environment. In a failed airway scenario, there is a possibility to cancel and postpone the procedure. But in emergency department (ED) especially in crashed airway scenario, it will be like "do or die" situation and emergency room is always considered as an uncontrolled environment. Nowadays, emergency clinicians have a wide range of new options for improving airway management skills few examples are various airway techniques and procedures combined with recent advances in rapid sequence intubation (RSI), video laryngoscopy, and further advanced airway techniques.

How to approach airway in emergency room: Initial patient assessment forms the cornerstone of further advanced airway management, and the primary evaluation should focus on the quick identification of those who may need respiratory support. This evaluation includes assessment for the patency of the airway and adequacy of ventilatory effort, potential hypoxia, or presence of illness or injury that could result in further deterioration of the patients' respiratory status.

We will have two categories of patients. First one are those who require urgent airway intervention and another one who are stable and less urgent. In first category are belonging to crash airway where need to interfere as quickly as possible and in second category we need time for planning and systematic approach. *How do you know airway is patent/first step to identify a compromised airway?* 10-second assessment of airway: Just talk with your patient. If someone should able to talk in full sentence means he is maintaining his airway. But there are certain conditions where we must be careful about dynamic airways which will be present as normal, but deteriorate subsequently such as angioedema, neck trauma burns, etc. Indictor of airway patency is level of consciousness, ability to speak in response to any query (upper airway and the level of consciousness are checked), able to clear his or her own secretions.

APPLIED ANATOMY

Mouth and nose are both connected to the airway. Fairly complex structures that serve distinctly different functions and have distinctly different anatomy. Mouth opens into the oropharynx a muscular structure containing large dexterous muscle, the tongue, teeth, and multiple glands. Main purpose is to bring food into the digestive tract and begin to break it down. The nares are specialized structure designed to filter, warm, and humidify air open into the nasopharynx. The structures are essentially mucous membranes stretched over the cartilage. The hard palate divides the oropharynx and nasopharynx and a posterior soft palate, a floppy structure that minimizes reflux of food and fluid into the nasopharynx (**Fig. 1**).

Mandible and Hyoid

One of the most sophisticated structural support systems in the body lurks just anterior to the mandible—the hyoid bone. This is a horse shaped. This is the only bone that does not articulate with another bone in the body. It is attached by a continuous set of ligaments. The internal structures of the neck like tongue (attached to the tongue and, via the hyoepiglottic ligament to

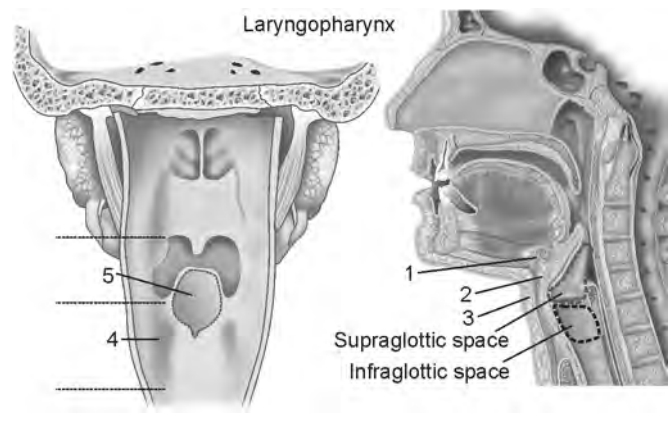


FIG. 1: Anatomy of airway: 1—hyoid bone, 2—thyrohyoid membrane, 3—laryngeal prominence, 4—piriform recess, and 5—laryngeal inlet.

the epiglottis) move wherever the hyoid moves. The hyoid is attached directly the mandible also, and moves with the hyoid.

Hypopharynx

Epiglottis, an anterior, leaf-shaped structure that is essentially attached to the base of the tongue. Lower airway starts below epiglottis and lower airway structure consists of aryepiglottic folds, false cords, and the true vocal cords or glottis. Movement of the thyroid and cricoid cartilage is helpful in speaking, coughing, and airway protection.

The fallen back tongue was considered as the common cause of airway obstruction. "*Loud and noisy breathing* in an unresponsive patient is the sign of airway obstruction. *Partially obstructed airway* by soft tissue or liquid (e.g., blood and emesis) clinically presents as snoring or gurgling noises. *Complete airway obstruction is present as silent chest* but may manifest transiently as retractions of the accessory muscles of respiration (suprasternal, supraclavicular, intercostal, and subcostal) or as cyanosis, until frank respiratory arrest supervenes.

ADVANCED AIRWAY MANAGEMENT

Main aim of advanced airway management (definitive airway) is protection of the airway, sometime useful in temporary or readily reversible condition, such as opioid overdose. Identify whether a ventilatory failure or oxygenation failure using clinical assessment, pulse oximetry with or without capnography, and observation of improvement or deterioration in the patient's clinical condition. In an agitated patient, always ruled out hypoxia first and if the patient is obtunded, think about hypercarbia. Pulse oximeter and capnography are the two very important tools in critical airway management. Someone tolerating OPA means, it indicates that he/she requires definitive airway (**Table 1**).

Definitive Airway

Definitive airway requires a tube placed in the trachea with the cuff inflated below the vocal cords, the tube connected to oxygen-enriched assisted ventilation, and the airway secured in place with an appropriate stabilizing method. Definitive airway can be divided into three types: (1) orotracheal tube, (2) nasotracheal tube, and (3) surgical airway (cricothyroidotomy and tracheostomy). The criteria for establishing a definitive airway in a trauma patient are based on clinical findings and include:

- Inability to maintain a patent airway by other means, with impending or potential airway compromise (e.g., following inhalation injury, facial fractures, or retropharyngeal hematoma)
- Inability to maintain adequate oxygenation by face mask oxygen supplementation, or the presence of apnea
- Altered mental status or combativeness resulting from cerebral hypoxia
- Glasgow Coma Scale score of 8 or less, head injury/with seizures, need protection of lower airway from aspiration of blood or vomitus.

Dynamic Airway

An airway apparently looks like normal but deteriorate quickly and which requires urgent intervention, e.g., angioedema and anaphylaxis, thermal and caustic injuries, bullet injuries of neck, etc.

Four steps to be taken before any intubation:

1. Rapidly assess the patient's need for intubation and the urgency of the situation.
2. Determine the best method of airway management based on assessment of the patient's predicted difficulty and pathophysiology.
3. Decide which pharmacologic agents are indicated, in what order, and in what doses.
4. Prepare a plan in the event that the primary method is unsuccessful, know in advance how to recognize when the planned airway intervention has failed or will inevitably fail, and clearly lay out the alternative (rescue) technique(s).

In emergency room, patients with airway management issues may be divided into those who need an immediate

TABLE 1: Clinical conditions which require advanced airway.

Airway	Mouth and neck infection, tumors, foreign bodies, and bleeds	Causes stridor, hoarseness, dysphonia, dysphagia, dyspnea, and secretions
Breathing	Failure of oxygenation or ventilation	Often amenable to medical or noninvasive therapies. Think NIV and HFNC
Circulation	Sepsis and shock	Intubation and ventilation support tissue oxygen delivery and unloading muscles of respiration
Disability	CNS catastrophe and CNS depression, ongoing seizures, weakness	• Avoid gag—assess ability to swallow and handle secretions (pooling, drooling, and gurgling) for neuromuscular weakness: FVC < 12 mL/kg and NIF < 20 cmH_2O • Vomiting in the obtunded patient is a particular concern
Expected course	• Anticipated decline • Transfer to radiology or another institution	
Feral	• Need for prompt, aggressive sedation to protect patient/others *especially with potential or undiagnosed medical instability*	

(FVC: forced vital capacity; HFNC: high-flow nasal cannula; NIF: negative inspiratory force; NIV: noninvasive ventilation)

definitive intervention versus those who are more stable or less urgent. The first category is generally identified as a *crash airway* and must be managed without delay. The second group may be assessed in a more systematic fashion in an effort to determine the next best step in treatment and to identify factors that could make airway management difficult.

AIRWAY ASSESSMENT

Proper airway assessment is crucial and most import step before starting advanced airway management. Unfortunately, we may fail to carry out this step and very often we may land up in big troubles. Remember time is a big factor in ER airway management scenario and once an airway emergency strikes the clock will start run in reverse direction and if you fail to manage crises it will end up in a disaster. Airway assessment is aiming to identify and anticipate airway difficulties. Four levels of assessment for airway difficulties

1. Difficulty for bag mask ventilation (BMV)
2. Difficulty for endotracheal intubation
3. Difficulty for supraglottic airway (SGA) insertion
4. Difficulty for surgical airway insertion

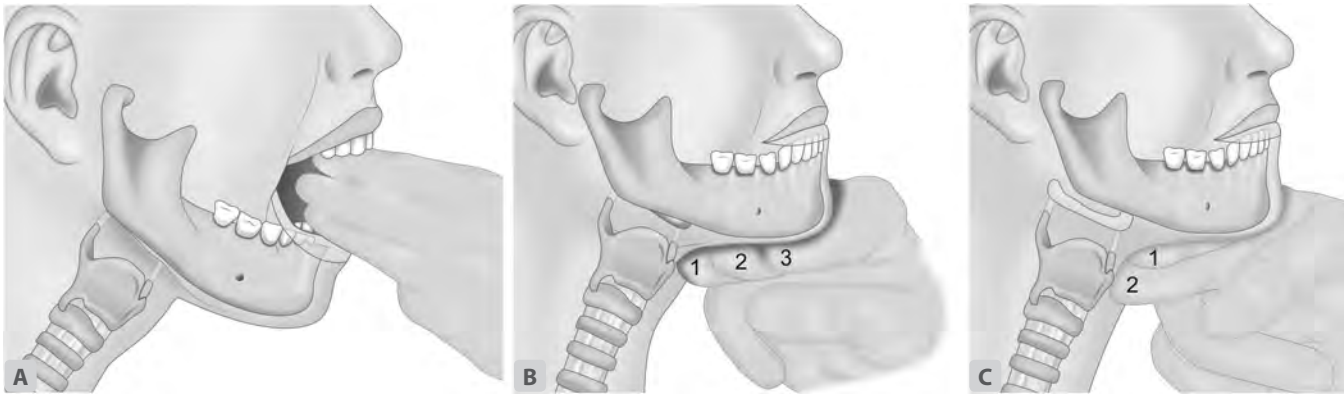
Difficulty for Bag Mask Ventilation (MOANS)

M—mask seal compromise or difficulty. *O—obstruction* (particularly supraglottic obstruction, but can be anywhere in the airway) or *Obesity*—body mass index > 26 (because of redundant upper airway tissue, chest wall weight, and resistance of abdominal mass) or *Obstetric* patient. *A—* advanced *age* (best assessed by physiologic appearance of the patient, but age > 55 years increases risk). *N—no teeth* (edentulous) which independently interferes mask seal. *S—stiffness or resistance to ventilation* (asthma, COPD, pulmonary edema, restrictive lung disease, and term pregnancy) may contribute to increased difficulty with BMV. The difficulty with BMV of the edentulous patient is the basis of the advice often cited for patients with dentures: "teeth out to intubate, teeth in to ventilate." Another approach involves placing the mask inside the patient's lower lip. This may limit air leak in patients without teeth and eliminates the risk of aspiration associated with dental prosthetics or rolled gauze. Take a gamji pad and make a diamond cut in the center. Keep the pad over the face in such a way that the diamond opening at mouth and keep mask over it. This will be useful in edentulous or patients with nasogastric tube in situ.

Difficulty in Endotracheal Intubation (Direct Laryngoscopy)

LEMON evaluation is used to assess the difficulty in intubation and direct laryngoscopy.

- *L—Look externally*: A quick external examination of the patient for potential signs of airway problems and their management. First external markers of difficult intubation, should be examined which are based on the specialist clinical impression. For example, the severely combative trauma patient with facial fracture, immobilized in a cervical collar on a spine board, gives immediate impression of anticipated difficult intubation.
- *E—Evaluate 3-3-2 rule*: Examine the airway for structural and anatomic factors that may make intubation difficult. Normally, a mouth opening should accommodate three of the patient's fingers, three fingers distance/measurement from the mentum to the hyoid bone, and a distance of two fingers from the hyoid bone to the thyroid notch. When present, these factors predict sufficient spatial relationships between the mouth, the mandible, temporomandibular joint mobility, and the larynx to allow for successful direct laryngoscopy and eventual endotracheal intubation (**Figs. 2A** to **C**).
  - Interincisor distance less than three fingers means inadequate mouth opening which leads to difficulty in inserting laryngoscope.
  - Thyromental distance less than three fingers mean larynx is anterior and it leads difficulty in visualization of vocal code.
  - Thyrohyoid distance is less than two fingers means high larynx which make vocal code visualization is more difficult.
- *M—Mallampati score*: Assessment of the posterior oropharyngeal structures visualized when the mouth is opened and the tongue is fully protruded (**Fig. 3**). Visibility of the oral pharynx ranges from complete visualization, including the tonsillar pillars (class I), to no visualization at all, with the tongue pressed against the hard palate (class IV). Classes I and II signify adequate oral access, class III signifies moderate difficulty, and class IV signifies a high degree of difficulty.
- *O—Obstruction*: Obstruction of upper airway by foreign bodies, local edema, stridor, or soft tissue masses makes intubation difficult or impossible. Examine the patient for any airway obstruction and assess the patient's voice



FIGS. 2A TO C: 3-3-2 rule assessment: (A) Interincisor distance; (B) Thyromental distance; (C) Thyrohyoid distance.

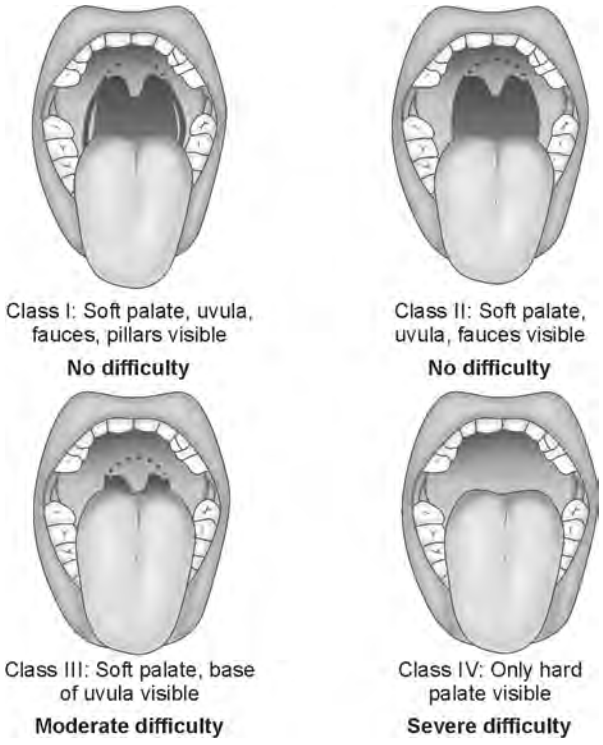

Class I: Soft palate, uvula, fauces, pillars visible
No difficulty
Class II: Soft palate, uvula, fauces visible
No difficulty
Class III: Soft palate, base of uvula visible
Moderate difficulty
Class IV: Only hard palate visible
Severe difficulty

FIG. 3: Mallampati classification.

to confirm the evaluation. Conditions which make the definitive airway placement difficult are epiglottitis, cancer of head and neck, Ludwig's angina, hematoma of neck, glottis swelling, or glottic polyps. Obese patients generally are more difficult to intubate than their nonobese counterparts, they desaturate quickly and cause increased difficulty with ventilation using BMV or an extraglottic devices (EGD).

- *N—Neck mobility*: Neck positioning is maintained to achieve optimum angles for visualization of the glottis to facilitate definitive airway. Neck movement is restricted in conditions such as cervical spine injuries, rheumatoid arthritis, or degenerative arthritis. Neck mobility is assessed by flexion and extension of the patient's head and neck through a full range of motion. Neck extension is the most important motion, but placing the patient in the full sniffing position provides the optimal laryngeal view by direct laryngoscopy. The "S" in *LEMONS* referring to the patient's *oxygen saturation*.

Difficulty for Supraglottic Airway Insertion

Mnemonic RODS is used to predict difficulty in achieving placement or ventilation. Restricted mouth opening, Obstruction or obesity, Distorted anatomy, and Stiffness (resistance to ventilation). Placement of an EGD, such as a laryngeal mask airway (LMA), Combitube, laryngeal tube airway (LTA) (Kings airway), or similar upper airway device, often can convert a cannot intubate, cannot oxygenate situation to a cannot intubate, can oxygenate situation, which allows time for rescue of a failed airway. EGDs are placed blindly and balloon is inflated which obstructs the oropharynx proximally and esophageal inlet distally, permitting indirect ventilation. Poor seal and ineffective ventilation can result due to distorted upper airway anatomy.

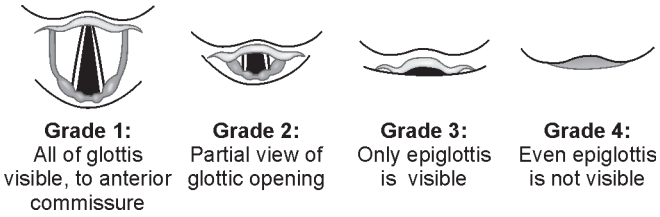


FIG. 4: Cormack and Lehane—laryngoscopic grading for intubation.

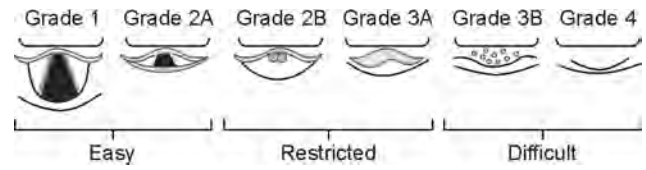


FIG. 5: Modified Cormack and Lehane's classification of laryngeal grade.

Difficulty for Surgical Airway Insertion

Difficult cricothyrotomy can be anticipated whenever there is limited access to the anterior neck or obscured laryngeal landmarks and can be remembered by the mnemonic SMART (Surgery Mass Access/anatomy problem Radiation, Tumor). Causes of difficult cricothyrotomy are history of surgery, hematoma, tumor, abscess, radiation-induced scarring local trauma, obesity, and local edema.

LARYNGOSCOPIC GRADING FOR DIFFICULT INTUBATION

The actual degree to which an intubation is difficult is highly subjective, and quantification is challenging. The CL (Cormack and Lehane) system (**Fig. 4**) is the most widely used system for grading a laryngoscopic view of the glottis, which grades laryngoscopy according to the extent to which laryngeal and glottic structures can be seen. CL devised a scoring system that, although limited by an element of intra- and interobserver variability, provided an objective descriptive measure of the glottic view during laryngoscopy.

The definitions they used are as follows:

- *Grade 1*: Larger part of glottis is visible.
- *Grade 2*: Only the posterior part of glottis is visible.
- *Grade 3*: Only the epiglottis is visible. Glottis is not visible.
- *Grade 4*: Epiglottis is also not visible.

The intubation difficulty will increase from the grade 1 to 4.

Grade 1—extrinsic manipulation of larynx is not required, grade 2—extrinsic manipulation of larynx is required, grade 3—intubation possible with stylet/gum elastic budgie guided, and grade 4—failed intubation.

Perhaps the most useful modification of this basic system is *modified CL's classification* (**Fig. 5**) one that a grade 3 view into a grade 3A, in which the epiglottis can be lifted off the posterior pharyngeal wall, and grade 3B, in which it cannot be lifted.

POSITION FOR INTUBATION

Comfortable intubating position that allows in-line visualization of the airway to the operators is the key for

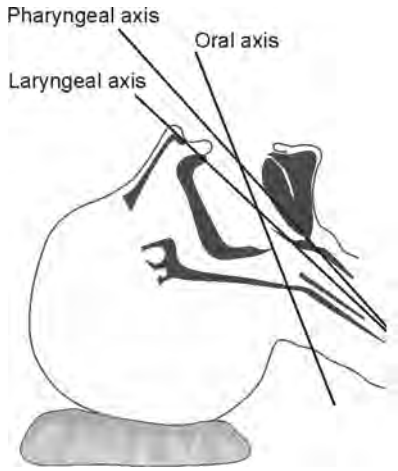


FIG. 6: Aligning laryngeal and pharyngeal axes by placing a pillow under head (not under shoulder in adult).

successful laryngoscopy and placing the definitive airway. This can be achieved by adjusting the height of the patient or the height of the intubator to bring the airway into the laryngoscopist's central field of vision. Jackson advocated full head extension, and Magill recommended the ''sniff'' position, whereby the neck is flexed on the torso and the head is slightly extended on the neck (the flex-extend position). Bannister (an anesthetist) and Macbeth propose the triple-axis alignment. The "sniffing position"—lower cervical flexion and atlanto-occipital extension and is helpful in aligning the oral, pharyngeal, and laryngeal axes of the upper airway and optimizes the laryngoscopic view (**Fig. 6**). Two steps will align these axis's together:

- Keep a pillow under head to align laryngeal and pharyngeal axis
- Extend head to align oral axis to the rest
- Avoid if any contraindication exist

TECHNIQUE OF INTUBATION

- Open the mouth as much as possible.
- Insert the blade and sweep the tongue to the left.
- Advance the tip of the blade down the tongue carefully, lifting, and until the epiglottis is located. The epiglottis is the main anatomic landmark for performing intubation because the glottis can be consistently found just posterior and inferior to it.
- Next step is lifting of the epiglottis. Epiglottis can be displaced indirectly by pressing against the hyoepiglottic ligament at the base of the vallecula if using the curved blades. Epiglottis can be lifted directly with the tip of the straight blade.
- Identify the posterior cartilages and interarytenoid notch. These structures make up the posterior border of the glottis and separate the tracheal inlet from the esophagus. Visualize the vocal cords (**Fig. 7**).
- Pass the tube through the vocal cords and into the trachea.

RAPID SEQUENCE INTUBATION

Rapid sequence intubation is the most widely used technique for emergency intubation of patients without identifiable difficult airway attributes, with recent large registry data

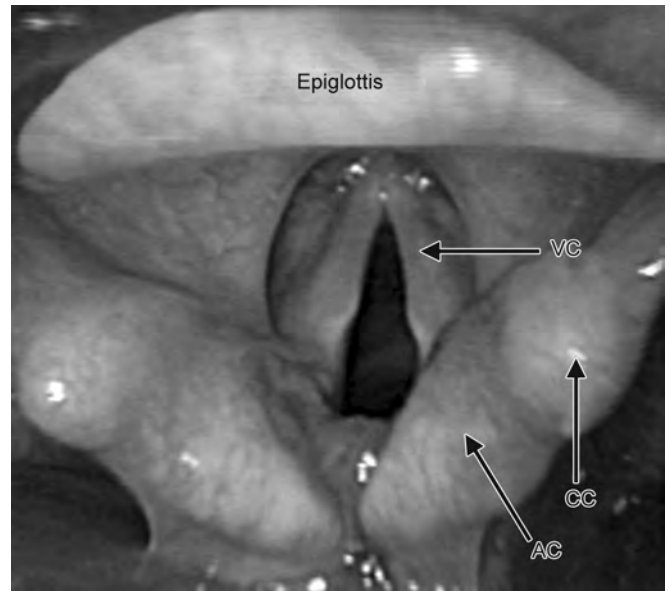


FIG. 7: Laryngoscopic view—anatomy of the laryngeal inlet revealed at direct laryngoscopy. Beneath the epiglottis (E), a view is sought of the whitish vocal cords (VC) in their triangular orientation. The rounded paired posterior (corniculate) cartilages (CC) and arytenoid cartilages (AC) are also shown. ***(For color version, see plate 2)***

showing that it is used in 85% of all ED intubations. This approach provides optimal condition for intubation with minimal risk of aspiration of gastric content. This procedure (RSI) is performed with the help of induction agents (potent sedative) and neuromuscular blocking agents (NMBA) (succinylcholine or rocuronium).RSI is based on the concept that with the help of neuromuscular paralytic agent, conscious spontaneously breathing patient taken to a state of unconsciousness with complete neuromuscular paralysis. Thus positive-pressure ventilation is avoided until the ETT-endotracheal tube is placed correctly in the trachea, with the cuff inflated.

Rapid sequence intubation facilitates successful endotracheal intubation by causing complete relaxation of the patient's musculature, allowing better access to the airway. Finally, RSI permits pharmacologic control of the physiologic responses to laryngoscopy and intubation, mitigating potential adverse effects. These effects include further elevations in intracranial pressure (ICP) in response to the procedure and to the sympathetic discharge resulting from laryngoscopy. The process of RSI is carried out in a very systematic way through 7 Ps. The emergency physician should know every minute aspects of this steps 7 Ps of RSI:

1. Preparation
2. Preoxygenation
3. Pretreatment
4. Paralysis with induction
5. Positioning
6. Placement of tube and confirmation
7. Postintubation management

Preparation

Preparation is the most important step in RSI and very often people will forget or taken for granted in this step. An unprepared RSI may invariably land up in many unavoidable

crisis and airway disasters. *The preparation may in four levels preparation of patient, preparation of drugs and equipment, preparation of the intubator and assistant, and prepare for the difficulties.*

1. *Patient preparation* includes get informed consent, complete airway evaluation including (artificial dentures, loose tooth, etc.) and clinical evaluation including past medical history, allergic history, previous intubation, and anesthetic history, trauma, cervical spine diseases-related to mobility, drug history, and last meal (fasting) are very important. Once patient in the intubation table establish cardiac monitor, pulse oximeter, blood pressure [noninvasive (NIBP)], end-tidal carbon dioxide ($ETCO_2$), etc. Establish two patent IV line. Keep intubation pillow or towel under head (not under the shoulder in adults).
2. *Preparation of equipment and drugs is essential.* ET intubation equipment (**Fig. 8**) and drugs (**Table 2**) are summarized below. Standard tube sizes kept in adult intubation kit are 8/8.5 for male and 7–7.5 for female. But it should keep one size above and below respectively. Drugs should be loaded and labeled. All drugs and equipment should be available at your arm span distances.
3. *Preparation of intubator and assistant*: Wear essential personal protection equipment, communicate the plan to patient bystander, team members and primary consultant, and Anesthetist if needed. Check the checklist. Assign the role for the team members.
4. *Prepare for the difficulties*: Make sure that all back up devices and back support are ready and available. The biggest airway disaster is "cannot intubate, cannot oxygenate" (CICO) scenario.

FIG. 8: Essential equipment for rapid sequence intubation.

TABLE 2: Equipment and drugs for rapid sequence intubations.

- BVM
- Suction
- Airways (oropharyngeal and nasopharyngeal)
- ET tubes of appropriate sizes
- Stylet
- Laryngoscope
- Laryngoscope blades (both curved and straight)
- Magill forceps
- 10-mL syringe
- Stethoscope

Drugs: Pretreatment, induction, and paralysis (PIP)

Pretreatment—LOAD	*Induction*	*Paralysis*
L—Lignocaine	Etomidate	Suxamethonium
O-Opioids—Fentanyl	Propofol	Rocuronium
A—Atropine	Ketamine	Vecuronium
D—Defasciculating agents	Midazolam	Atracurium

(BVM: bag valve mask; ET: endotracheal)

Preoxygenation

Preoxygenation is the crucial step in RSI and it aims to fill the functional reserve of lung [functional residual capacity (FRC)] with 100% oxygen. Through preoxygenation we are removing nitrogen from lung so it is also called denitrogenation. Preoxygenation will help to overcome the apnea period during RSI from paralytic agent to intubation. It also helps to carry out nonbagging technique in RSI (no bag ventilation after the intubating dose of paralytic agent). Risk for dysrhythmia, hemodynamic decompensation, hypoxic brain injury, and death occurs if patients desaturate below 70%.

Administer 100% oxygen for 3 minutes in a normal healthy adult which provides adequate oxygen reservoir and permits 6–8 minutes of safe apnea before oxygen desaturation to <90%.

Desaturation time in *obese patients* can be prolonged by preoxygenating with the patient in a *head-up position* and by *continuing supplemental oxygen* (via nasal cannula at a flow rate of 5–10 L/min) It has been suggested to use LMA for preoxygenation but if the LMA is used as a preoxygenation method, its introduction per se might worsen optimal preoxygenation, as its proper use usually requires deep sedation, which leads to apnea, or at least to severe hypoventilation.

Pretreatment

Pretreatment is the drugs administered 3 minutes before paralytic agents and intubation. Intubation is intensely stimulating and results in a sympathetic discharge, or reflex sympathetic response to laryngoscopy (RSRL). Pretreatment helps to attenuate the sympathetic response of the laryngoscopy and intubation. Fentanyl (3 μg/kg IV) can be administered 3 minutes before RSI can optimize the patient's hemodynamics in patients suffering from a hypertensive emergency. Patients with reactive airways disease can exhibit worsening pulmonary mechanics after intubation as a result of bronchospasm pretreatment for—reactive airway disease—albuterol, 2.5 mg, by nebulizer. If time does not permit albuterol nebulizer, give lidocaine 1.5 mg/kg IV. Cardiovascular disease—fentanyl, 3 μg/kg, to mitigate sympathetic discharge. Elevated ICP—fentanyl, 3 μg/kg, to mitigate sympathetic discharge and attendant rise in ICP. Preload—bolus 500 mL crystalloid solution may be given to reduce postinduction hypotension.

Paralysis with Induction

In this step, a potent sedative agent is administered by rapid intravenous (IV) push in a dose capable of producing unconsciousness rapidly. This is immediately followed by

rapid administration of an intubating dose of a NMBA, either succinylcholine (depolarizing muscle relaxant) at a dose of 1.5 mg/kg IV or rocuronium (nondepolarizing muscle relaxant), 1 mg/kg. It is usual to wait 45 seconds from when the succinylcholine is given and 60 seconds from when rocuronium is given to allow sufficient paralysis to occur. The results from two large meta-analyses have revealed that intubating conditions provided by each drug are equivalent as long as rocuronium is dosed between 1.0 and 1.2 mg/kg IV.

Positioning

Positioning is aiming to align all three axes for better visualization of vocal cords. It is typically described as sniffing position attained by pillow under head and neck extension. Routine use of Selleck's maneuvers is not recommended. It should be considered optional, applied selectively, and released or modified early if the laryngeal view is poor or tube passage is difficult.

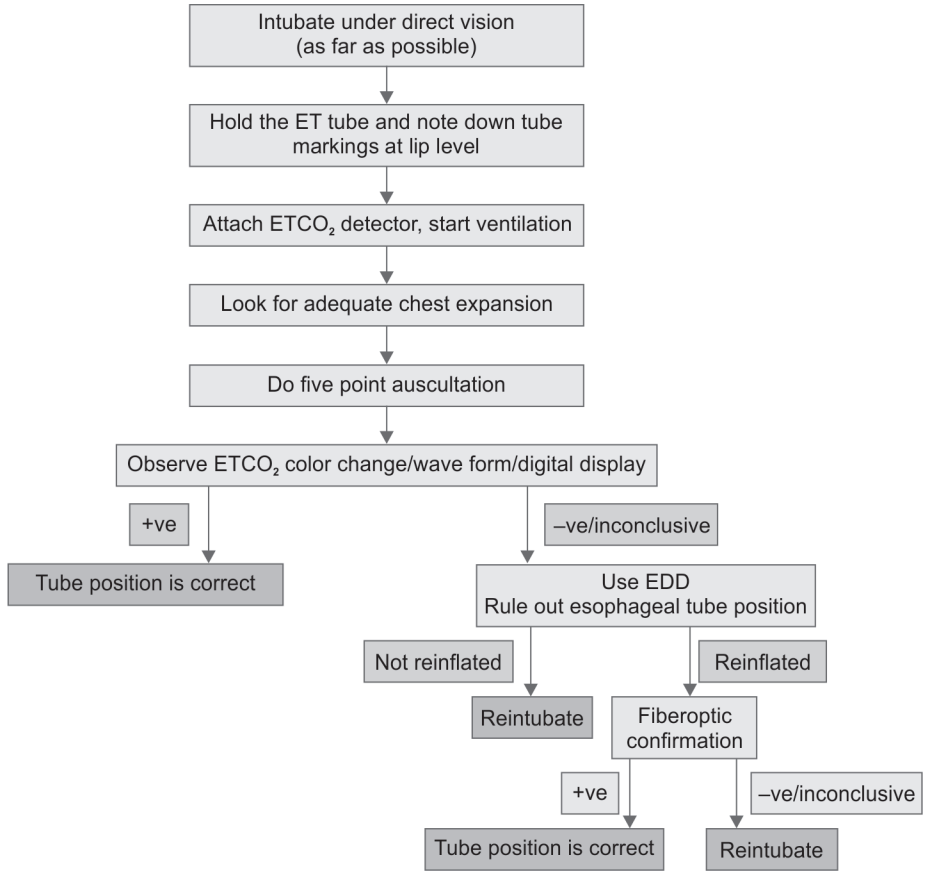
Placement of Tube and Position Confirmation

Patient is relaxed sufficiently approximately 45–60 seconds after administration of the NMBA, and laryngoscopy can be performed. Operator can assess this condition easily by moving the mandible to check absence of muscle tone. At this point ETT can be passed during glottic visualization with the laryngoscope. If the first attempt is unsuccessful but oxygen saturation remains high, it is not necessary to ventilate the patient with a bag and mask between intubation attempts. If the oxygen saturation is approaching 90%, the patient may be ventilated briefly with a bag and mask between attempts to reestablish the oxygen reservoir.

Confirmation of tube placement is equally important as intubation. Various methods are available to confirm tube position. End tidal carbon dioxide is the standard method to confirm tube position. All other methods are with less specificity and sensitivity and chances of errors are more. Gold standard is visualization of tracheal rings using fiberoptic scope. But not recommendable for routine scenario. But in difficult airway scenario, fiberoptic confirmation is gold standard. Ultrasound is useful in tube positioning. But the main challenge is its operator-dependent variability. While doing five point auscultation, it should always start from epigastrium to rule out an esophageal intubation first. An esophageal detector device (EDD) is a device rather used to rule out the esophageal intubation than tracheal tube placement. Suggested systematic approach to confirm tube position is shown in **Flowchart 1**.

Various methods are used to confirm correct position of the endotracheal tube.

- Waveform capnography
- Colorimetric $ETCO_2$ detector
- Auscultation of breath sounds
- Ultrasonography
- Direct visualization of the tube between the cords
- Self-inflating esophageal bulb
- Fogging of the ET tube
- Rise and fall of the chest
- Esophageal detector device
- Pulse oximetry readings



FLOWCHART 1: Approach to confirm tube position after direct laryngoscopy and intubation.

- Improvement in the patients' condition (color and heart rate)
- Fiberoptic scope

X-ray chest is only useful to rule out endotracheal tube position.

Postintubation Management

Confirm tube position by $ETCO_2$ and continues $ETCO_2$ monitoring if available. Take an X-ray chest to rule out endobronchial intubation. Fix ETT appropriately and note the lip mark and document it. Plan and administer postintubation sedation and analgesia. Generally, avoid paralysis with NDNMB such as vecuronium and pancuronium. Make sure that no tube bite, tube block, coughing, and fighting with ventilator. Manage postinduction hemodynamic instability with IV fluids and vasopressors if required. An adequate dose of a benzodiazepine (e.g., midazolam, 0.1–0.2 mg/kg IV) and opioid analgesic (e.g., fentanyl, 3–5 μg/kg IV, or morphine, 0.2–0.3 mg/kg IV) is given to improve patient comfort and decrease sympathetic response to the ETT.

Propofol infusion (5–50 μg/kg/min IV) with supplemental analgesia is an effective method for managing intubated patients who do not have hypotension or ongoing bleeding and is especially helpful for management of neurologic emergencies because its clinical duration of action is very short (<5 min), allowing frequent neurologic examinations. An NMBA is added only if appropriate use of sedation and analgesia fails to control the patient adequately or when ventilation is challenging because of by muscular activity.

Two dangerous emergent issues in the immediate post RSI phase is *hypoxia and hypotension* which should be addressed as quick as possible. *Look for DOPE in all cases of post-RSI hypoxia or hypotension*—D—Displacement (tube)/drugs, O—Obstruction, P—Pneumothorax, E—Equipment failure.

Rapid sequence intubation time line is summarized in **Table 3**.

DELAYED SEQUENCE INTUBATION

Delayed sequence intubation (DSI) is considered as "procedural sedation" using IV. Ketamine 1 mg/kg, in certain cases where preoxygenation with conventional methods such as face mask is difficult due to agitation, delirium, and confusion.

TABLE 3: Time line in rapid sequence intubation.

Time	*Steps*
Minus 10 min	Preparation
Minus 5 min	Preoxygenation
Minus 3 min	Pretreatment
Zero	Paralysis with induction
Plus 30 s	Positioning and cricoid pressure optional
Plus 45 s	Placement of ETT, confirm tube position
Plus 2 min	*Postintubation management*: • Sedation and analgesia as indicated • Initiate mechanical ventilation • NMBA only if needed after adequate sedation and analgesia

(ETT: endotracheal tube; NMBA: neuromuscular blocking agent)

INTUBATION WITHOUT PHARMACOLOGIC AGENTS

Crash Airway

Conditions (like arrested or near-death)—patient may not require pharmacologic agents for intubation, but some time even an arrested patient may retain sufficient muscle tone (which make intubation difficult) administration of a single dose of succinylcholine alone may facilitate laryngoscopy.

Awake Intubation

Awake oral intubation is a technique in which sedative and topical anesthetic agents are administered to permit management of a difficult airway without neuromuscular blockade.

- Topical anesthesia may be achieved by spray, nebulization, or local anesthetic nerve block.
- Aliquots of ketamine at a dose of 0.5 mg/kg IV, titrated to the desired level of sedation and procedural tolerance, are an effective method.
- Dexmedetomidine, alone or in combination with benzodiazepines, can be used for awake airway evaluations. A typical dose is 1.0 mg/kg IV infused over 5–10 minutes. After the patient is sedated, and topical anesthesia has been achieved, gentle direct video laryngoscopy or flexible endoscopic laryngoscopy is performed to determine whether the glottis is visible and intubation possible.

DIFFICULT AIRWAY

A difficult airway is considered in whom anatomical irregularities/deviation predict difficulty in securing the airway. A failed airway is considered in which the chosen technique has failed, and rescue technique is implemented. Obviously, there is much overlap, but it is important to keep the two notions distinct. Difficult airway can be divided into two categories: (1) An anatomically difficult airway, and (2) A physiologically difficult airway. The anatomical difficult airway requires anatomical or logistical manipulation for successful intubation, whereas the physiologic difficult airway requires optimization of overall patient management (correction of low oxygen saturation, blood pressure, or metabolic derangement, such as severe metabolic acidosis).

Difficult airway can be a difficulty in BMV, intubation, insertion SGA, or front of neck access to airway. This can be an anticipated or unexpected airway difficulty. The perception of a difficult airway is relative, and many emergency intubations could be considered difficult. Systematic approach can be adopted for identifying the potentially difficult airway by LEMON, MOANS, RODS, and SMART assessments.

FAILED AIRWAY

A failed airway can be considered when any of the following conditions is met: (1) Oxygen saturation is maintained during or after one or more failed laryngoscopic attempts; or (2) Three failed attempts of orotracheal intubation by an experienced specialist, even when oxygen saturation can be maintained.

- *Cannot intubate, cannot oxygenate:* Airway must be secured immediately (no time to evaluate). Avoid any further rescue

attempt and the airway must be secured immediately to maintain oxygen saturation by BMV or with an EGD.
- *Cannot intubate, can oxygenate:* Various rescue options can be executed (time to evaluate) because the patient is oxygenated.

Airway management failure can be avoided by identifying and anticipating patient with difficult for intubation.

PROTECTED INTUBATION IN HIGHLY INFECTED PATIENT—IN VIEW OF COVID-19

Challenges

- Potential for virus spread
- Inherent complication of intubation
- Inherent pathophysiologic implications of COVID-19
- Intubation, BMV, and suctioning are the procedures with highest aerosolization
- Optimal intubation condition is compromised
- Bag mask ventilation and preoxygenation with high-flow oxygen are dangerous.
- Coughing, sneezing, and tube disconnections are dangerous in terms of viral spread.
- Complex team dynamics
- COVID protocol-related difficulties

Rapid Sequence Intubation Modification

- Appropriate personal protective equipment (PPE) (full PPE for intubator)
- Don under supervision
- Adequate preparation
- Prepare for difficult airway
- Prepare for cardiac arrest
- Plan the procedure and always use checklist
- Most experienced member should intubate.
- Team and role assignment
- "Hot team" will be present inside the intubation room to manage the protected intubation
- "Cold team" will be present outside the room to help in crisis
- Proper communication system between cold and hot team
- Limit the number of persons in the hot team (maximum 3)
- Negative pressure room
- Use intubation hood or box and if not available, use a transparent plastic sheet cover, and do all airway manipulations under the plastic cover
- Preoxygenation with tight mask with two hand ventilation with viral filter and nonrebreather mask (NRB) with oxygen flow of 10–15 L/min
- Preoxygenation with high-flow nasal cannula
- Limited use of noninvasive ventilation (NIV)
- Limited use of nebulization
- Use closed suction only
- Rapid sequence intubation is the choice.
- High dose ketamine (2 mg/kg) is the induction agent of choice.
- High dose rocuronium 1 mg/kg or high dose succinylcholine 2 mg/kg is the paralytic agent.
- Cricoid pressure is desirable.
- Inflate cuff immediately after intubation
- No positive pressure ventilation before intubation and cuff inflation
- Use video laryngoscope for intubation
- Attach viral filter always between breathing circuit and ETT
- Tube positioning with direct visualization in video laryngoscopy and $ETCO_2$ monitoring
- No auscultation to confirm tube positioning
- Always clamp the ETT while changing from BMV to ventilator or vice versa
- Use second generation SGA such as I-GEL in failed intubation scenario
- Plan oxygenation strategy in failed first attempt intubation scenario
- Prepare and do front of neck airway access incase CICO
- Do protected code blue incase cardiac arrest happened
- Ventilator setting should be lung protective (tidal volume 6 mL/kg. RR 16–18/mt, inspiratory flow rate 60–80 L/min, PPlat <30 cm of H_2O and start positive end-expiratory pressure (PEEP) at 5 cm of H_2O and titrate up to get optimum arterial partial pressure of oxygen (PaO_2) at an acceptable fraction of inspired oxygen (FiO_2).
- Do appropriate postintubation care including sedation and paralysis, avoid tube disconnections, coughing, and bucking
- Doff under supervision and follow proper BMW (biological waste management) protocol
- Take shower in case any breach in PPE is detected.

CAPNOGRAPHY

Capnography is a mandatory tool in airway management in ED and ambulances. It is essential to confirm tube placement after intubation, monitoring of intubated patients in ED and also during medical transport. Capnometry is the continuous measurement of CO_2 in a sample of gas and represented as graphic form (time on X-axis and expired partial pressure of CO_2 on the Y-axis). The $ETCO_2$ is the maximal partial pressure or concentration of CO_2 in the respiratory gases at the end of an exhaled breath. A capnometry monitor displays the $ETCO_2$ value alone, whereas a capnography monitor displays the $ETCO_2$ value plus a continuous capnography waveform.

Capnography wave has got four phases—normal capnography wave morphology (**Fig. 9**)

1. *Phase I* (inspiratory phase) represents inspiratory phase, so no CO_2 is detected. The end of phase I represents the beginning of expiration, but because the initial gases expired originate from unventilated dead space, the capnography trace remains at zero.
2. *Phase II* (expiratory upstroke) represents expiration of both dead space gas and alveolar gas from the respiratory bronchioles and alveoli.
3. *Phase III* (alveolar plateau) represents phase of expiration of alveolar gases. At the end of phase III, the maximal value of CO_2 measured is equivalent to the $ETCO_2$. Note that if the alveoli all contained exactly the same partial pressure of CO_2, phase III would be completely horizontal.
4. *Phase IV (expiratory downstroke)* represents the beginning of the next breath, with the CO_2 content returning rapidly

to zero. Healthy patients with normal respiratory function will produce a capnography trace with this form. Lung pathologies will change the appearance of the capnograph due to a number of different factors—bronchoconstriction and obstruction to airflow, destruction of alveoli, an increase in the range of alveolar time constants (alveoli that empty at different rates), and an increase in V/Q spread (variation in CO_2 content of each alveolus). As a result, the slope of phase III is often markedly increased in respiratory disease that empty at different rates), and an increase in V/Q spread (variation in CO_2 content of each alveolus). As a result, the slope of phase III is often markedly increased in respiratory disease.

Morphology of Capnography

A healthy patient with normal lungs when ventilated via a patent tracheal tube or tracheostomy, the continuous waveform produces a typical *"square wave"* capnography trace and provides visual breath-by-breath assessment of a patient's airway and ventilation. Morphology of capnography traces is shown in **Figures 10A** and **B**.

- *Capnography waveform with up-sloping plateau phase*: It signifies bronchospasm, airway is partially blocked or that the endotracheal tube has migrated beyond the carina and into a main bronchus.
- *Capnography waveform with a peaked, triangular appearance*: This suggests that there is a significant leak around the tracheal tube or tracheostomy.
- *Flat capnography trace*: This suggests one of the following:
  - The esophagus has been mistakenly intubated instead of the trachea.
  - The tracheal tube or tracheostomy has become displaced.
  - The breathing circuit has become disconnected.
  - The airway has become obstructed: with secretions, or tracheal tube bitten by patient and occluded.
- *A sudden drop in $ETCO_2$, but with a square wave capnography trace still seen*, suggests a sudden drop in lung perfusion, either caused by an obstruction to blood flow through the lungs (caused by thrombus, air or fat) or by a reduction in cardiac output. When $ETCO_2$ falls because of reduced pulmonary perfusion, the arterial CO_2 will rise due to the inability of the lungs to excrete CO_2. The clinician may need to give consideration to increasing alveolar ventilation in this circumstance.
- *A steady increase in the $ETCO_2$ value, again with a square wave trace*, suggests hypoventilation, but may rarely represent malignant hyperpyrexia if associated with rise in temperature (malignant hyperthermia).

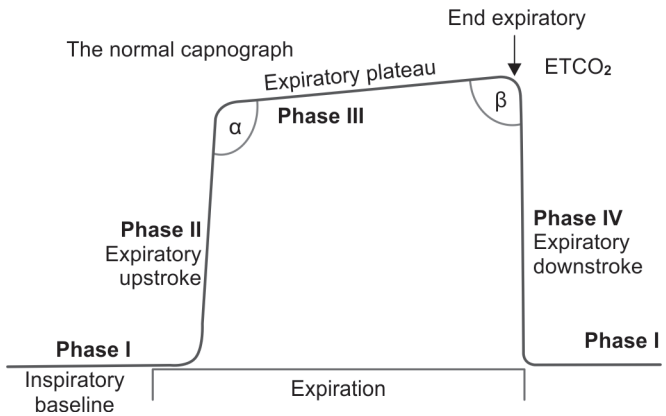
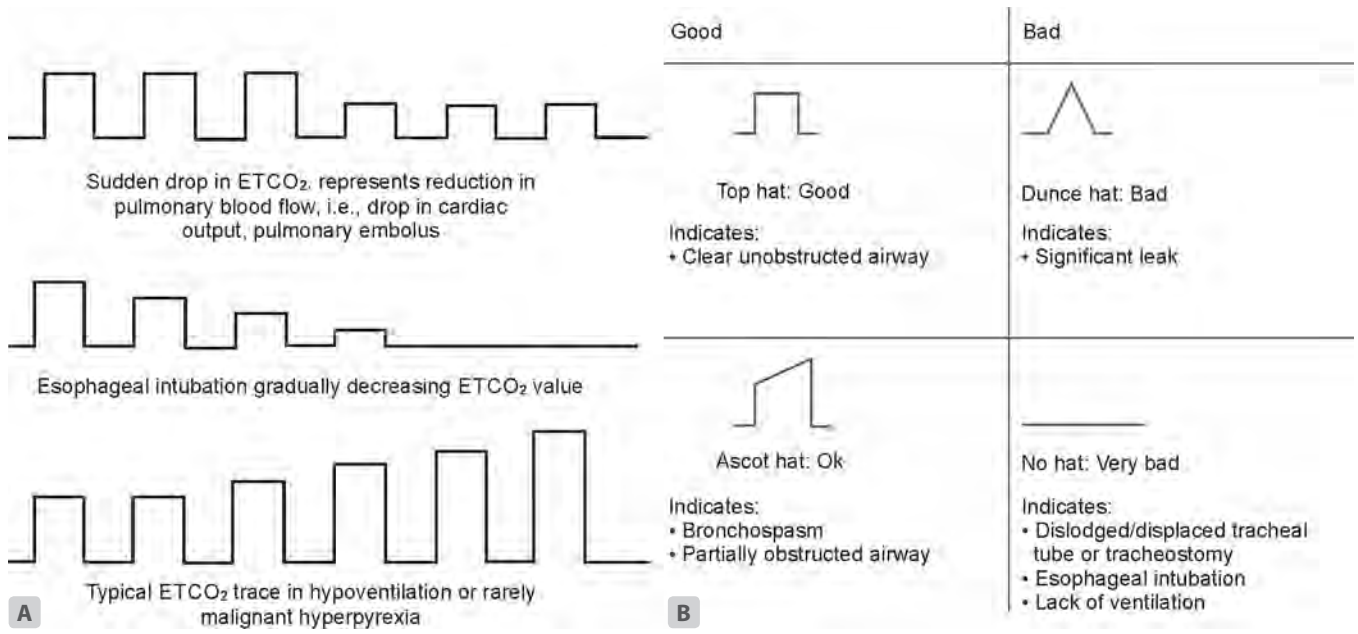


FIG. 9: Morphology of normal capnography wave.

SUMMARY

All emergency physicians must be aware about advanced airway management skill. During resuscitation of medical and trauma patients, timely and effective airway interventions are a critical procedure. In ED which is always considered as



FIGS. 10A AND B: Morphology of capnography (A) critical $ETCO_2$ wave; (B) "hats and caps" in $ETCO_2$ trace.

an uncontrolled environment, especially in crashed airway scenario, it will be like "do or die" situation. Nowadays, emergency clinicians have a wide range of new options for improving airway management skills few examples are various airway techniques and procedures combined with recent advances in RSI, video laryngoscopy, and further advanced airway techniques.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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33 CHAPTER

Cardiopulmonary Resuscitation

Mabel Vasnaik

INTRODUCTION

Cardiopulmonary resuscitation (CPR) is a skill every physician should master, particularly physicians in an emergency department. In the event of a cardiorespiratory arrest, a systematic approach to resuscitation and early restoration of spontaneous circulation greatly improves the prognosis of the patient. Cardiac arrest is the cessation of cardiac mechanical activity. It is a clinical diagnosis, confirmed by unresponsiveness, absence of a detectable central pulse, and apnea (agonal respiration). Three types of rhythms can be seen during a cardiac arrest.

1. Ventricular fibrillation (VF) or ventricular tachycardia without a pulse (pulseless VT)
2. Asystole
3. Pulseless electrical activity (PEA)

A cardiorespiratory arrest can be either an in hospital or an out of hospital arrest. Patients who are in the hospital can arrest if they are critically ill with serious cardiac, respiratory, and metabolic conditions. The algorithmic approach to resuscitation increases the chance of return of spontaneous circulation (ROSC) in these patients. A large number of cardiorespiratory arrests are out of hospital arrests and occur either at home, in the workplace, on the road, in an open space or in an ambulance en route to a hospital. Most out of hospital cardiac arrests are sudden and unexpected and most often due to a cardiac or respiratory illness.

The approach to such patients is BLS or basic life support. Checking unresponsiveness along with an initial assessment and management of the circulation, airway and breathing are the components of BLS (*CAB's of resuscitation*). It includes the diagnosis of cardiac arrest, calling for help and actions to restore spontaneous circulation by chest wall compressions, ventilation, and defibrillation if an automated external defibrillator (AED) is available. BLS has to be started at the scene of arrest and continued till the patient reaches a hospital or an ambulance. Once the patient reaches a hospital or if the ambulance is well-equipped with drugs, advanced airway equipment, and a defibrillator, ACLS or advanced cardiac life support is performed.

Basic life support and ACLS are two ends of the resuscitation spectrum. ACLS is an extension of BLS and includes BLS plus advanced techniques such as endotracheal intubation, intravenous (IV) drugs, defibrillation, etc. Well-performed BLS and ACLS are essential in order to achieve early ROSC and give the patient the best chance of survival.

STEPS OF RESUSCITATION

Step I: Assessment of Responsiveness

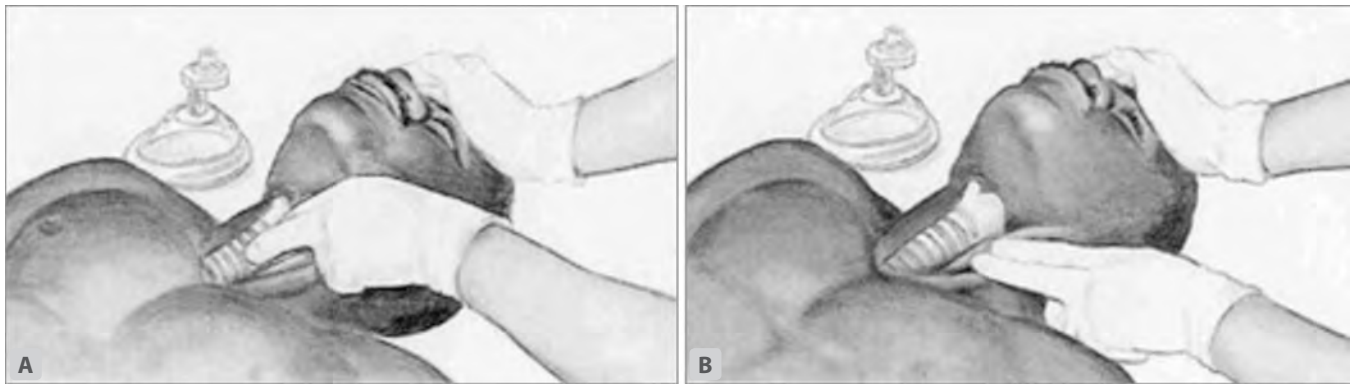
After assessing scene safety, assess responsiveness by gently shaking and calling. If not responsive call for help and an AED/defibrillator. After calling for help, position the patient on a firm, flat surface. Check for breathing by looking for chest rise and also for a carotid pulse simultaneously. If the patient is not breathing or only gasping and there is a pulse, give the patient rescue breaths at the rate of 10–12 breaths/min. If there is no breathing or only gasping and no carotid pulse then start CPR immediately (**Figs. 1A** and **B**).

Step II: Cardiopulmonary Resuscitation

- Give the patient 30 chest compressions at a rate of 100–120 compressions a minute (**Fig. 2**). The chest should be compressed to at least 5 cm depth. The chest should completely recoil after each compression and there should be minimum interruptions in chest compressions. After chest compressions open the airway with a head tilt, chin lift maneuver (**Fig. 3**).
- One hand is placed on the forehead to tilt (extend) the head. Two fingers of the rescuer's other hand lift the mandible outward by lifting the chin.
- If a cervical spine injury is suspected, do only the jaw-thrust maneuver (**Fig. 4**). Use two or three fingers of each hand to lift the jaw, while the remaining fingers guide the jaw upward and outward.

The above two maneuvers ensure airway patency.

- Give two breaths to make the chest rise.
- Use a pocket mask or any other barrier device if available to give the breaths. In an ambulance or hospital breaths are delivered with an artificial mechanical breathing unit (AMBU) bag and a mask connected to oxygen.



FIGS. 1A AND B: Determining pulselessness. (A) Locate the larynx while maintaining the head-tilt position (top). (B) Slide your fingers into the groove between the trachea and the muscles at the side of the neck where the carotid pulse can be felt (bottom).

FIG. 2: External chest compression. Locate the correct hand position on the lower half of the sternum; proper position of the rescuer, with shoulders directly over the victim's sternum and elbows locked. Note that the body weight of the rescuer falling forward provides the force to depress the sternum. The sternum should be depressed approximately 1.5–2 inches.

Courtesy: Sinoy Jose.

FIG. 3: Head tilt and chin lift maneuver.

FIG. 4: Jaw thrust maneuver.

Courtesy: Dr Amit Nabar.

- In case, you do not have a mask or any other barrier device, then do mouth-to-mouth resuscitation.
- Each breath should be delivered over 1 second and sufficient time should be given for exhalation between the breaths. Chest compressions should be resumed in <10 seconds.
- Keep alternating 30 chest compressions with 2 breaths.
- Five sets of 30 compressions and 2 breaths should take approximately 2 minutes.
- At the end of two minutes switch compressors in order to avoid compressor fatigue.

Step III: Defibrillation

The following rhythms are observed during a cardiopulmonary arrest.

- *Ventricular fibrillation/pulseless VT:* These are the most common rhythms seen in victims of cardiac arrest the incidence being up to 80% of adult cardiac arrests.
- *Asystole:* There will be a flat line on the electrocardiogram (ECG) monitor.
- *Pulseless electrical activity:* There will be electrical complexes seen on the ECG monitor (other than VF or VT) in the absence of a palpable carotid pulse and other signs of life.

Defibrillation is the only effective treatment for VF/pulseless VT. The sooner the patient is defibrillated the better are the chances of the shock being effective. If the shock is

delivered in the first minute of cardiac arrest, the chances of the shock being successful are up to 80%. For every minute delay in defibrillation, the chances of the shock being effective reduce by 8–10%. Hence if a shock is delivered after around 12 minutes after a cardiac arrest, the chances of the shock being effective is nearly nil. However, if the patient is receiving CPR then the time for responsiveness of the heart to a shock is increased. In the event of asystole or pulseless electrical activity (PEA), CPR should be continued while efforts are on to identify the cause of cardiac arrest. Defibrillation is not indicated in these situations as it stuns the myocardium and reduces the chances of recovery. The two types of defibrillators in use are the AED and the manual defibrillator.

Automated External Defibrillator

Since it is very important to shock a patient immediately after the onset of VF and pulseless VT a defibrillator should be readily available at all times and in all places. Unfortunately, very few people have a cardiac arrest in a hospital as most cardiac arrests occur at home, in the neighborhood or in one's workplace. When these arrests occur bystander, CPR has to be started and this is almost always done by nonmedical personnel. Hence the AED was designed so that it could be used by lay people during CPR. The AED is a computerized device which is able to recognize whether the cardiac rhythm is shockable or nonshockable. It uses voice and visual prompts to particularly guide lay providers to defibrillate a patient safely. Method of operating an AED is as follows:

- When a patient is diagnosed to be having a cardiac arrest, CPR is begun and an AED is immediately asked for.
- The AED has to be switched on. As soon as it is switched on the voice prompts begin.
- The pads have to be applied on to the bare chest and the AED starts analyzing the heart rhythm. During the analysis, the patient should not be touched and hence CPR has to be momentarily stopped.
- If the rhythm is shockable, the button that is used to shock the patient is highlighted and the voice prompts the rescuer to press that button. The shock is then delivered. After delivery of the shock, CPR has to be continued for a further five cycles or 2 minutes after which the AED will reanalyze the heart rhythm. The cycle thus continues.
- Once the AED paddles have been applied, they should not be removed throughout the resuscitation. Every two minutes the AED paddles continue to analyze the rhythm.
- The AED paddles are disposable, hands free paddles that stick on to the surface of the chest. They act as electrodes as well as deliver a shock to the patient.

Manual Defibrillator

Manual defibrillators are available in an ambulance or hospital setting. Method of defibrillation is as follows:

- In an unresponsive patient, the first step is to call for help as well as a defibrillator.
- As soon as the defibrillator arrives, it is switched on, put on paddle mode and paddles are applied on to the chest. One paddle is applied below, the right clavicle and the second paddle in the left axilla and a quick look at the rhythm is obtained.
- If the rhythm is a VF or a pulseless VT, the defibrillator is charged to 200 Joules and a shock is delivered to the patient. Before delivering the shock, it is important to make sure that the person delivering the shock and everyone else performing the resuscitation are not in contact with the patient or the bed.
- As soon as the shock is delivered, CPR is continued.
- Every 2 minutes or after every five cycles of 30 chest compressions and 2 breaths, the rhythm is reanalyzed and a shock is delivered if it is still a shockable rhythm.
- The strength of the first shock and every subsequent shock is 200 Joules.
- There is no upper limit to the number of shocks that can be delivered. The patient needs to be defibrillated as long as a shockable rhythm continues.
- Before shocking the patient, sufficient electro gel needs to be applied on to the paddles in order to overcome the resistance of the chest wall.
- The paddles need to be pressed onto the chest wall with a force of 25 pounds/sq inch in order to overcome the impedance of the chest wall.

Step IV: Intravenous Access and Drugs

Cannulate a peripheral vein, preferably a vein of the upper limb, with a 16 gauge IV cannula, and administer drugs through it. Elevating the arm and flushing the cannula with a bolus of 20 mL of normal saline helps the entry of the drug into the central circulation. If an IV access cannot be obtained drugs can be given through an intraosseous (IO) route. Drugs used in CPR are as follows:

- *Adrenaline*:
  - Adrenaline is indicated in all types of cardiac arrests.
  - *Dose*: 1 mg IV every 3–5 minutes as long as CPR is continued.
- *Antiarrhythmic drugs*: Antiarrhythmic drugs are indicated during CPR in patients with a cardiac arrest due to a VF or pulseless VT when defibrillation and adrenaline have failed to restore a normal perfusing rhythm.
  - *Amiodarone*: The first dose is 300 mg diluted in 20 mL of 5% dextrose IV bolus. The second dose is 150 mg which is given after 3–5 minutes for persistent VF/VT.
  - *Lignocaine*: In case amiodarone is not available, lignocaine may be administered. The first dose is 1–1.5 mg/kg IV bolus. The second and subsequent doses are 0.5–0.75 mg/kg at 5–10-minute intervals to a maximum dose of 3 mg/kg.
  - *Magnesium sulfate*: This drug is used in the presence of torsades de pointes. The loading dose is 1–2 g IV diluted in 10 mL of 5% dextrose or normal saline given over 5–20 minutes. Routine administration of magnesium sulfate in cardiac arrest patients is not recommended.

Step V: Advanced Airway

The airway should be secured by using either an endotracheal tube or a supraglottic advanced airway device. See Chapter 32 for detail about advanced airways. Proper endotracheal tube placement should be confirmed. End-tidal capnometry can be used if available. After securing an advanced airway ventilation and chest compressions are done independently of each other. The patient is ventilated around 10 times a minute and continuous chest compressions are given at 100–120 times a minute.

Checking for Reversible Causes

While performing CPR one should simultaneously check for the cause of the cardiac arrest many of which are reversible. The common reversible causes leading to a cardiac arrest are summarized in the pneumonic 5 H's and 5 T's. The 5 H's are hypoxia, hypovolemia, hypo- or hyperkalemia, hypothermia, and hydrogen ion excess or acidosis. The 5 T's are tension pneumothorax, cardiac tamponade, cardiac or pulmonary thrombus, and toxins. Ultrasound can be used without interrupting CPR to identify some of the above causes. It is important to quickly identify and treat the underlying cause during CPR itself in order to obtain ROSC.

Importance of Team Effort

Successful CPR requires good team effort. The members of the team should all be well versed with the steps of CPR. There should be good coordination and communication within the members of the team.

POSTCARDIAC ARREST CARE

Once perfusing rhythm is restored, postcardiac arrest care is very important to sustain the spontaneous circulation and to prevent a rearrests. Post-ROSC care is summarized in **Table 1**.

- Adequate oxygenation (supplemental oxygen, endotracheal intubation, and assisted ventilation)
- Adequate circulation (IV fluids and infusion with one of the vasopressors given below):
  - IV epinephrine (0.1–0.5 μg/kg/min)
  - IV dopamine (5–10 μg/kg/min)
  - IV norepinephrine (0.1–0.5 μg/kg/min)
- 12-lead ECG to find out if there is a myocardial infarction.
- To protect the brain in patients who are not conscious, targeted temperature management should be done. The patients' temperature should be maintained between 32°C and 36°C for at least 24 hours. This is most often done by infusing ice-cold fluids postresuscitation. Other surface cooling measures can also be used.
- Treat the underlying cause
- Relevant investigations should be done (arterial blood gas, complete blood count, electrolytes, renal functions, blood sugar, and chest X-ray).
- Monitoring O_2 saturation, ECG, central venous pressure (CVP), blood pressure (BP), and urine output
- Measures to support other organ systems
- Reassessment of the patients' history and physical examination
- All resuscitated patients should be transferred to an intensive care unit for further monitoring and treatment.

TABLE 1: Post-ROSC checklist.

System	*Intervention*
Airway	• Intubation • Ventilation • Tidal Volume @ 6–8 mL/kg • Placement of nasogastric/orogastric tube • Chest X-ray
Breathing	• Adjust PEEP FiO_2 to achieve saturation >94% • Adjust respiratory rate to achieve $EtCO_2$ 30–40 mm Hg
Circulation	• 12-lead ECG activate cardiac catheterization laboratory • Cardiology consultation • Place central and arterial line • Goal SBP > 90 mm Hg (MAP—65 mm Hg) • Use of fluid noradrenaline adrenaline infusion • Point of care ultrasound for cardiac lung and IVC view • Send laboratory investigation ABG serum lactate • Place foleys catheter (Goal UO 1 mL/kg/h) • Rule out PE by CT chest angiography
Disability	• Begin cooling • Targeted temperature management—32–36°C • Consider CT heat

(ABG: arterial blood gases; MAP: mean arterial pressure; PEEP: positive end expiratory pressure; ROSC: return of spontaneous circulation; SBP: systolic blood pressure)

CARDIOPULMONARY RESUSCITATION IN CHILDREN-HOW IS IT DIFFERENT?

Classification in Children

1–28 days of life: Neonate, we will not be discussing CPR in a neonate in this chapter. *28 days–1 year Infant***:** *1 year to onset of puberty-child (*onset of puberty is taken as appearance of axillary hair in a male and breast development in a female). CPR is done in the same manner as adults in infants and children with a few exceptions which are given below.

- *Step 1*: *Calling for help after assessing responsiveness (common for infant and child)*:
  - *Witnessed arrest*: If the rescuer is present when the child has collapsed then he calls for help after assessing unresponsiveness and then only starts CPR.
  - *Unwitnessed arrest*: If the rescuer enters a room and finds that a child has collapsed and is unresponsive, he first gives 2 minutes of CPR. After 2 minutes of CPR he calls for help.
- *Step 2*: *Pulse check*:
  - *Infant*: The brachial artery in the arm is palpated to look for a pulse.
  - *Child*: The carotid or femoral artery is palpated to look for a pulse.
- *Step 3*: *Chest compressions*:
  - *Hand placement*:
    - *Infant*: Hand placement varies depending whether it is single rescuer or two-rescuer CPR. In single rescuer, CPR chest compression is done one finger's width below the intermammary line using the middle and ring fingers (**Fig. 5**). Sternal compression is performed by the "two-thumb-encircling hands" technique in two-rescuer CPR (second rescuer taking care of the airway) (**Fig. 6**).
    - *Child*: Compressions should be performed with the heel of one hand over the lower half of the sternum. If it is a bigger child two hands can be used as in adults.

FIG. 5: Chest compressions in infants. Single rescuer CPR—two finger sternal compressions.

FIG. 6: Chest compressions in infants. Two-rescuer CPR—the "two-thumb-encircling hands" chest compression technique.

Courtesy: Sinoy Jose.

  - *Compression depth*:
    - *Infant*: At least one-third of the AP diameter of the chest (1.5 inches or 4 cm)
    - *Child*: At least one-third of the AP diameter of the chest (2 inches or 5 cm)

In an unresponsive infant or child with adequate breaths but a pulse rate <60 beats per min starts chest compressions with ventilations.

- *Ventilation*
- *Breathing techniques*: In infants, mouth-to-mouth and nose technique are preferred. However, if one cannot cover the infant nose and mouth with your mouth then the mouth-to-mouth technique can be used.
- *Rescue breathing*: Give 12–20 breaths/min in both infants and children who have a pulse but are not breathing.
- *Compression ventilation ratio*:
  - *Infant*: When there is a single rescuer, it is 30 compressions to 2 breaths. When there are two rescuers, it is 15 compressions and 2 breaths.
  - *Child*: The ratio is 30 compressions and 2 breaths whether, it is single rescuer or two rescuers.
- *Defibrillation*
- *Use of AED*: A pediatric capable AED should be used if available. These are designed to be used both in adults and children and automatically deliver a reduced dose of shock when the pediatric pads are used.
- *Infants*: In infants, a manual defibrillator is preferred to an AED as lower energy joules can be set.
- In case a manual defibrillator is not available then an AED with a pediatric dose attenuator should be used. If not available, then an AED without a pediatric dose attenuator can be used. Child pads should be used. In case, there are no child pads then adult pads can be used but they should be placed on the anterior and posterior surface of the chest so that they do not touch each other.
- *Children <8 years of age*: Use an AED as soon as it is available. An AED with a pediatric dose attenuator is preferred. Use child pads if available. If not available then adult pads can be used on the anterior and posterior surface of the chest.
- *Children 8 years of age of older*: Use and AED as soon as it is available. Use adult pads. Pediatric pads should not be used because they might give too low a dose of shock.
- *Shock dose*: If the AED that is being used cannot deliver the pediatric dose, then the adult dose may be delivered.
- *Use of a manual defibrillator*: If a manual defibrillator is being used, the child pads have to be applied.
- The initial dose of the shock delivered is 2 Joules/kg. The subsequent doses should be 4 Joules/kg or higher. It should not exceed 10 Joules/kg or the standard adult dose.

Drug Dosages in Children during CPR

- *Injection adrenaline*: IV/IO dose: 0.01 mg/kg (0.1 mL/kg of 1:10,000 concentration). Administer every 3–5 minutes during arrest. Note that the maximum dose that can be administered is 1 mg.
- *Intraosseous infusion* is used in a child when an IV access is not available. The flat anteromedial surface of the tibia, approximately 1–3 cm below the tibial tuberosity is the preferred site for infants and children < 6 years of age, since the marrow cavity in that location is very large and the potential for injury to tissues is minimal.

SPECIAL SITUATIONS

The following precautions need to be taken in the following situations:

- *Trauma*: Unnecessary movement of the head and neck should be avoided when providing CPR to patients with trauma. The airway should be opened using the jaw-thrust technique without extension of the head. While securing a definitive airway, one person should stabilize the head in a neutral position. Manual spinal restriction is preferable to the use of immobilization devices. Spinal immobilization devices can be used during transport.
- *Pregnancy*: When doing chest compressions in a pregnant woman, a wedge should be inserted under the right hip so that there is a left sided tilt. This prevents aortocaval compression and CPR is thus made effective.
- *Cardiopulmonary resuscitation in a highly infectious patient (e.g., patient who is infected with COVID-19)*: When approaching a patient who is suffering from a highly infectious condition, it is important that the

healthcare providers take adequate precautions to protect themselves and their colleagues from exposure. This is very relevant when faced with a pandemic situation. *Certain precautionary measures to prevent exposure*:

- Before approaching the patient and beginning the resuscitation, all healthcare personnel should don personal protective equipment that protects both against contact with airborne as well as droplet particles.
- Minimum number of healthcare personnel should be involved in the resuscitation.
- All healthcare providers in the vicinity should be informed about the infected state of the patient.
- Resuscitation can be attempted in a separate area reserved for the same, if possible. It would be beneficial if such an area was provided with negative suction facilities.
- Manual chest compressions can be replaced with mechanical CPR devices, if available as this will reduce rescuer fatigue.
- Early intubation as bag mask ventilation is a highly aerosol producing procedure.
- Passive oxygenation with nonrebreathing face mask can be used as an alternative to bag mask ventilation.
- Connect a high-efficiency particulate air (HEPA) filter when ventilating the patient.
- A person who is skilled in intubation should intubate the patient as failed intubation increases the chances of aerosol generation.
- Video laryngoscopy if available can be used.
- Chest compressions should be paused during intubation.
- Feasibility of resuscitation should be taken into account and prolonged resuscitation should not be attempted in patients who have a very poor prognosis.

DEFIBRILLATION

A defibrillator is a device that administers a controlled electrical shock to patients to terminate a cardiac arrhythmia. The technique of administering the electrical shock is usually referred to as defibrillation, if it is used to terminate VF or cardioversion if it is given for unstable patients with arrhythmias such as atrial fibrillation, atrial flutter, supra-VT, or VT with a pulse. A direct current defibrillator consists of a variable transformer allowing the operator to select a variable voltage potential, an AC to DC converter that includes a capacitor to store the energy, a charge switch that allows the capacitor to charge, and discharge switches to complete the circuit from the capacitor to the electrodes.

Importance of Early Defibrillation

The most frequent initial rhythm in sudden cardiac arrest in adults is VF. The only effective treatment for VF is electrical defibrillation. The probability of successful defibrillation diminishes rapidly over time. Hence defibrillation should be performed as soon as a VF is detected. The probability of successful defibrillation and subsequent survival to hospital discharge is directly related to the time interval between the onset of VF and delivery of the first shock. VF tends to convert to asystole within a few minutes. CPR should be performed while waiting for the defibrillator as it appears to prolong VF and contributes to preservation of heart and brain function.

Energy, Current, and Voltage

A defibrillation shock passes a large flow of electrons through the heart over a brief period. This flow of electrons is called current, which is measured in amperes. The pressure pushing this flow of electrons is referred to as the electrical potential, and potential is measured in volts. There is always a resistance to this flow of electrons, which is called impedance, measured in ohms. In short, electrons flow with a certain pressure for a certain period of time, (usually milliseconds) through a substance that has resistance. Although the operator selects the shock energy in joules, it is the current flow in amperes that actually defibrillates. With a constant amount of energy stored in the capacitor, the delivered current depends on the impedance (resistance) present between the defibrillator electrodes.

Transthoracic Impedance

Defibrillation is accomplished by passage of sufficient electric current (amperes) through the heart. The energy chosen (joules) and the transthoracic impedance (ohms), or resistance to current flow, determine the current flow. Factors that determine transthoracic impedance include energy selected, electrode size, paddle-skin coupling material, number and time interval of previous shocks, phase of ventilation, distance between electrodes (size of the chest), and paddle electrode pressure. The average adult human impedance is approximately 70–80 ohms. When transthoracic impedance is too high, a low energy shock will not generate enough current to achieve defibrillation. To reduce transthoracic impedance, the defibrillator operator should always press firmly on handheld electrode paddles and use a gel or cream or saline-soaked gauze pads between handheld electrode paddles and the chest. Self-adhesive monitor defibrillator electrode pads do not require additional pressure. Use of bare hand-held paddles without a coupling material between electrodes and the chest wall creates high transthoracic impedance. Male patients with a hirsute chest have poor electrode to chest contact plus air trapping. This results in high impedance with occasional arcing. Although extremely rare, in an oxygen rich environment such a critical care unit this arcing has been known to produce fires if an accelerant is present.

Electrode Position

The electrodes should be placed in positions to maximize current flow through the myocardium. The standard placement is one electrode just to the right of the upper sternal border below the clavicle. The second electrode should be placed to the left of the nipple with the center of the electrode in the midaxillary line (**Fig. 7**). An acceptable alternative is to place the apex paddle anterior, over the left precordium and the other paddle-labeled sternum posterior to the heart in the right infrascapular location. Care should be taken to see that the electrodes are well separated and that paste or gel is not smeared on the chest between the paddles, because the current may follow a superficial pathway along the chest wall, missing the heart. When performing cardioversion or defibrillation in patients with permanent pacemakers or implantable

FIG. 7: Chest pads placement for defibrillation and cardioversion. *Courtesy*: Sinoy Jose.

cardioverter defibrillators (ICDs), electrodes should not be placed near the device generator, because defibrillation can cause malfunction. A pacemaker or ICD also may block some current to the myocardium during defibrillation, delivering suboptimal energy to the heart. Finally, because some of the defibrillation current flows down the pacemaker lead, the pacing threshold should always be evaluated aftershocks are given to patients with permanent pacemakers. ICD function also should be evaluated.

Electrode Size

In general, the larger the electrode, the less the impedance, but too large an electrode can result in inadequate contact with the chest or a large portion of the current traversing extracardiac pathways and missing the heart. For adults most defibrillation electrodes range from 8.5 to 12 cm in diameter and these are effective. Infants and children require smaller electrodes. However, high transthoracic impedance in children is found when small pediatric paddles are used. Thus larger adult paddles should be used as soon as the paddles will fit completely on the child's chest. This transition occurs at approximately 10 kg, the average weight of a 1-year-old child.

Principle of Working

Massive amounts of electrical energy are delivered by defibrillator shocks over a few milliseconds. This electrical energy passes between the positive and negative defibrillator paddles placed on the chest wall and passes through the fibrillating heart. The current flow totally depolarizes the entire myocardium and produces a complete electrical silence. This allows spontaneously repolarizing pace making cells within the heart to recover. The regular cycles of repolarization and depolarization of these pacemaker cells allow coordinated contractile activity to resume if the cells are not damaged. Although the defibrillator operator selects the shock energy in joules it is the current flow in amperes through the heart that actually defibrillates the patient. Hence defibrillation is achieved by generating an amplitude of current flow which is sustained for a time interval. *Shock energies*: The recommended energy for shocks is 200 Joules.

Indications for Defibrillation

The only indication for defibrillation is a VF and a pulseless VT during a cardiac arrest. Successful defibrillation depends on the electrical and metabolic state of the myocardium, the amount of myocardial damage that has occurred during the arrest, the prior functional state of the heart and the cause of the VF. Prolonged VF exhausts the energy stores of ATP in the myocardium, particularly from the cardiac pacemaker cells. Hence the longer the VF persists, the energy stores will be depleted and there will be a lot of myocardial deterioration. Therefore, the myocardium will not respond to defibrillation and shocks will not be effective. Hence it is very important to shock the patient as soon as possible after a VF before depletion of ATP and myocardial damage occurs.

Procedure for Defibrillation

- The patient should be placed in a safe environment, away from pooled water or a metal surface under either the patient or the rescuer.
- Electrode gel or paste should be applied to the hand-held electrodes or readymade electrode pads should be used.
- The defibrillator should be turned on.
- An energy level of 200 Joules should be selected to shock a VF or pulseless VT.
- The capacitor should be charged.
- The electrodes should be properly placed on the chest, one electrode below the right clavicle and the other over the apex. Firm pressure should be applied over hand-held paddle electrodes. There should be no smearing of the coupling material between the paddles, as the current may preferentially follow this low resistance pathway along the chest wall, missing the heart. Any transdermal medication patches should be removed.
- No personnel should be directly or indirectly in contact with the patient. If ventilation via a bag mask device or endotracheal tube is being performed, the rescuer should step back and momentarily release the bag. It is unnecessary to disconnect a bag from an endotracheal tube if the tube is well secured.
- The electric shock should be delivered by depressing both discharge buttons simultaneously.
- *Disarming the defibrillator*: Once the defibrillator has been charged, if one does not wish to deliver the shock as the rhythm is not shockable, the disarm button on the defibrillator needs to be pressed in order to remove the charge.
- *False asystole*: An asystole should not be defibrillated. However, occasionally a VF can present as a false asystole due to technical errors such as no power, leads unconnected, gain set to low, or incorrect lead selection.

Monophasic and Biphasic Defibrillators

Defibrillators deliver energy or current in waveforms. The two broad categories of waveform are monophasic and biphasic.

1. *Monophasic defibrillators*: Monophasic defibrillators deliver energy in monophasic waveforms. Monophasic waveforms deliver current in primarily one direction. Monophasic defibrillators require high levels of energy to be delivered, namely 360 Joules for the first shock as well as for every subsequent shock.

2. *Biphasic waveform defibrillators*: Biphasic waveform defibrillators developed recently and approved for clinical use. Monophasic waveforms deliver current in one direction. Biphasic waveforms in contrast, deliver current that flows in a positive direction for a specified duration. The current then reverses and flows in a negative direction for the remaining milliseconds of the electrical discharge. Biphasic waveforms have proved superior to monophasic waveforms for defibrillation by implantable defibrillators. Current research confirms that biphasic shock energies ≤200 Joules are safe and effective. Nonescalating biphasic energies appear to have success rates for VF termination equivalent to or better than monophasic shocks that increase in energy for each shock.

The postresuscitation arrhythmias seen are much less with the biphasic defibrillators and hence these defibrillators have replaced the monophasic ones.

Charging the Battery of the Defibrillator

Every defibrillator has a battery and the shock is delivered from this battery. Hence it is important to make sure that the battery is always well charged for the shock to be properly delivered. The power cord of the defibrillator should be connected to the main power supply with the defibrillator in the switched off mode. This ensures that the battery of the device is being charged. The defibrillator should be checked every day to make sure that it is in a proper working condition and that the battery is charged.

Pediatric

In children, separate pediatric paddles have to be applied which are smaller in size. The pediatric paddles are applied in the same place as in adults. The first shock delivered in case of a VF or a pulseless VT is 2 Joules/kg body weight and the second and subsequent shocks are 4 Joules/kg body weight.

Special Situations

- In case a person is sweating profusely or has been rescued from water, the anterior surface of the chest needs to be wiped before applying the paddles as the current will pass from one paddle to another and not through the heart as water is a good conductor of electricity.
- A medicine patch needs to be removed from the chest if present before the shock is delivered for fear of a burn occurring.
- In case of an implantable pacemaker or ICD being in place, the paddles need to be placed at least 2.5 inches away from the device. If placed closer, the ICD may block some current to the myocardium during defibrillation causing delivery of suboptimal energy to the heart.
- In addition to the special situations mentioned above, in case of a patient with a hairy chest, the hair should first be shaved before the paddles are applied, or else the pads will not be able to stick firmly to the chest wall and rhythm analysis will not be possible.
- *Pediatric patients*: AED's have a separate pediatric mode as well as smaller pediatrics pads to be applied on children. The preset joules in the pediatrics mode are less than that in an adult patient. The pediatric pads in children are applied in the same position as in adults. Since they are disposable adhesive pads they can also be applied on the anterior surface of the chest and posteriorly over the back.

CARDIOVERSION

Cardioversion is the delivery of a synchronized shock to a patient who has an unstable tachyarrhythmia. The shock is synchronized with the QRS complex of the ECG. This is achieved by pressing the sync button present on the defibrillator. Synchronization avoids delivery of the shock during the relative refractory period of the cardiac cycle, when a shock itself can push the myocardium into a VF.

Principle of Working

Reentry rhythms are caused by an abnormal rhythm circuit which allows a wave of depolarization to travel in a circuit, recirculating the same path over and over again. Delivery of a shock can stop these rhythms because a shock interrupts the circulating pattern. *Cardioversion is indicated for unstable tachyarrhythmias* such as supra-VT, atrial flutter and fibrillation, and VT with a pulse.

Cardioversion requires much lower energy levels to be delivered than defibrillation as the cardiac rhythm is an organized rhythm and not a disorganized rhythm as occurs in a VF. *Quantum of synchronized joules for the different arrhythmias are*: Supraventricular tachycardia—50–100 Joules: *Atrial fibrillation*—120–200 Joules: *Atrial flutter*—50–100 Joules*: VT with a pulse*—100 Joules

Steps of Cardioversion

- Once a tachyarrhythmia has been diagnosed and the patient has been found to be unstable the defibrillator is switched on and ECG leads are attached to the patient.
- Consent is obtained from the patient or his attenders for the procedure.
- The crash cart with resuscitation drugs and airway equipment is kept at the bedside in case of an untoward event requiring resuscitation.
- The patient is given an adequate dose of a sedating agent as well as analgesia as the shock can be very painful.
- The sync button of the defibrillator is switched on, the paddles are applied to the patient after applying electrogel.
- The required amount of joules is selected, the device is charged, it is made sure that neither the operator nor anyone else is touching the patient, and the bed and the shock is delivered.
- In case the rhythm has not reverted, another shock is delivered with increased number of joules as indicated for the rhythm.
- After the shock is delivered, sync button is switched off.
- The heart rate and the BP are recorded.

Atrial Fibrillation

The recommended initial energy for cardioversion of atrial fibrillation is 100–200 Joules. Atrial flutter and paroxysmal supraventricular tachycardia (PSVT) generally require less energy. An initial energy of 50–100 Joules is often sufficient with stepwise increases in energy if initial shocks fail.

Ventricular Tachycardia

The amount of energy required for cardioversion of VT depends on the morphological characteristics and rate of the arrhythmia. Monomorphic VT (regular form and rate) with or without a pulse responds well to cardioversion shocks at initial energies of 100 Joules. Polymorphic VT (irregular morphology and rate) responds similarly to VF, the initial shock energy should be 200 Joules. The shocks can be increased stepwise, if the first shock fails to cardiovert. The energy delivered should be synchronized with the QRS complex to reduce the possibility of inducing VF, which can occur when a shock hits the relative refractory portion of the cardiac cycle. Synchronization to prevent this complication is recommended for hemodynamically stable wide complex tachycardia requiring cardioversion, supra-VT, atrial fibrillation, and atrial flutter. VF requires unsynchronized defibrillation mode. It is important to note that synchronization in VT may be difficult and misleading because of the wide complex and variable forms of ventricular arrhythmia. The VT patient who is pulseless, unconscious, hypotensive, or in severe pulmonary edema should receive unsynchronized shocks to avoid the delay associated with attempts to synchronize. The healthcare provider should be prepared to deliver another unsynchronized shock within seconds, if VF or pulseless VT remains or recurs. The defibrillator is used both for defibrillation as well as for cardioversion. One should make sure that the sync button is removed after each cardioversion so that in case the patient goes into a pulseless rhythm it is possible to defibrillate the patient. It is not possible to defibrillate a patient when in the sync mode.

RECENT ADVANCES

Current-based defibrillation and other cardiac arrhythmias can be terminated by electric shock when sufficient current passes through the myocardium. A promising alternative approach to defibrillation is the use of electric current amperes instead of energy joules. This approach would prevent attempts to deliver inappropriately low energy levels to a patient with high impedance. Current-based therapy would also prevent high energy shocks to patients with low impedance which result in excessive current flow, myocardial damage, and failure to defibrillate.

Implantable cardioverter defibrillators—certain high-risk patients with cardiac arrhythmias are implanted with a device that can pace, detect a cardiac arrhythmia and automatically perform defibrillation or cardioversion. These devices are called implantable cardioverters/defibrillators. They protect the patient from undergoing a cardiac arrest by intercepting and pacing or cardioverting an arrhythmia. Also in case the patient has a cardiac arrest, it can recognize a shockable rhythm and defibrillate the patient.

RECENT UPDATES ON CARDIOPULMONARY RESUSCITATION

The American Heart Association (AHA) guidelines for adult, pediatric, and neonatal, resuscitation is revised in year 2020. These guidelines are helpful for the resuscitation providers and instructors during cardiac arrest resuscitation and also result in changes in resuscitation training and practice. The changes in the 2020 AHA Guidelines for CPR summarize below.

- Easy to remember resuscitation scenarios, algorithms, and visual aids guidance for BLS and advanced cardiovascular life support (ACLS) are developed.
- Re-emphasis is given on the importance of early initiation of CPR by lay rescuers
- Early epinephrine administration has been reaffirmed with emphasis like previous guidelines.
- Use of real-time audio-visual feedback is suggested as a means to maintain CPR quality.
- To improve CPR quality, continuous measure of arterial blood pressure and end-tidal carbon dioxide ($ETCO_2$) during ACLS resuscitation is emphasized.
- Routine use of double sequential defibrillation is not recommended as per recent evidences.
- For medication administration during ACLS resuscitation, IV access is the preferred route but IO access is acceptable if IV access is not available.
- After ROSC, patient care requires close attention to oxygenation, blood pressure control, evaluation for percutaneous coronary intervention, targeted temperature management, and multimodal neuroprognostication.
- Post cardiac arrest recovery is long and continues process after the initial hospitalization, patients should have formal assessment and support for their physical, cognitive, and psychosocial needs.
- Debriefing after resuscitation for lay rescuers, EMS providers, and hospital-based healthcare workers is beneficial to support their mental health and well-being.
- Management of cardiac arrest in pregnancy focuses on maternal resuscitation and improves the chances of successful resuscitation of the mother with preparation for early perimortem cesarean delivery if necessary to save the infant.

The changes in algorithms and other performance aids are:

- A sixth link, *recovery,* is added to the "resuscitation"—Chains of Survival (**Fig. 8**).

Early recognition and prevention of causes of cardiac arrest
Activation of Emergency Response System
High quality CPR and Defibrillation
Advanced Resuscitation
Post Cardiac Arrest Care
Recovery

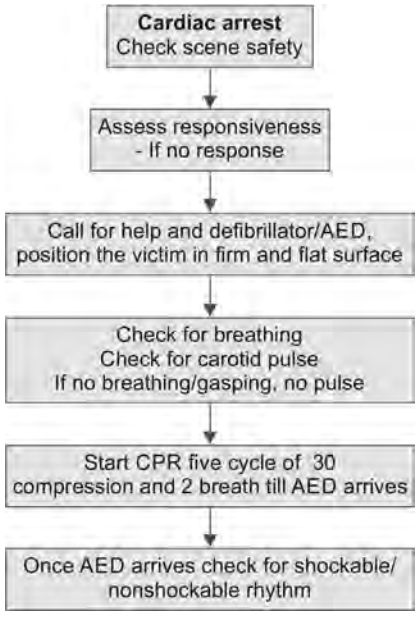
(CPR: cardiopulmonary resuscitation)

FIG. 8: Resuscitation: Updated chain of survival.

- The emphasis is given on the role of early epinephrine administration for patients with nonshockable rhythms in the universal "Adult Cardiac Arrest Algorithm" (modified now).
- Two new algorithms for "opioid-associated emergency" have been added for lay rescuers and trained rescuers
- The Post-cardiac Arrest Care Algorithm was updated to emphasize the need to prevent hyperoxia, hypoxemia, and hypotension.
- In post-cardiac arrest care section, new diagram is added to guide and inform neuroprognostication.
- A new algorithm has been added to address "Cardiac Arrest in Pregnancy."

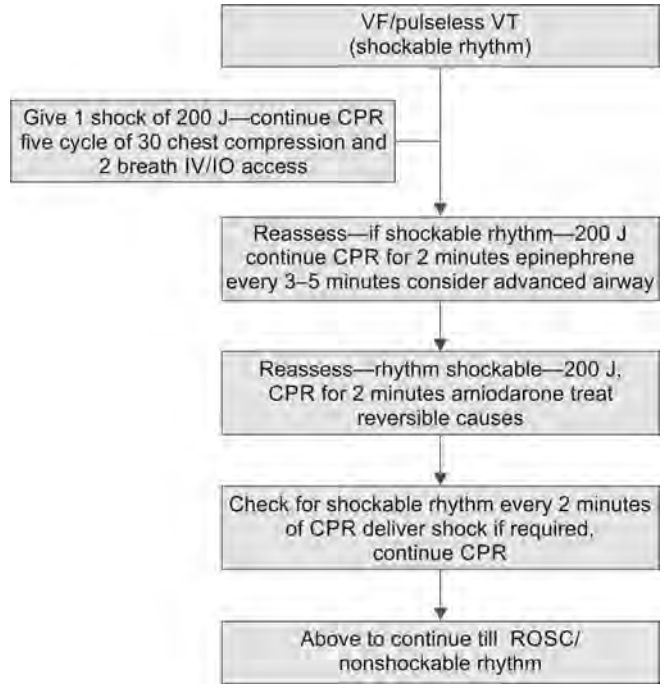
SUMMARY

Cardiac arrest is most often the consequence of serious respiratory and circulatory conditions causing the patient to decompensate. Early recognition of a cardiac arrest and early good quality CPR improve the chances of ROSC. BLS and ACLS are two ends of the same spectrum. The most common rhythm seen during an adult cardiac arrest is a VF. The treatment for VF and pulseless VT is immediate defibrillation. Cardioversion is used for unstable tachyarrhythmias. It is important to press the sync button during cardioversion and to remove it once the shock has been delivered. The defibrillator is a very important device and should be checked on a regular basis to make sure that it is functioning properly. The algorithmic approach to resuscitation (**Flowcharts 1** to **3**) increases the chance of ROSC in cardiac arrest patients. CPR summarized in algorithm for cardiac arrest, VF/pulseless VT, and asystole/PEA.


Cardiac arrest
Check scene safety
Assess responsiveness
- If no response
Call for help and defibrillator/AED,
position the victim in firm and flat surface
Check for breathing
Check for carotid pulse
If no breathing/gasping, no pulse
Start CPR five cycle of 30
compression and 2 breath till AED arrives
Once AED arrives check for shockable/
nonshockable rhythm

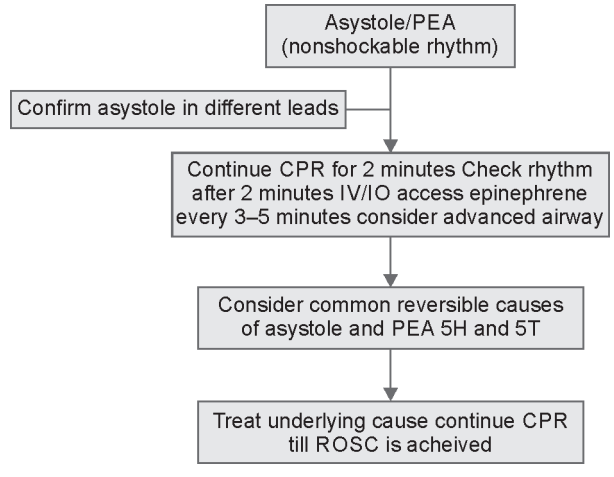
(AED: automated external defibrillator; CPR: cardiopulmonary resuscitation)

FLOWCHART 1: Cardiac arrest.


VF/pulseless VT
(shockable rhythm)
Give 1 shock of 200 J—continue CPR
five cycle of 30 chest compression and
2 breath IV/IO access
Reassess—if shockable rhythm—200 J
continue CPR for 2 minutes epinephrene
every 3–5 minutes consider advanced airway
Reassess—rhythm shockable—200 J,
CPR for 2 minutes amiodarone treat
reversible causes
Check for shockable rhythm every 2 minutes
of CPR deliver shock if required,
continue CPR
Above to continue till ROSC/
nonshockable rhythm

(CPR: cardiopulmonary resuscitation; IV: intravenous; IO: intraosseous; ROSC: return of spontaneous circulation; VF: ventricular fibrillation; VT: ventricular tachycardia)

FLOWCHART 2: Shockable rhythm (VF/VT).


Asystole/PEA
(nonshockable rhythm)
Confirm asystole in different leads
Continue CPR for 2 minutes Check rhythm
after 2 minutes IV/IO access epinephrene
every 3–5 minutes consider advanced airway
Consider common reversible causes
of asystole and PEA 5H and 5T
Treat underlying cause continue CPR
till ROSC is acheived

(CPR: cardiopulmonary resuscitation; IV: intravenous; IO: intraosseous; PEA: pulseless electrical activity; ROSC: return of spontaneous circulation; VF: ventricular fibrillation; VT: ventricular tachycardia)

FLOWCHART 3: Nonshockable rhythm (asystole/PEA).

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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Cardiopulmonary Resuscitation in Special Situation

34 CHAPTER

Jesús Daniel López Tapia, Andrea Pechir Cerrillo

INTRODUCTION

The proper cardiopulmonary resuscitation (CPR) is based on guidelines which outline the proper technique of CPR and the indications on how and when to use it. There are special circumstances which make room for changing the steps and techniques previously established for CPR. The management of this special situation can be divided in three groups: (1) Special causes, (2) Special patients, and (3) Special locations. By mentioning special causes, this refers to those etiologies which are potentially reversible and can cause a cardiac arrest. It is important to recognize these causes due to the high success rates once they are reverted. We can divide them in two groups which are mentioned in **Table 1**.

Special patients are those who have chronic comorbidities or physiological conditions such as pregnancy or advanced age which forces the physician to consider different factors in the decision-making toward management and treatment of these patients. By special locations, we mean those specific places where the universal guidelines must be modified due to environmental factors that may make difficult the usual techniques of CPR.

HYPOXIA

Hypoxia is the reduction of oxygen in the blood usually due to pathological changes in the oxygen-carbon dioxide exchange between the lungs and the air. During these cases, it is essential to use oxygen supplementation while performing CPR. It is recommended the use of capnography to monitor an effective assisted ventilation hoping to maintain values between 10–20 mm Hg when the CPR technique is adequate. Role of oxygen therapy is discussed in detail in Chapter 36.

TABLE 1: Special causes of cardiac arrest: The 4 H's and 4 T's.

4 H's	*4 T's*
Hypoxia	Cardiac tamponade
Hypo-/hyperpotassemia (and other electrolyte abnormalities)	Tension pneumothorax
Hypo-/hyperthermia	Thrombosis (Coronary, pulmonary)
Hypovolemia	Toxins (intoxications and poisoning)

ELECTROLYTE IMBALANCES

Abnormalities in electrolytes may be the cause of cardiac arrhythmias and cardiac arrest. It is recommended to manage each electrolyte abnormality in an individual manner as shown in **Table 2** and continue to follow the CPR protocol. Management of electrolyte imbalance is discussed in detail in Chapter 46.

HYPOTHERMIA

A body temperature of <35°C (95°F) is defined as hypothermia. When the body is going through hypothermia, the oxygen consumption levels diminish which gives vital organs such as brain and heart priority on oxygen consumption. This could potentially lead to a complete neurological recovery after a prolonged cardiac arrest (for details of accidental hypothermia and cold injuries Chapter 239).

Management on hypothermic patients consists on removing the patient from cold location as well as remove clothing to prevent any more heat loss and use heated or normal blankets to restore heat as well as administer IV liquids at approximately 40°C (104°F). Any gastric, peritoneal, or vesical lavage should use liquids of this temperature. Increases in body temperature should be gradual of 1–1.5°C/h (33.8–34.7°F/h). Administration of oxygen at 40°C (104°F) is also recommended after intubation. It is important to monitor serum electrolytes due to frequent electrolyte imbalances when reheating patients.

When practicing CPR on hypothermic patients, remember the thorax may be more rigid than that of a normal temperature patient which may require greater pressure when compressing and ventilating to guarantee a successful CPR technique. Patients exhibiting cardiac instability should be transferred to an extracorporeal life support center without any delays.

TABLE 2: Intervention in electrolyte imbalance.

Electrolyte imbalance	*Management*
Hyperpotassemia	• It is the most common cardiac arrest cause and the most serious one • When serum potassium is >6.5 mmol/L, it is considered potentially mortal • Acidosis enhances hyperpotassemia due to potassium leaking into extracellular space • *Management*: Administer one rapid bolus of calcium chloride 10%, 10 mL IV; sodium bicarbonate 50 mEq, 1M and short-acting insulin 10 U + 50 g glucose
Hypopotassemia	• Less common, usually occurring in hospitalized patients • It is considered severe when values reach < 2.5 mmol/L • The management is based on administration of IV potassium
Hypocalcemia	• A serum calcium of <8.5 mg/dL or 2.1 mmol/L is considered hypocalcemia • Causes usually are sepsis, large corporal surface burns, acute pancreatitis, and intoxication due to calcium antagonists • Management with IV calcium chloride 10% administration, 10–40 mL and magnesium sulfate 10% 2 g is recommended
Hypermagnesemia	• Serum magnesium > 1.1 mmol/L is considered hypermagnesemia • Management consists on ClCa 10%, 10 mL administration
Hypomagnesemia	• Serum magnesium < 0.6 mmol/L. Usually is accompanied by hypopotassemia • Management consists of 2 g of magnesium sulfate 50% administration

HYPOVOLEMIA

Hypovolemia may be caused by hemorrhages or severe vasodilation as is the case in sepsis and anaphylaxis. The CPR should follow the same guidelines as a normovolemic cardiac arrest while correcting the hypovolemic cause. Discussed in detail in Chapter 48.

CARDIAC TAMPONADE

When there is pre-existing trauma, cardiac tamponade is responsible for 10% of cardiac arrests. When the trauma is penetrating thorax or epigastrium, the thoracotomy or ultrasound-guided pericardiocentesis are the immediate actions to follow. Cardiac tamponade and pericardiocentesis are discussed in Chapter 71.

TENSION PNEUMOTHORAX

Tension pneumothorax is suspected when at auscultation the respiratory sounds are unequal in each lung. Treatment is immediate and is a decompression throughout thoracentesis with a needle or a unilateral or bilateral thoracotomy. Pneumothorax and steps in insertion of chest tube are discussed in Chapter 88.

THROMBOSIS (CORONARY AND PULMONARY)

Patients with a cardiac arrest in whom we suspect it has a cardiac origin, the most frequent cause is an acute coronary thrombosis or an acute myocardial infarction, should start CPR right away while in hospital transfer. When patient reaches hospital, they should be transferred directly to a catheterization laboratory or hemodynamic laboratory to proceed with a percutaneous coronary intervention. For details of acute coronary syndrome, see Chapter 65. Pulmonary thromboembolism is suspected when the patient experiences dyspnea, thoracic pain, and syncope. The treatment of choice is fibrinolytic therapy even though an embolectomy may also be appropriate if indicated. After fibrinolytic therapy administration CPR should continue for around 60–90 minutes. Detail about pulmonary embolism is discussed in Chapter 76.

TOXINS (POISONING AND INTOXICATIONS)

Intoxications may be accidental or self-induced. When a patient has a cardiac arrest while intoxicated there should be a decontamination of the substance, promote its elimination and use specific antidotes. Usually, in these cases the reason for cardiac arrest is the obstruction of the airway due to bronchopulmonary aspiration of gastric content.

Gastrointestinal decontamination with activated charcoal is highly effective within the first hour of the ingestion. When there is an overdose of antidepressants especially tricyclic antidepressants, IV sodium bicarbonate must be administered. When overdose on local anesthetics, a lipidic emulsion infusion is the treatment of choice. General management of poisoned patient is described in Chapter 199.

Opioid overdose causes respiratory depression which may be corrected with an initial naloxone dose of 0.4–2 mg via intravascular, intramuscular, subcutaneous, or intraosseous every 2–3 minutes until patients breathing is adequate or protective airway reflexes are present.

SPECIAL PATIENTS

By special patient, we refer to those that due to physiological reasons such as pregnancy or advanced age or to comorbidities such as asthma, cardiac insufficiency with ventricular assistance device, neurological diseases, or obesity specific guidelines, must be followed during CPR.

Polytraumatic Patient

Victims of cardiac arrest during or after traffic or work accidents have a high mortality and neurological disability sequelae.

Global survival rate increases when CPR techniques are started within the first 3 minutes of cardiac arrest.

Pregnant Patient

Cardiac arrest management in pregnancy will require a manual left uterine displacement while performing CPR technique. The uterus overpasses the umbilicus around the 20th gestational week and can then compress the inferior vena cava and aorta preventing the venous return and cardiac output leading to a cardiac arrest. The displacement may be unimanual or bimanual. While performing chest compressions, the hands must be placed slightly higher over the sternum especially in third trimester patients. Early intubation may be considered with a 0.5–1 mm tube to facilitate pulmonary ventilation due to increased intra-abdominal pressure.

The main causes of cardiac arrest during pregnancy are hemorrhages, amniotic fluid embolism, eclampsia, and preeclampsia. Fetal survival rate is greatly dependent on maternal survival. Initial CPR should be focused on the pregnant patient. The evacuation of gravid uterus by cesarean section alleviates aortocaval compression which makes it a part of the resuscitation technique after second trimester. Resuscitation in pregnant is described in detail in Chapter 159. Some studies show a spontaneous return of circulation after delivery via C-section in pregnant patients with cardiac arrest.

Asthmatic Patients

When a cardiac arrest is due to an asthma exacerbation, it regularly means the patient has been having a considerate amount of time under hypoxia due to severe bronchospasms. The management for this patient is to maintain oxygen saturation between 94% and 98%, administer inhaled beta-2 agonists such as 5 mg of inhaled or IV salbutamol, nebulized anticholinergics such as 0.5 mg of ipratropium bromide every 4–6 hours, nebulized magnesium sulfate, IV corticosteroids, bronchodilators and 5 mg/kg of weight of aminophylline. An early tracheal intubation is preferred keeping 8–10 respirations per minute while performing CPR maneuvers to minimize air trapping. Dynamic hyperinflation due to air trapping may be causing transthoracic impedance which could lead to a nonsuccessful first electric discharge and a need for increasing energy in the defibrillation process.

Special Locations

Special locations are those that due to their geographic or environmental location may lead to situations which demand an adaptation to CPR techniques. Some examples of these locations are cardiac surgeries or interventions, catheterization laboratories, dialysis units, dental surgery, commercial airplanes and helicopters, high altitudes, avalanche and drowning victims, electricity lesions, and massive incidents.

Cardiopulmonary Resuscitation in Cardiac Interventions

In the catheterization laboratories and operating rooms, there should be defibrillators present and in high-risk patients, the patches may be placed before the procedure takes place. The use of thoracic compression machines is encouraged to reduce the health personnel exposure to radiation in the need of CPR while in angiography. When the cardiac rhythm is shockable for example in the ventricular fibrillation or pulseless ventricular tachycardia, it is recommended to perform three defibrillation shocks before starting thoracic compressions. Cardiac arrest during a major cardiac surgery is relatively common especially during the postoperative phase.

Cardiopulmonary Resuscitation in Airplanes

When there is a cardiac arrest victim in a commercial airplane flight, it is encouraged to follow the basic life support algorithm. The immediate deviation of the plane to the nearest airport will be a priority.

Cardiopulmonary Resuscitation in Athletes

When there is a sudden loss of consciousness during physical activity, the most probable origin is cardiac, and a rapid recognition of cardiac arrest is essential to start basic life support and an early shockable defibrillation.

Cardiopulmonary Resuscitation in Drowning Victims

The early rescue is essential. The patient must be removed from the water quickly. Oxygenation and good ventilation are the management pyramids. If patient presents hypothermia, it must be managed as mentioned earlier in this chapter. See Chapter 242 for details about drowning.

Cardiopulmonary Resuscitation in Great Altitudes and Avalanche Victims

Cardiopulmonary resuscitation in great altitudes or for avalanche victims does not differ from standard CPR, but it is important to consider that when there is a great altitude, the person who is performing the thoracic compressions will be exhausted far earlier than performing the same activity at sea level and this could lead to less effective compressions. Patients who were victims of avalanche usually have associated trauma and hypothermia, there should be a careful management of spinal column and seek an effective immobilization. Extracorporeal vital support is indicated when patient was buried under snow for >60 minutes, corporeal temperature at extraction was <30°C (86°F) and serum potassium is ≤8 mmol/L. See Chapter 243 for details about high altitute emergencies.

SUMMARY

There are various circumstances that require an adaptation to the standard vital life support techniques in order to deliver an optimal medical care service in any place to everybody. The knowledge and dominance of vital life support are essential to guarantee the best care.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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35
CHAPTER

Postcardiac Arrest Syndrome

Devendra Richhariya, Bhawana Sharma

INTRODUCTION

Complete recovery from cardiac arrest is considered with successful return of spontaneous circulation (ROSC). Postcardiac arrest syndrome is the complex pathophysiological processes that occur following whole body ischemia during cardiac arrest and the subsequent reperfusion response during cardiopulmonary resuscitation (CPR). Severity of the postcardiac arrest syndrome depends on the cause of the cardiac arrest, and the many patients will require multiple organ support. Quality of the neurological recovery and overall outcome is depending on the treatment they receive during this postresuscitation period.

Once ROSC is achieved and patient is stabilized, the patient is transferred to the most appropriate high-care area [e.g., emergency room, cardiac catheterization laboratory, or intensive care unit (ICU)] for the postresuscitation phase care, continued diagnosis, monitoring, and treatment. The key interventions are required to optimize outcome for these patients (**Flowchart 1**). Depending on the cause of arrest, system and quality of care of these comatose patients admitted to ICUs after cardiac arrest, as many as 40–50% survive to be discharged from hospital, majority have a good neurological outcome although many have subtle cognitive impairment.

POSTCARDIAC ARREST SYNDROME—PATHOPHYSIOLOGY

The postcardiac arrest syndrome consists of:

- Postcardiac arrest brain injury
- Postcardiac arrest myocardial dysfunction
- Systemic ischemia/reperfusion response
- Persistent precipitating pathology

Duration and cause of cardiac arrest determine the severity of this syndrome. If the cardiac arrest is brief, it may not occur at all. Postcardiac arrest brain injury may present as coma, seizures, myoclonus, and varying degrees of neurocognitive dysfunction and brain death. Brain injury is the major cause of death in out-of-hospital cardiac arrest (OHCA). In the first 3 days, most deaths are due to cardiovascular failure and brain injury responsible for most of the later deaths. *Risk factors for the postcardiac arrest brain injury* are microcirculatory failure, impaired autoregulation, hypotension, hypercarbia, hypoxemia, hyperoxemia, pyrexia, hypoglycemia, hyperglycemia, and seizures. As discussed earlier, there is significant myocardial dysfunction after cardiac arrest but start recovering after 2–3 days but full recovery takes longer time. On the other hand, immune and coagulation pathways activated after whole body ischemia/reperfusion of cardiac arrest contributing to multiple organ failure and increasing the risk of infection. Intravascular volume depletion, vasodilation, endothelial injury, and abnormalities of the microcirculation are feature of the postcardiac arrest syndrome which mimics sepsis. Important steps in management of postcardiac arrest syndrome are described below.

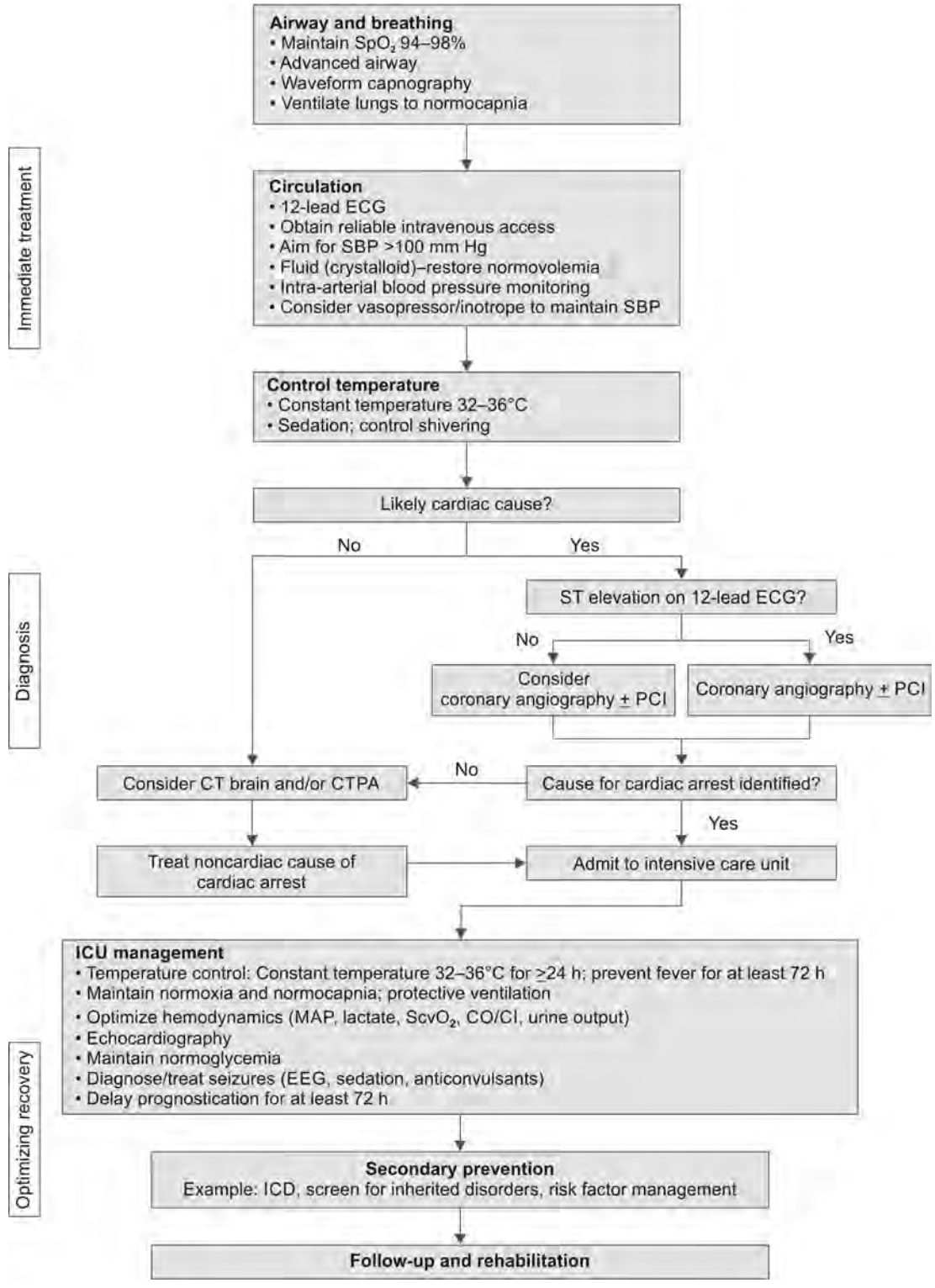
AIRWAY AND BREATHING

Control of Oxygenation

Those patients who recovered from brief period of cardiac arrest responding immediately to appropriate treatment (immediate return of normal cerebral function) can be managed with oxygen via a face mask. These patients do not require tracheal intubation and ventilation. If hypoxemia and hypercarbia are not treated timely, lead to further cardiac arrest and contribute to secondary brain injury. In the OHCA and after ROSC, it is difficult to obtain reliable arterial blood oxygen saturation values using pulse oximetry. If arterial blood oxygen saturation cannot be monitored reliably, possibility of myocardial dysfunction, increased neurological injury after cardiac arrest. Blood gas analysis and/or pulse oximetry should be monitored reliably as soon as possible to maintain the arterial blood oxygen saturation in the range of 94–98%. Avoid hypoxia, which is harmful and ensure reliable measurement of arterial oxygen saturation before reducing the inspired oxygen concentration.

Control of Ventilation

In any patient with obtunded cerebral function, consider tracheal intubation, sedation, and controlled ventilation. Endotracheal tube should be positioned correctly. Do not allow hyperventilation to occur as it causes cerebral ischemia. Cerebral vasoconstriction and a decreased cerebral blood


Immediate treatment
Airway and breathing
• Maintain SpO2 94–98%
• Advanced airway
• Waveform capnography
• Ventilate lungs to normocapnia
Circulation
• 12-lead ECG
• Obtain reliable intravenous access
• Aim for SBP >100 mm Hg
• Fluid (crystalloid)–restore normovolemia
• Intra-arterial blood pressure monitoring
• Consider vasopressor/inotrope to maintain SBP
Control temperature
• Constant temperature 32–36°C
• Sedation; control shivering
Diagnosis
Likely cardiac cause?
No
Yes
ST elevation on 12-lead ECG?
No
Yes
Consider coronary angiography ± PCI
Coronary angiography ± PCI
Consider CT brain and/or CTPA
No
Cause for cardiac arrest identified?
Yes
Treat noncardiac cause of cardiac arrest
Admit to intensive care unit
Optimizing recovery
ICU management
• Temperature control: Constant temperature 32–36°C for ≥24 h; prevent fever for at least 72 h
• Maintain normoxia and normocapnia; protective ventilation
• Optimize hemodynamics (MAP, lactate, ScvO2, CO/CI, urine output)
• Echocardiography
• Maintain normoglycemia
• Diagnose/treat seizures (EEG, sedation, anticonvulsants)
• Delay prognostication for at least 72 h
Secondary prevention
Example: ICD, screen for inherited disorders, risk factor management
Follow-up and rehabilitation

(ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; MAP: mean arterial pressure; PCI: percutaneous coronary intervention; $ScvO_2$: central venous oxygen saturation)

FLOWCHART 1: Key interventions in postcardiac arrest syndrome.

flow occur if hypocarbia persists. Apply protective lung ventilation—tidal volume 6–8 mL kg^{-1} ideal body weight and positive end-expiratory pressure 4–8 cm H_2O. Use adequate doses of sedative preferably as per sedation protocol, which will reduce oxygen consumption. If using targeted temperature management (TTM) bolus doses of a neuromuscular blocking drug may be required. Infusions of neuromuscular blocking drugs not advisable as this interfere with clinical examination and may mask seizures. To detect seizures in these patients, especially when neuromuscular blockade is used, continuous electroencephalography (EEG) is recommended. Obtain a chest radiograph to check the position of the tracheal tube, gastric tube and central venous lines, assess for pulmonary edema, and detect complications from CPR such as a pneumothorax

associated with rib fracture. Gastric tube should be inserted to decompress the stomach; gastric distension caused by mouth-to-mouth or bag-mask ventilation will splint the diaphragm and impair ventilation.

CIRCULATION

Hemodynamic Management

Postresuscitation myocardial dysfunction causes hemodynamic instability, which manifests as hypotension, low cardiac index, and arrhythmias. Perform early echocardiography in all patients in order to detect and quantify the degree of myocardial dysfunction. Postresuscitation myocardial dysfunction needs inotropic support. Noradrenaline, with or without dobutamine, and fluid therapy is usually the most effective treatment. Blood pressure, heart rate, urine output, rate of plasma lactate clearance, and central venous oxygen saturation should be monitored during the treatment. In the ICU setting, an arterial line for continuous blood pressure monitoring is essential. In hemodynamically unstable patients' serial echocardiography may also be used. Cardiac output monitoring may help to guide treatment in hemodynamically unstable patients. Some studies advocate use of an intra-aortic balloon pump (IABP) in patients with cardiogenic shock. Specific systolic blood pressure (>90 mm Hg) and mean arterial blood pressure (>65 mm Hg) should be targeted, to achieve an adequate urine output (1 mL kg^{-1} h^{-1}). Normal or decreasing plasma lactate values is desirable. During mild-induced hypothermia, oxygen requirements are reduced and the normal physiological response is bradycardia. As long as blood pressure, lactate and urine output are sufficient, a bradycardia of ≤40 $minutes^{-1}$ may be left untreated as studies suggest bradycardia associated with good outcome. Postcardiac arrest period is associated with hyperkalemia. Further in due course, hypokalemia occurs due to endogenous catecholamine release and correction of metabolic and respiratory acidosis promotes intracellular transportation of potassium. Hypokalemia should be corrected promptly as it may predispose to ventricular arrhythmias.

Coronary Reperfusion

Out-of-hospital cardiac arrest frequently caused by acute coronary syndrome (ACS), the invasive management, early coronary angiography followed by immediate percutaneous coronary intervention (PCI) is recommended by many studies, particularly those having prolonged resuscitation and nonspecific ECG changes, though it is controversial also because of the lack of high-quality evidence and significant burden on use of resources (transfer of patients to PCI centers).

Acute coronary lesion is more likely (>80%) in patients with ST segment elevation (STE) or left bundle branch block (LBBB) on the post-ROSC electrocardiogram (ECG). Immediate angiography and PCI when indicated should be performed in resuscitated OHCA patients whose initial ECG shows ST-elevation, even if they remain comatose and ventilated. Observational studies also indicate that by implementing combination of TTM and PCI optimal outcomes after OHCA can be achieved. Thus this strategy can be included as a standardized postcardiac arrest protocol to improve neurologically intact survival. In contrast to the usual presentation of ACS, those presenting with non-STE, there are conflicting data from observational studies on the potential benefit of emergent cardiac catheterization strategy. Factors which influence the decision to undertake the intervention in the acute phase or to delay it are patient age, duration of CPR, hemodynamic instability, presenting cardiac rhythm, and neurological status upon hospital arrival. Implantable cardioverter defibrillators (ICDs)—in ischemic patients (primary coronary event induced ventricular arrhythmias) with significant left ventricular dysfunction, insertion of an ICD can be considered.

Brain and chest CT scan can be performed at hospital admission, before or after coronary angiography for early identification of a respiratory or neurological cause. Perform coronary angiography first if there is clinical or ECG evidence of myocardial ischemia or in absence of signs or symptoms suggesting a neurological or respiratory cause (e.g., headache, seizures, or neurological deficits for neurological causes, shortness of breath or documented hypoxemia).

DISABILITY-OPTIMIZING NEUROLOGIC RECOVERY

Cerebral Perfusion

Studies suggested that there are various changes regarding cerebral perfusion following ROSC, there is a short period of multiple areas of cerebral no-reflow followed by transient global cerebral hyperemia (1 for 5–30 min) and then followed by cerebral hypoperfusion (up to 24 h till cerebral metabolic rate gradually recovers). Which means that cerebral perfusion varies with cerebral perfusion pressure, autoregulation of cerebral blood flow is impaired for some time after cardiac arrest.

Sedation

Although there are no high-level data to support a defined period of ventilation, sedation, and neuromuscular blockade after cardiac arrest but it is common practice to sedate and ventilate patients for at least 24 hours after ROSC. A combination of opioids and hypnotics is usually used to adequately sedate the patient during treatment with TTM, and the duration of sedation and ventilation is influenced by this treatment. Adequate sedation helpful in reducing the oxygen consumption. Use short-acting drugs (e.g. propofol, alfentanil, and remifentanil) helpful in reliable and earlier neurological assessment and prognostication.

Control of Seizures

In approximately one-third of patients who remain comatose after ROSC seizures are common after cardiac arrest. Most common seizures are myoclonus (15–25%) followed by focal or generalized tonic-clonic seizures or a combination of seizure types. To detect epileptic activity in patients with clinical seizure manifestations, intermittent EEG should be used. Patients with a diagnosed status epilepticus (SE) need effective treatment so consider continuous EEG monitoring. Seizures may adversely affect the outcome, exacerbate brain injury by increasing the cerebral metabolic rate: antiepileptic drugs such as sodium valproate, levetiracetam, phenytoin,

benzodiazepines, propofol, or a barbiturate are used to treat the seizures. Postanoxic myoclonus can be treated effectively with clonazepam, sodium valproate, and levetiracetam which are antimyoclonic drugs. In postcardiac arrest patient's, routine seizure prophylaxis is not recommended because of adverse effects and the poor response to antiepileptic drugs among patients with clinically and electrographic diagnosed seizures. Treatment of seizures with sedatives decreases the reliability of a clinical examination so prolonged observation may be necessary in these patients. Seizure activity (myoclonus SE) is related to a poor prognosis.

Glucose Control

High blood glucose, severe hypoglycemia, or increased blood glucose variability is associated with increased mortality and unfavorable neurological outcome after cardiac arrest. Following ROSC maintain the blood glucose at ≤10 mmol L^{-1} (≤180 mg/dL) and avoid hypoglycemia. Do not implement strict glucose control in adult patients with ROSC after cardiac arrest because it increases the risk of hypoglycemia.

Treatment of Hyperpyrexia

A period of hyperthermia (hyperpyrexia) is common in the first 48 hours after cardiac arrest. Although the effect of elevated temperature on outcome is not proven, it seems reasonable to treat hyperthermia occurring after cardiac arrest with antipyretics and to consider active cooling in unconscious patients.

TARGETED TEMPERATURE MANAGEMENT

Studies suggest that after achieving ROSC (period of global cerebral hypoxia-ischemia), mild-induced hypothermia is used as a neuroprotective and outcome improving measures. Mild-induced hypothermia suppresses the many pathological process leading to delayed cell death, including apoptosis (programmed cell death). Hypothermia reduces the release of excitatory amino acids, free radicals and decreases the cerebral metabolic rate for oxygen ($CMRO_2$) by about 6% for each 1°C reduction in core temperature. Hypothermia reduces the inflammatory response associated with the postcardiac arrest syndrome. The previous term therapeutic hypothermia is replaced by new term TTM. Several treatment recommendations on TTM by "The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation" (ILCOR) are discussed below.

Targeted temperature management is indicated for adults after OHCA with an initial shockable/nonshockable rhythm or any other initial rhythm that remains unresponsive after ROSC. Temperature is maintained between 32°C and 36°C with temperature control monitoring system. Minimum duration of TTM should be at least 24 hours. Following the TTM trial, many intensive care clinicians elected to use 36°C as the target temperature for postcardiac arrest temperature control. This has several advantages of selecting temperature of 36°C compared with a target temperature of 33°C. Vasopressor support is reduced to minimum with lower lactate levels. The rewarming phase is shorter and chances of rebound hyperthermia after rewarming are less.

How to Control Temperature

The TTM application is divided into three phases: (1) Induction, (2) Maintenance, and (3) Rewarming. For initiation and maintaining the TTM, external and/or internal cooling techniques can be used. An infusion of 30 mL kg^{-1} of 4°C saline is given if a lower target temperature (e.g., 33°C) is chosen, approximately 1.0–1.5°C decrease in core temperature is probably safe in a well-monitored environment. This method should not be used for prehospital cooling because of increased risk of pulmonary edema and rearrest during transport to hospital. *Methods of inducing and/or maintaining TTM include*:

- The first inexpensive method is by simple ice packs and/or wet towels; for nursing staff, this method is time consuming, also temperature fluctuations will be more, and controlled rewarming is not possible.
- Cooling blankets or pads
- Water or air circulating blankets
- Water circulating gel-coated pads
- Transnasal evaporative cooling—large multicenter randomized controlled trial is needed.
- Intravascular heat exchanger, placed usually in the femoral or subclavian veins
- Extracorporeal circulation [e.g., cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO)]

Initially soon after ROSC because the temperature normally decreases within this first hour in most cases, it is easy to cool patients. Allow a slow passive rewarm if a target temperature of 36°C is chosen. If a target temperature of 33°C is chosen, magnesium sulfate, neuromuscular blockade and sedation, is used to prevent shivering. In the maintenance phase, a cooling method with effective temperature, monitoring system should be chosen to avoid temperature fluctuations. A thermistor is placed in the bladder and/or esophagus for monitoring the temperature. Slow rewarming is recommended with rate of 0.25–0.5°C of rewarming per hour. During rewarming electrolyte imbalance, intravascular volume, and metabolic rate can change rapidly. Adverse neurological outcome is reported due to rebound hyperthermia. Thus, choosing a strategy of 36°C will reduce this risk.

Complications of Hypothermia

Well-known physiologic effects and complications of hypothermia should be managed carefully:

- Shivering will increase metabolic and heat production, the occurrence of shivering is a sign of a normal physiological response, indication of good neurological outcome; in patient with ROSC after cardiac arrest. A sedation protocol is required (discussed earlier in this chapter).
- Mild-induced hypothermia causes arrhythmias (usually bradycardia), this may be beneficial, it reduces diastolic dysfunction and its occurrence has been associated with good neurological outcome.
- Mild-induced hypothermia causes a diuresis and electrolyte abnormalities such as hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcemia.
- Hyperglycemia can occur due to hypothermia (decreases insulin sensitivity and insulin secretion), which will need insulin therapy.

- Increased infection rates due to hypothermia (impaired the immune system)
- During hypothermia, increase in serum amylase concentration is reported.
- At core temperature closer to 37.0°C, clearance of sedative and neuromuscular blockers drugs is near normal while clearance is reduced by up to 30% at a core temperature of 34°C.

Contraindications to Hypothermia

Generally recognized contraindications to TTM at 33°C, but which are not applied universally, include—severe systemic infection and preexisting medical coagulopathy (fibrinolytic therapy is not a contraindication to mild-induced hypothermia).

PROGNOSTICATION

Hypoxic-ischemic brain injury is common cause of mortality after resuscitation following OHCA. When predicting poor prognosis about patients who are comatose after resuscitation from cardiac arrest, tests should have 100% specificity or zero false positive rate (FPR). Most prognostication studies done only on few patients that it is very difficult to be completely confident in the results. Prognostication of the comatose postcardiac arrest patient should involve multiple types of tests of brain injury, and should be done after 72 hours from cardiac arrest, by this time any neurological recovery and full clearance of sedatives can occur. The tests are as follows:

- *Clinical examination*—GCS score, pupillary response to light, corneal reflex, and presence of seizures
- *Neurophysiological studies*—somatosensory evoked potentials (SSEPs) and EEG
- *Biochemical markers*—neuron-specific enolase (NSE) is the most commonly used.
- *Imaging studies*—brain computed tomography (CT) and magnetic resonance imaging (MRI)

Clinical Examination

Bilateral absence of pupillary light reflex at 72 hours from ROSC predicts poor outcome with close to 0% FPR. Similar performance has been documented for bilaterally absent corneal reflex. An absent or extensor motor response to pain at 72 hours from ROSC is with high FPR (about 27%). Myoclonus is sudden, brief, involuntary jerks caused by muscular contractions and prolonged period of continuous and generalized myoclonic jerks (>30 min) is commonly described as status myoclonus. A status myoclonus starting within 48 hours from ROSC is considered as a poor outcome (FPR 0%). Thorough clinical evaluation is recommended after stopping all sedation in patient with postarrest status myoclonus; in those patients, EEG evaluation should be done with recording of EEG signs of awareness and reactivity and coexistent epileptiform activity. Clinical examination is inexpensive and easy to use, for predicting the poor outcome therefore their results may potentially influence clinical management.

Electrophysiology

Apart from its prognostic significance, recording of EEG, either continuous or intermittent, in comatose survivors of cardiac arrest both during therapeutic hypothermia and after rewarming is helpful to assess the consciousness level, which may be masked by prolonged sedation, neuromuscular dysfunction, or myoclonus, and to detect and treat nonconvulsive seizures, which occur in about 25% of comatose survivors of cardiac arrest.

- *Short-latency somatosensory evoked potentials*: Bilateral absence of the N_20 SSEP wave predicts death or vegetative state with high reliability (FPR 0–2%). Appropriate skills and experience are required for SSEP recording, avoid electrical interference from muscle artifacts or from the ICU environment while SSEP recording. Bilateral absence of N20 SSEP has been used as a criterion for deciding on withdrawal of life-sustaining treatment (WLST) in most prognostication studies.
- *Electroencephalography*: Absence of EEG reactivity—absence of EEG background reactivity predicts poor outcome with a FPR of 0–2%.
- *Status epilepticus*: In TTM-treated patients, the presence of SE is almost invariably—but not always—followed by poor outcome (FPR 0–6%), especially in presence of an unreactive or discontinuous EEG background.
- *Burst-suppression*: Burst-suppression defined as >50% of the EEG record consisting of periods of EEG voltage <10 μV, with alternating bursts. During the first 24–48 hours, after ROSC burst-suppression may be compatible with neurological recovery, while at ≥72 hours from ROSC a persisting burst-suppression pattern is consistently associated with poor outcome.

Biochemical Markers

Neuron-specific enolase and S-100B are protein biomarkers that are released following injury to neurons and glial cells, respectively. Their blood values after cardiac arrest are likely to correlate with the extent of anoxic-ischemic neurological injury and, therefore, with the severity of neurological outcome. Advantages of biomarkers over both EEG and clinical examination include quantitative results and likely independence from the effects of sedatives. Their main limitation as prognosticators is that it is difficult to find with a high degree of certainty a consistent threshold for identifying patients destined to a poor outcome.

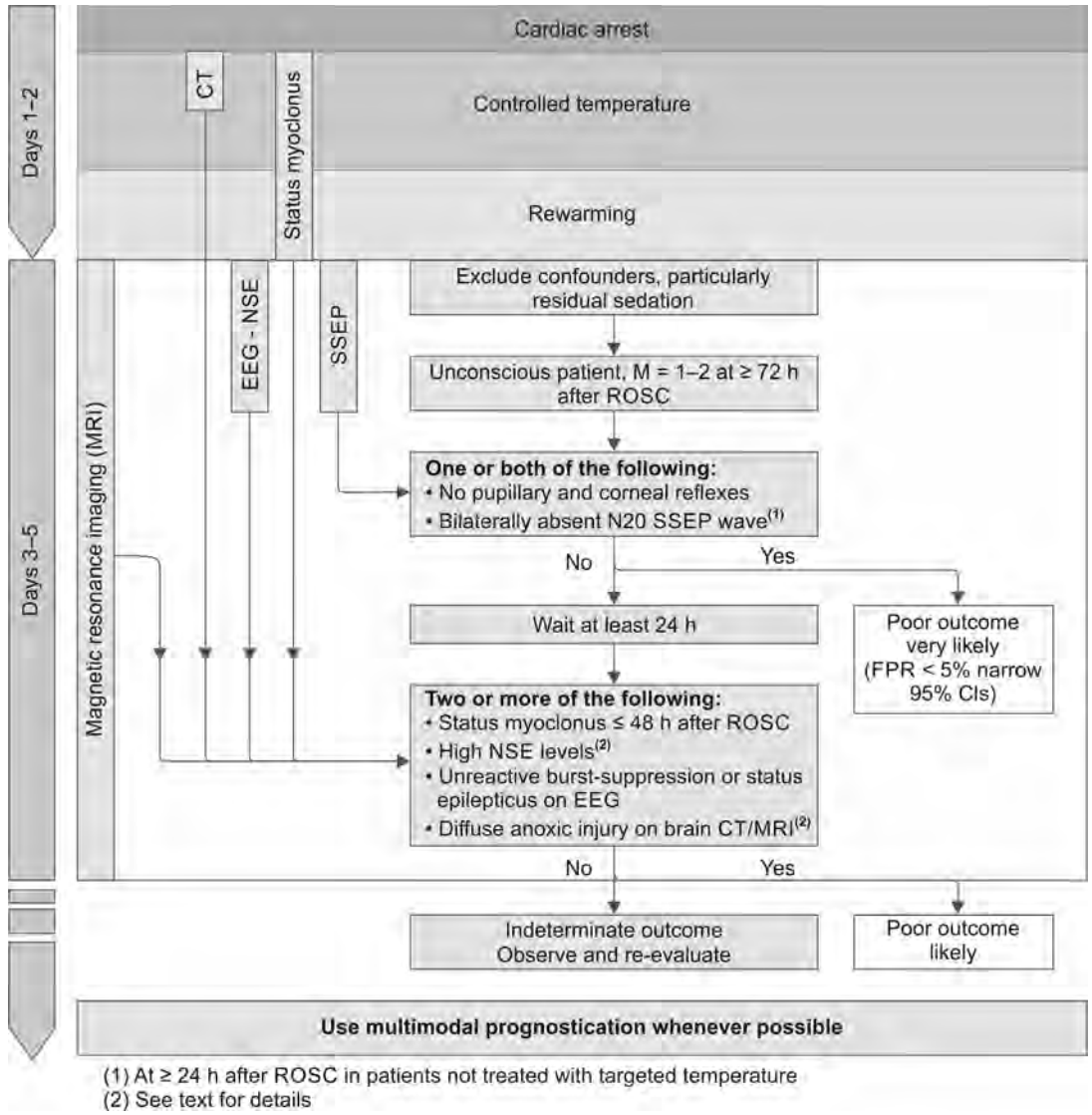
Imaging

The main brain CT finding of global anoxic-ischemic cerebral insult following cardiac arrest is cerebral edema, which appears as a reduction in the depth of cerebral sulci (sulcal effacement) and an attenuation of the gray matter/white matter (GM/WM) interface, due to a decreased density of the GM, which has been quantitatively measured as the ratio (GWR) between the GM and the WM densities. The GWR threshold for prediction of poor outcome with 0% FPR in prognostication studies ranged between 1.10 and 1.22. Brain MRI is more sensitive than CT for detecting global anoxic-ischemic brain injury caused by cardiac arrest; however, its use can be problematic in the most clinically unstable patients. MRI can reveal extensive changes when results of other predictors such as SSEP are normal. All studies on prognostication after cardiac arrest using imaging have a small sample size requested at the discretion of the treating physician, which may have caused a selection bias and overestimated their performance.

Suggested Prognostication Strategy

For prognostication of the comatose patient after cardiac arrest, a careful clinical neurological examination remains the cornerstone. A thorough clinical examination should be performed daily to detect signs of neurological recovery (any purposeful movement) or monitor brain stem reflexes. Within 72 hours from arrest in most of the patients, the process of brain recovery following global postanoxic injury is completed. Major confounders must be excluded, e.g., sedation and neuromuscular blockade, hypothermia, severe hypotension, hypoglycemia, and metabolic, and respiratory derangements before making any conclusion. Short-acting sedative is preferred over long-acting sedative or neuromuscular blocking drugs to avoid interference with clinical examination. Consider using antidotes to reverse the effects of these drugs when residual sedation/paralysis is suspected. The prognostication strategy algorithm (**Flowchart 2**) can be used to all patients who remain comatose with an absent or extensor motor response to pain at ≥72 hours from ROSC.

- Evaluate the most reliable predictors first, with highest specificity and precision (FPR < 5% with 95% CIs < 5% in patients treated with controlled temperature), they include bilaterally absent pupillary reflexes and bilaterally absent SSEP N20 wave predict poor outcome.
- If none of the signs above is present to predict a poor outcome, a next group of predictors can be evaluated (less accurate). These predictors include the presence of early status myoclonus (within 48 hours from ROSC), high values of serum NSE at 48–72 hours after ROSC, an unreactive malignant EEG pattern (burst-suppression and SE) after rewarming, the presence of a marked reduction of the GWR or sulcal effacement on brain CT within 24 hours after ROSC or the presence of diffuse ischemic changes on brain MRI at 2–5 days after ROSC.
- Expert suggest waiting at least 24 hours after the first prognostication assessment and combining at least two of these predictors for prognostication. When dealing with an uncertain outcome, clinicians should consider prolonged observation.


Cardiac arrest
Days 1–2
CT
Status myoclonus
Controlled temperature
Rewarming
Days 3–5
Magnetic resonance imaging (MRI)
EEG - NSE
SSEP
Exclude confounders, particularly residual sedation
Unconscious patient, M = 1–2 at ≥ 72 h after ROSC
One or both of the following:
• No pupillary and corneal reflexes
• Bilaterally absent N20 SSEP wave(1)
No
Yes
Wait at least 24 h
Poor outcome very likely (FPR < 5% narrow 95% CIs)
Two or more of the following:
• Status myoclonus ≤ 48 h after ROSC
• High NSE levels(2)
• Unreactive burst-suppression or status epilepticus on EEG
• Diffuse anoxic injury on brain CT/MRI(2)
No
Yes
Indeterminate outcome Observe and re-evaluate
Poor outcome likely
Use multimodal prognostication whenever possible
(1) At ≥ 24 h after ROSC in patients not treated with targeted temperature
(2) See text for details

(CT: computed tomography; EEG: electroencephalography; NSE: neuron-specific enolase; ROSC: return of spontaneous circulation; SSEP: somatosensory evoked potential)

FLOWCHART 2: Prognostic algorithm for postcardiac arrest syndrome.

REHABILITATION

Cognitive and emotional problems and fatigue are common in the majority of cardiac arrest survivors. Cognitive impairments remain for longer period of time in half of survivors. Memory followed by attention problem and executive of functioning (planning and organization) is the main problem in cardiac arrest survivors. Cerebral performance categories (CPC) or the Mini-Mental State Examination (MMSE) is used to detect mild cognitive impairment. Emotional problems, including depression, anxiety, and post-traumatic stress can affect a patient's daily functioning, return to work and quality of life.

ORGAN DONATION

In those comatose patients in whom a decision is made to withdraw life-sustaining therapy, who fulfill criteria for death using neurological criteria organ donation should be considered after circulatory death occurs. Organ retrieval is classified as controlled or uncontrolled. Controlled donation performed after planned withdrawal of treatment after nonsurvivable injuries. Uncontrolled donation performed from patients with unsuccessful CPR.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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36 CHAPTER

Oxygen Therapy and Oxygen Delivery System

Bhawana Sharma, Devendra Richhariya

INTRODUCTION

Oxygen though ubiquitously present is actually a drug, it can be lifesaving but can also be lethal in some cases. Oxygen is essential to cellular metabolism; unfortunately, it is difficult to assess cellular function. Certain organs are very dependent on oxygen such as brain and heart thus it is possible that even minor degrees of hypoxia can produce varying effects on coronary or cerebral circulation. Studies have shown a PaO_2 of 30 mm Hg is generally adequate to maintain cellular metabolism.

INDICATIONS

Oxygen therapy is generally first and commonly initiated therapy in hypoxic state in emergency department as oxygen saturation level is directly correlating with the clinical presentation (**Table 1**) Commonly, there are four types of hypoxia (**Table 2**), describe in clinical practice on the basis of their different pathophysiology in which oxygen therapy is indicated:

- Hypoxemic and hypercapnic respiratory failure
- Acute myocardial infarction
- Postoperative and perioperative states
- Acute asthma and exacerbation of chronic obstructive pulmonary disease (COPD)
- Conditions of tissue hypoxia with normal PaO_2 (normoxic hypoxia):
  - Anemic condition—supplemental oxygen may be used as a temporary measure.
  - Carboxyhemoglobin—in these cases, PaO_2 may be characteristically normal, PaCO level has to be measured. If PaCO level is >40% indicates brain involvement, hence hyperbaric therapy if available is indicated.

TABLE 1: Correlation of PaO_2/SpO_2 and clinical outcome.

PaO_2 values—SpO_2 values	*Clinical significance*
97 mm Hg—100%	Normal young person
80 mm Hg—95%	Normal young person during sleep
70 mm Hg—93%	Lower limit of normal
60 mm Hg—90%	Respiratory failure
50 mm Hg—85%	Significant respiratory failure, patient needs admission
40 mm Hg—75%	Significant respiratory failure, normal venous blood values
30 mm Hg—60%	Unconscious

TABLE 2: Types of hypoxia.

Types	*Mechanism*	*Causes*
Hypoxic hypoxia	Low PaO_2 caused by low oxygen supply	• High altitude • Ventilatory failure—postarrest, NM disease • *Shunt*: Anatomical—R to L shunt Physiologica—pneumonia, pneumothorax, and acute respiratory distress syndrome (ARDS)
Anemic hypoxia	Arterial oxygen tension is normal but less availability due low or physiological abnormal hemoglobin	Massive hemoptysis, carbon monoxide poisoning, and methemoglobinemia
Stagnant hypoxia	Inadequate circulation causing insufficient oxygen tension	Left ventricular failure, pulmonary embolism, and hypovolemia
Cytotoxic hypoxia	Normal transport of oxygen but inadequate cellular metabolism	Cyanide toxicity and arsenic toxicity

- Sickle cell crisis—it is documented that deoxygenated states can cause sickling of cells, hence oxygen would be useful. However, oxygen toxicity should also be avoided in these conditions.
- Respiratory distress
- Shock
- Hypotension
- To prevent postsurgical infections.

CLASSIFICATION OF OXYGEN DELIVERY SYSTEM

It is very important to have in depth knowledge of oxygen delivery system so that proper device is selected according to patient need and clinical problem. Oxygen delivery devices can be classified on the basis of their design. There are three basic designs available—*(1) Low-flow system, (2) Reservoir, and (3) High-flow system while the fourth available design is enclosure* ***Table 3***. So, the physician should be able choose the appropriate oxygen delivery system on the basis of two important questions, (1) how much oxygen can be delivered by system and (2) whether fraction of inspired oxygen (FiO_2) delivered remain fixed or can be altered according to patient requirement. On the basis of FiO_2 delivered the system can be further divided in to low (<35%), moderate (35–65%), high (>70%) oxygen concentration delivery devices.

Fraction of inspired oxygen delivered depends on *patient factors* (inspiratory flow rate, tidal volume, respiratory rate, and presence of a respiratory pause) and *device factors* (volume of the mask, tightness of fit, oxygen concentration, and air vent size). Characteristic of various low- and high-flow oxygen devices are summarized in **Table 4**.

Components of Oxygen Devices

- *Oxygen source and flow control*: Generally, oxygen is supplied through cylinders, concentrators, or central oxygen supply of the hospital. There is a valve device to control flow, rate often indicated by a flow meter.
- *Connecting tubes*: The bore of the tube is important as narrower the bore, the lesser the amount of oxygen delivered.
- *Reservoir*: Reservoir is important as it ensures the oxygen supply for the next breathing effort, however, too large a reservoir has the problem of CO_2 rebreathing. In a nasal cannula, nasopharynx is the reservoir, the mask is the reservoir in a face mask, and tent is the reservoir in an oxygen tent.

TABLE 3: Classification oxygen delivery system.

Low-flow oxygen therapy system	*High-flow oxygen therapy system*	*Enclosures*
• Nasal cannula • Nasal catheters • Transtracheal catheters • Reservoir cannula • Simple mask • Partial rebreathing mask • Nonrebreathing mask • Nonrebreathing circuit (closed)	• Air entrainment (Venturi) mask (AEM) • Air entrainment nebulizer • Blending system • High-flow nasal cannula system • (HFOT)	Oxyhood isolette tent

- *Expiratory device*: It is important to let out the expired air out in the environment, so that the air is not rebreathed. A face mask has holes in ask to let out the air. A continuous positive airway pressure (CPAP) system has holes in the expiratory limb.
- *Humidification*: It is important in especially in high-flow systems, may cause excess dryness and irritation. In that case, external humidifier or heat and moisture exchanger can be used. Other systems use natural humidification of nasopharynx.

LOW-FLOW SYSTEM

Nasal cannula and face mask are considered as low-flow oxygen delivery devices.

Nasal Cannula

These are easy to use, disposable, low cost, and well tolerated by patient but main drawbacks are they can be easily dislodged, unstable; patient becomes uncomfortable with high-flow oxygen. Nasal cannula can be best used in patient with low FiO_2 requirement, home care with long-term oxygen therapy (LTOT) and while eating. The oxygen flow rate and FiO_2 can be delivered through nasal cannula is (1 L/min—24% 2 L/min—28%, 3 L/min—32%, 4 L/min—36%, 5 L/min—40%, and 6 L/min—44%) (**Fig. 1**).

Face Mask

There are two types of face mask are used, simple face mask and reservoir face mask. Simple face mask is also easy to use disposable and inexpensive, it has to be removed while eating. Simple face mask can be best used in emergency when moderate FiO_2 is required (**Fig. 2**).

Reservoir Face Mask

It is a high oxygen, low-flow, variable performance device. The reservoir empties during inspiration, ambient air is entrained from vents. The mask with a reservoir bag must remain inflated during both inspiration and expiration. The patient inhales oxygen preferentially from the reservoir. The rate of oxygen delivered depends on mask fit, capacity of reservoir bag, oxygen flow rates, and patients inspiratory flow rate. There are two types of reservoir mask—(1) Partial rebreathing; and (2) nonrebreathing.

- *Partial rebreathing mask*: Simple mask with a reservoir bag. Oxygen flow should always be supplied to maintain the reservoir to at least one-third to one-half on inspiration. The reservoir receives fresh gas exhaled gas approximately equal to the volume of the patient's anatomic dead space. Minimum flow rate required is 10 L/min to avoid collapse of bags during inspiration and the system provides FiO_2 of 40–70%.
- *Nonrebreathing mask*: Do not permit mixing of exhaled gases with fresh gas supplied. The remaining exhaled air exits through vents. The presence of one-way valve ensures a fresh oxygen supply with minimal dilution from the entrainment of room air. It provides a higher FiO_2 than partial rebreathing mask provided the mask fits correctly. Minimum flow rate required is 10 L/min, delivered FiO_2 of this system is 60–80% at flow rates of 12–15 L/min (**Fig. 3**).

TABLE 4: Oxygen delivery devices and their characteristics.

Methods	*Amount of O_2 flow/ FiO_2*	*Precaution*	*Advantages*	*Disadvantages*
Low-flow oxygen therapy				
Nasal cannula	• Low flow-(1–6 L/min) • FiO_2 24–44%	• To check whether both prongs are in patients' nostrils • In patient with chronic lung disease to deliver 2–3 L/min	• Patient able to talk and eat • Can be used in home setting • Well tolerated • Inexpensive	• May cause irritation to nasal mucosa • May cause epistaxis
Simple face mask	• Low flow (5–10 L/min) • FiO_2 35–50%	• Frequently check placement of mask • Check for claustrophobia • CO_2 retention may occur unless flow rate <2 L/min or minute ventilation is high	• Can provide increased oxygen demand for a limited period of time	• Tight seal required • Difficult to keep mask over mouth and nose • Oxygen wasting • Uncomfortable for patient while speaking or eating • Problematic with RT in situ
Partial rebreather mask	• Minimum 10 L/Min • FiO_2 40–70%	• Reservoir bag should be two-thirds filled during inspiration • Reservoir bag should be free of kinks	Patient can inhale room air through openings in mask if oxygen supply briefly interrupted	Tight seal required (eating and talking are difficult)
Nonrebreathing mask	• Minimum 10 L/min (prevent bag collapse on inspiration) • FiO_2 60–80%	• Maintain flow rate so that reservoir bag collapses only slightly during inspiration • Check valves are functioning properly	• Delivers highest possible oxygen concentration • Suitable for spontaneously breathing patient with severe hypoxemia	• Not useful for long-term therapy • Malfunction can cause CO_2 retention • Feeling of suffocation • Expensive
High-flow oxygen therapy (HFOT)				
Air Entrainment Mask (AEM) Venturi system	• Variable flow can be set • FiO_2 24–50% • Fixed system	FiO_2 varies with back pressure Different colored vent are used for achieving different FiO_2	Easy to apply disposable low-cost system Precise FiO_2 can be achieved	Only be used in adult FiO_2 >40% not sure FiO_2 varies with back pressure
High-flow oxygen cannula system	• Flow rate up to 50 L/min or more FiO_2 35–90%	• FiO_2 is ensured but system dependent	Wide range of FiO_2, relative/ absolute humidity can be used in adult children and infants	FiO_2 is depend on system input and patient breathing pattern Infection risk

FIG. 1: Nasal cannula.

FIG. 2: Simple face mask.

HIGH-FLOW SYSTEM

Air Entrainment (Venturi) System

Oxygen concentration is determined by the Venturi principle—oxygen passing through a small orifice entrains air to a predictable dilution. The Venturi principle depends on the Bernoulli's effect, when fluid flows through a narrow constriction, it accelerates, gaining kinetic energy from the surrounding potential energy, thus a negative pressure surrounding is created this entrains the surrounding fluid through the constriction (**Figs. 4A** and **B**). The FiO_2 is adjusted by changing the Venturi "valve" and setting the appropriate oxygen flow rate. The larger orifice results in the system behaving like a simple mask. However, a fixed delivery system is possible at a lower FiO_2, higher the FiO_2 required, lower the oxygen flow rate (**Fig. 5**). The correct flow rate/FiO_2 of oxygen is varying with specific color of mask and written on the mask blue—2–4 L/min oxygen 24% FiO_2, white—4–6 L/min oxygen 28% FiO_2, yellow—8–10 L/min oxygen 35% FiO_2, red—10–12 L/min oxygen 40% FiO_2, and green—12–15 L/min oxygen 60% FiO_2.

SELECTION OF OXYGEN DELIVERY SYSTEM

It is very important to choose appropriate oxygen delivery system in emergency department to achieve targeted FiO_2 and correction of hypoxia which is the final goal of the oxygen therapy. There are many factors which help in choosing the appropriate oxygen delivery system and patient initial assessment is one of them. Generally, 3 Ps (*purpose, patient, and performance*) are considered helpful in selection of the appropriate oxygen delivery system.

We all know the purpose or goal of the oxygen therapy is to raise the FiO_2 adequately so that arterial hypoxia can be corrected resulting features of hypoxia and cardiopulmonary work load is reduced.

Patient-related factors very important while selecting the oxygen delivery system is patient age group (adult, children, and infant), severity and causes of hypoxia, level of alertness and consciousness of patient, mouth/nose breathing patient, presence or absence of tracheal airway, and stability of minute ventilation.

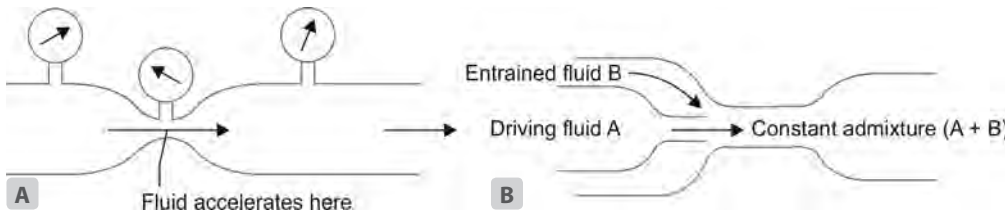
Performance of delivery system should also be considered, e.g., FiO_2 delivery to patient and stability of FiO_2 with changing demand of the patient. Critically ill patient needs more and stable FiO_2. **Table 5** guides the physician in selecting the oxygen delivery system on the basis of level and stability of FiO_2 required by patient.

INITIATION OF OXYGEN THERAPY IN EMERGENCY DEPARTMENT

- *Patient severely hypoxemic, critically ill*—start at 15 L/min via reservoir face mask, once stabilized, can be tapered to maintain saturation between 94 and 98%.If at risk of type 2 respiratory failure to maintain SpO_2 between 88 and 92%.
- *Patient seriously ill moderately hypoxemic*: Start O_2 via face mask at 6 L/min, if no improvement in condition, increase to up to 15 L/min via reservoir bag. SpO_2 to be maintained between 94 and 98%.
- *Chronic obstructive pulmonary disease like condition, at risk of type 2 respiratory failure*: Venture mask (at 4 L/min) preferred, to maintain SpO_2 between 88 and 92%. Should repeat arterial blood gas (ABG) after 30–60 minutes to see the PaO_2 and $paCO_2$ levels.

FIG. 3: Nonrebreathing mask.

FIG. 5: Venturi device. ***(For color version, see plate 2)***



FIGS. 4A AND B: Bernoulli's principle effect air entrainment (Venturi) system.

TABLE 5: Selection of oxygen delivery system based on required FiO_2 level.

	Desired FiO_2 stability	
	Fixed	***Variable***
If low, FiO_2 (<35%) is desired	• Air entrainment mask (AEM) • Air entrainment nebulizer • Blending system • Incubators (infants) • Isolette	• Nasal cannula • Nasal catheter • Transtracheal catheter
If moderate, FiO_2 (35–60%) is desired	• Air entrainment nebulizer • Blending system • Oxyhood (infants)	• Simple mask • Air entrainment nebulizer • Tent (child)
If high, FiO_2 (>60%) is desired	• Blending system • Oxyhood (infants) • High-flow nasal cannula	• Partial rebreather • Nonrebreather

LONG-TERM OXYGEN THERAPY

Oxygen prescribed a low flow rate at least 16 hours a day including night. LTOT improves sleep, survival, and cognition. Oxygen sources include oxygen cylinder and oxygen concentrators. Oxygen delivered through nasal cannulae, transtracheal catheters, etc. If LTOT is prescribed during an acute exacerbation, ABG should be repeated in 30–90 days after discharge.

Indications—(1) Patient with $SaO_2 < 88\%$, $PaO_2 < 55$ mm Hg, (2) Patient with SaO_2 between 88 and 90%, PaO_2 between 55 and 60 mm Hg with—polycythemia and cor pulmonale.

Weaning—patients with chronic lung disease may require oxygen for longer periods of time

Weaning to be attempted once vitals such as respiratory rate, pulse rate, saturation of oxygen, and blood pressures are settled. The oxygen requirement should be assessed by reducing the FiO_2 and evaluating every 30 minutes using an ABG. However, pulse oximeter is preferred as is less invasive.

OXYGEN TOXICITY

Toxicity of oxygen is caused by free radical injury due to superoxide, hydroxyl, and oxygen singlet. At higher pressures, the protective natural scavenging mechanism of the body is lost. The toxicity is related to the FiO_2 of the air inspired. Generally, anything above 60% for >6 hours may be injurious. Studies have shown, if clinically allowed, can be tried for air brakes. Generally, normobaric therapy affects lungs, while hyperbaric therapy affects CNS, eyes in addition to lungs.

- *Symptoms and signs*: Nasal stuffiness, fatiguability, substernal chest pain**,** nasal stuffiness, and sore throat, headache**,** nausea, and vomiting, radiological signs of atelectasis (adhesive atelectasis)—mimicking ARDS and hypoventilation.
- *Evaluation of oxygen toxicity needs examination of* pattern and breathing rate**,** pink color in nail beds, conjunctiva, and lips, whether disorientation or difficulty in cognition present, regular ABG for PaO_2, and hemoglobin concentration.
- *Complications*: Absorption atelectasis**,** hypoventilation, bronchopulmonary dysplasia**,** retrolental fibroplasia, drying of mucous membranes (if humidifier not used), and fire-related hazards.

HIGH-FLOW NASAL CANNULA OXYGEN THERAPY

Oxygen support therapy should be given to the patients with acute hypoxic respiratory insufficiency in order to provide oxygenation of the tissues until the underlying pathology improves. Maximum flow rate of 15 L/min is produced by low-flow and high-flow conventional oxygen support systems and FiO_2 changes depending on the patient's peak inspiratory flow rate, respiratory pattern, the mask that is used, or the characteristics of the cannula. The inspiratory flow rate requirement of patients with respiratory insufficiency varies between 30 and 120 L/min. The inability to provide adequate airflow leads to discomfort in tachypneic patients. High-flow nasal oxygen (HFNO) cannulas are able to delivered warmed and humidified air matching the body temperature with the regulated flow rates of 5–60 L/min, and oxygen delivery varies between 21 and 100%.

Studies show that physiological parameters are improved with HFNO treatment when compared to conventional oxygen systems. Although there are studies indicating successful applications in different patient groups, there are also studies indicating that it does not create any difference in clinical parameters, but patient comfort is better in HFNO when compared with standard oxygen therapy and noninvasive mechanical ventilation (NIMV).

Physiological Effect of High-flow Nasal Oxygen Cannula Therapy

The physiological positive effects of HFNO therapy are summarized in **Box 1**. It was reported that by providing positive airway pressure, HFNO increases the end-expiratory lung volumes and functional residual capacity and decreases the inspiratory resistance. This leads to positive nasopharyngeal pressure and the elimination of CO_2 in the nasopharyngeal dead space. Thus, the metabolic load for gas exchange is reduced and it recovers oxygenation.

Set-up of the High-flow Oxygen Cannula Device

The HFNO device consists of an air/oxygen mixer, an active heater, a humidifier, a unidirectional inspiratory circuit hose, and a soft nasal cannula that is slightly larger than the standard nasal cannula. In the air/oxygen mixer, FiO_2 can be increased

BOX 1: Positive physiological effects of high-flow nasal oxygen.

- Generation of constant FiO_2
- Generation of a positive end-expiratory pressure
- Decrease in anatomical dead space
- Improved mucociliary clearance
- Decreased work of breathing

from 21% (room air) to 100% (pure oxygen) depending on the flow (up to a maximum of 60 L/min). The oxygen is hydrated with water vapor by the active humidifier, and the oxygen can be heated to 37°C prior to delivery to the patient through the unidirectional inspiratory circuit hose (**Fig. 6**).

Indications of High-flow Nasal Cannula Oxygen Therapy

Positive physiological effects produced by HFNO indicates that high-flow oxygen therapy (HFOT) is useful in the treatment of respiratory failure, which can be caused by many different conditions, such as hypoxemic respiratory failure, exacerbation of COPD, postextubation, preintubation oxygenation, sleep apnea, and acute heart failure (**Box 2**). High-flow nasal cannula (HFNC) has been gaining attention as an alternative respiratory support for critically ill patients after few large randomized clinical trials. Initial data of published trials are mostly available for neonates. In seriously ill adults, however, evidence for use of HFONT is not even because the studies included conditions of varying etiology, like hypoxemic respiratory failure, exacerbation of COPD, postextubation, preintubation oxygenation, sleep apnea, acute heart failure, and conditions entailing do-not-intubate orders.

Concern Regarding Use of High-flow Nasal Cannula Oxygen Therapy

Studies suggest that HFNC use decreases breathing frequency and work of breathing and reduction for the need of respiratory support escalation though the main concern regarding the use of HFNC has been that overuse of this modality may lead to unnecessary and potentially precarious delays in intubation. Further studies are required to resolve some important issues such as definitive indications for HFNC and criteria for timing the starting and stopping of HFNC and for escalating treatment. HFNC is emerging as an innovative and effective modality for early treatment of adults with respiratory failure with diverse underlying diseases despite some issues.

MEDICAL OXYGEN CYLINDERS: TYPES CAPACITY AND ESTIMATION OF RUNNING TIME

The amount of oxygen in the air is sufficient for a healthy person in normal conditions. However, patient with abnormal respiratory or cardiac conditions may require extra oxygen support. There are two types of medical devices that provide oxygen gas in accordance with health. These are oxygen cylinders and oxygen concentrators. Oxygen cylinders can be refilled, but oxygen concentrators do not require refilling because oxygen concentrators produce the oxygen gas to be given to the patient. Medical oxygen cylinders are available in different capacities. Oxygen cylinders have varieties according to the materials they are produced from, and their weights and usage purposes vary. Accessories used together vary depending

BOX 2: Recommended indications for high-flow oxygen therapy.

- Acute respiratory distress syndrome and acute hypoxemic respiratory failure
- Hypoxemia induced by severe heart failure
- Postextubation respiratory compromise
- Airway instrumentation (as adjunct during manipulation of the airway, e.g., bronchoscopy, intubation in patients with both low and high risk, i.e., hypoxemia and morbid obesity)
- Immune compromise
- End-of-life care

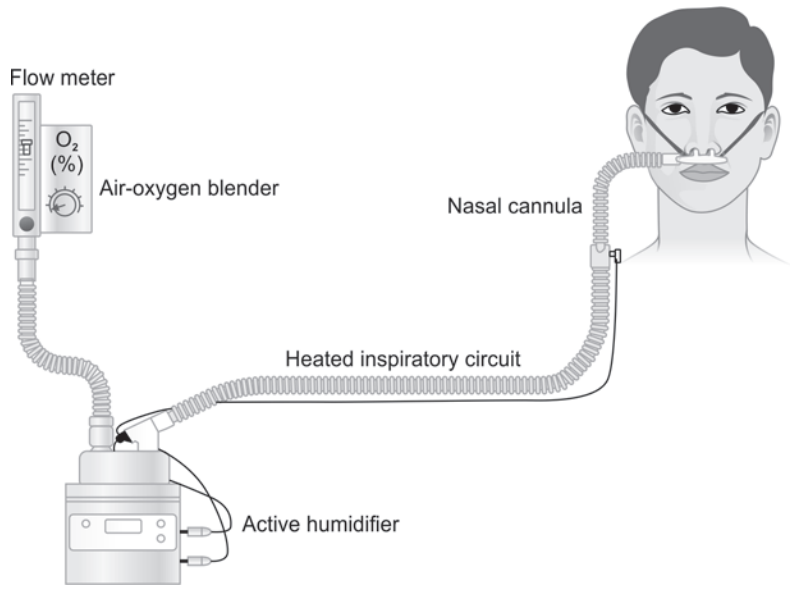


FIG. 6: Setup of the high-flow nasal cannula oxygen therapy—*Air/oxygen blender can generate up to 60//min flow. The gas is heated and humidified through active heated humidifier and delivered via single limb heated inspiratory circuit.*

on where and for what purpose the tube will be used. Oxygen cylinders can be used alone or with other oxygen delivering machine such as noninvasive ventilation and mechanical ventilation. Oxygen tubes are resistant to high pressure. The density of the oxygen gas in the oxygen cylinder is about 98% and 90–95% in oxygen concentrators.

What are the types of oxygen cylinders?

Medical oxygen cylinders are produced in different sizes and capacities (**Table 6**). This capacity is expressed in liters. The size of the oxygen tube increases as its capacity increases. There are steel and aluminum types according to the material from which the tube is made. Aluminum ones are lighter. Oxygen cylinders up to 10 liters capacities are portable, regardless of whether they are aluminum or steel. Cylinders with a capacity of >10 liters are almost impossible to carry by one person. Portable oxygen cylinders are generally used in ambulances, hospital emergency units, and homes. Since aluminum ones are lighter, they are also easier to carry and are preferred especially during patient transfer. There is a central gas system in hospitals, medical oxygen gas can be delivered to every point of need such as patient rooms, intensive care units, and operating rooms and emergency rooms. The gas used in the central system is stored either in large oxygen tanks or in many large oxygen cylinders depending on the capacity of the hospital. Oxygen cylinders contain high pressure gas and not possible to apply directly to the patient in this form. The pressure is reduced and made suitable for use and medical tube manometers are used to measure the pressures. Aluminum manometers with pin index (pin entry) are used because they are generally lighter in aluminum tubes. These are lighter than standard type manometers. If it is desired to use standard manometers in aluminum tubes, the connection part must be changed. Some consumables and adjuncts are required when using the oxygen cylinder. These are materials such as an oxygen mask, oxygen cannula, oxygen catheter, or water container (**Fig. 7**). It should be stored in adequate numbers in the ward. The mask attached to the oxygen tube is applied to the face covering the mouth and nose. Nasal oxygen cannulas and catheters are used by placing them in the nostrils. The water container is attached to humidify the oxygen gas coming out of the tube which is connected to the manometer. For refilling the oxygen cylinder, there are certified facilities and certain standards must be complied with in order to obtain quality certificate.

How long does oxygen cylinders use?

The duration of use of oxygen cylinders depends on the oxygen tube, volume, and flow setting. Running time of any oxygen cylinder can be calculated by formula given in **Table 7**.

TABLE 6: Oxygen cylinder size and capacity.

Size	*Capacity (L)*	*Pressure (psi)*	*Tare weight (kg)*	*Valve type*
B	200	1,900	2.27	Pin index
D	400	1,900	3.4	Pin index
E	660	1,900	5.4	Pin index
F	1,360	1,900	14.5	Bull nose
G	3,400	1,900	34.5	Bull nose
H	6,900	2,200	53.2	Bull nose
M	3,450	2,200	29.0	Bull nose

SUMMARY

Oxygen is a drug, hence, except for emergencies, should be prescribed. Oxygen is the treatment of hypoxemia and not breathlessness. The target saturation should always be prescribed—in case of type 1 respiratory failure between 94 and 98% and in type 2 respiratory failure between 88 and 92%. Various devices are available or delivery of oxygen, indication of use, patient comfort, target saturation, and efficient usage of oxygen to be considered while deciding the device. Oxygen has its own sets of complications, hence weaning should be attempted while patient has stable vitals.

FIG. 7: Medical oxygen cylinder and various consumables.

TABLE 7: Oxygen run time sheet: Cylinder type F (1,360 L) medium (Ward cylinder).

Pressure (kg/cm²)	*Pressure (psi)*	*Liters*	*Oxygen running time*				
			2 liters	*4 liters*	*6 liters*	*8 liters*	*10 liters*
140	1,990	1,360	11 h 17 min	5 h 38 min	3 h 45 min	2 h 49 min	2 h 15 min
130	1,848	1,263	10 h 28 min	5 h 14 min	3 h 29 min	2 h 37 min	2 h 5 min
120	1,706	1,165	9 h 40 min	4 h 50 min	3 h 13 min	2 h 25 min	1 h 56 min
110	1,564	1,068	8 h 52 min	4 h 26 min	2 h 57 min	2 h 13 min	1 h 46 min
100	1,422	971	8 h 3 min	4 h 2 min	2 h 41 min	2 h 1 min	1 h 37 min
90	1,280	874	7 h 15 min	3 h 38 min	2 h 25 min	1 h 49 min	1 h 27 min
80	1,138	777	6 h 27 min	3 h 13 min	2 h 9 min	1 h 37 min	1 h 17 min
70	996	680	5 h 39 min	2 h 49 min	1 h 53 min	1 h 25 min	1 h 8 min
60	854	583	4 h 50 min	2 h 25 min	1 h 37 min	1 h 13 min	58 min
50	712	486	4 h 2 min	2 h 1 min	1 h 20 min	1 h	48 min
40	568	387	3 h 13 min	1 h 36 min	1 h 4 min	48 min	39 min
30	426	290	2 h 24 min	1 h 12 min	48 min	36 min	29 min
25	356	242	2 h 1 min	1 h	40 min	30 min	24 min
Calculation methods							
1 kg/cm² (cylinder pressure gauge reading) = 14.22 psi							
So, if pressure gauze shows 100 kg/cm² = 1,422 psi							
0.68 × Pressure on gauge (in psi)/Required oxygen per minute = Oxygen run up to in minute							
9.6696 × Pressure on gauge (in kg/cm²)/Required oxygen per minute = Oxygen run up to in minute							

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Hyperbaric Oxygen Therapy

Amit Gupta

INTRODUCTION

Oxygen therapy is always considered as a drug and can be easily given under normal pressure but requires compression if we want to give it at >1 atmospheric pressure. Details of oxygen therapy are already described earlier. Hyperbaric oxygen therapy (HBOT) is the therapy when 100% oxygen is used for therapeutic indications at higher than the normal atmospheric pressure. This therapy is given in specialized chambers of various sizes. The chamber can accommodate one patient (called monoplace) or multiple patient chamber (multiplace). HBOT has been available for the last many decades and used for many indications. HBOT is considered a safe therapy with mild and reversible adverse effect. Systemic administration of 100% oxygen to lungs at >1 atmospheric absolute (ATA-typically 2–3 ATA) to increase the amount of oxygen dissolved in the blood to fight infection or minimize injury. The duration of each session lasts 30 min–2 hours and a person may need 5–40 treatments until clinical improvement is seen.

HISTORY

Historically, the first documented hyperbaric chamber was designed by British physician and clergyman, Nathaniel Henshaw in 1662, using bellows and unidirectional valves to change atmospheric pressure in a sealed chamber called *domicilium* almost a century before oxygen was invented. This was followed in 1690 by Edmond Halley who designed a diving bell with various modifications over time to extend underwater time to a little over 4 hours. A number of other hyperbaric chambers were designed all over the globe across three centuries with limited clinical success in various illnesses until in 1955–56, Churchill-Davidson evaluated the trials on HBOT at St. Thomas Hospital, London to augment the effects of radiation therapy in cancer patients which begin the era of its scientific use in clinical medicine. There has been a history of using HBOT from antiaging treatment to chronic neurological conditions with weak research background. This therapy is available since decades and used in various diseases with little or no evidence so HBOT also termed as *"therapy in search of diseases"*. Presently, the primary scientific body for clinical practice of hyperbaric medicine is Undersea and Hyperbaric Medical Society (UHMS), a nonprofit organization which was founded in 1967 and the European Committee for Hyperbaric Medicine (ECHM) which systematically review all scientific literature related to HBOT and formulate absolute indications for its use.

PHYSIOLOGY

Under normal condition, we live at 1 atmospheric pressure (ATA) or in medical term 760 mm Hg, (14.7 psi,760 torr, or 33 feet of undersea water). At the depth of 33 feet (10 m) diver is exposed to 2 ATA (1 ATA from the atmosphere above the water and 1 ATA 33 feet/10 m below the sea water). HBOT effect based on *Henry's law* which states that the amount of gas dissolved in a liquid is in proportion to the pressure of gas above the liquid and *Boyle's law* which states that volume and pressure are inversely proportional to each other, i.e., a gas will compress proportionately to the amount of pressure exerted on it.

Hyperbaric oxygen therapy is application of atmospheric pressure > 1 ATA. HBOT increases partial pressure of oxygen and hence its availability at cellular level. Tissues at rest extract 5–6 mL of oxygen per deciliter of blood, assuming normal perfusion. Administering 100% oxygen at normobaric pressure increases the amount of oxygen dissolved in the blood to 1.5 mL/dL; at 3 atmospheres, the dissolved-oxygen content is approximately 6 mL/dL, which is more than enough to meet resting cellular requirements without any contribution from hemoglobin. It is interesting to know that 100% oxygen at 3 ATA can supply enough dissolved oxygen to support life without hemoglobin.

RATIONALE OF USE OF HYPERBARIC OXYGEN THERAPY/MECHANISM OF ACTION

The main principle of using the HBOT is to improve tissue oxygenation. So, the primary indications are disease with *regional or global hypoxia*. Second indications are anaerobic infections which develop in hypoxic areas and lack of host response to infection. So, HBOT provides relief of ischemia and improves host response to *infection.* HBOT also provides stimulus for angiogenesis in hypoxic area (**Fig. 1**).

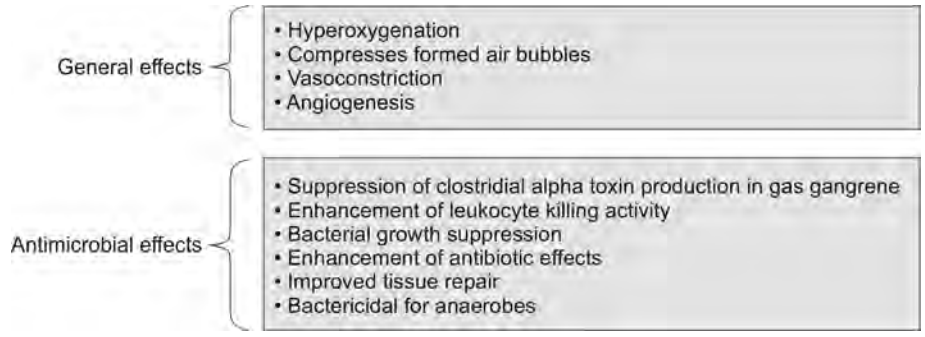
General effects
• Hyperoxygenation
• Compresses formed air bubbles
• Vasoconstriction
• Angiogenesis
Antimicrobial effects
• Suppression of clostridial alpha toxin production in gas gangrene
• Enhancement of leukocyte killing activity
• Bacterial growth suppression
• Enhancement of antibiotic effects
• Improved tissue repair
• Bactericidal for anaerobes

FIG. 1: Rationale of use of hyperbaric oxygen therapy.

EQUIPMENT AND PROCEDURE

Hyperbaric chambers are used to administer the HBOT. There are two types of hyperbaric oxygen chambers—(1) monoplace chamber and (2) multiplace chamber are used.

1. *Monoplace chamber*: It can accommodate one patient in supine position (**Fig. 2**), monitoring is done from outside, compressed with 100% oxygen, patient breathes without any mask, main advantages are its less cost and space requirement.
2. *Multiplace chamber*: Multicompartment treatment chamber where many patients (**Fig. 3**) can sit or accommodate multiple patients' beds with attendants, patient breathes oxygen through facemask endotracheal tube or face hood, monitoring is done inside the chamber which is compressed with air, this is suitable for critically ill patients requiring ventilation and continuous monitoring. Pressure and duration of therapy depends on situation, generally 2–6 ATA for 2–6 hours.

Care in Chamber—Practical Aspect

Fire safety measures need to be maintained by keeping electrical circuit outside the chamber, and through insulated cables. Use of defibrillation is controversial because of fire but decompression of the chamber is required before using defibrillation. Intravenous infusion can be given by flexible bags not by glass bottles. Battery-operated syringe infusion pump can be used. Tracheal tube cuff, face mask seal should be monitored closely. Positive pressure ventilation and volume cycle ventilators can be used.

Treatment Guidelines

Manage ABC, vascular access, 100% oxygen, and monitoring vitals. Treatment of primary causes immediate removal from source, early aggressive debridement, and antimicrobials in cases of infective etiology. Determine the need for HBOT, early transfer to facility with availability of HBOT chamber after weighing risks and benefits, if not available. Comprehensive physical examination to rule out any contraindications. Baseline examination before treatment including ABG for hypoxemia and chest roentgenogram to rule out pneumothorax. Fill all balloon devices with fluid in place of air to prevent rupture due to air expansion. Decongest, if sinus complaint and myringotomy in cases of otitis media.

- *Pressure*: HBOT usually starts at 2–2.5 ATA for infections, 2.8 ATA for decompression sickness
- *Duration*: 90–120 minutes

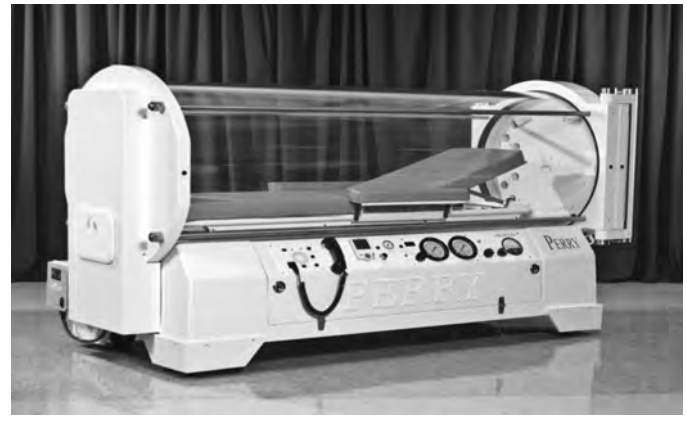

FIG. 2: Monoplace chamber for hyperbaric oxygen therapy.

FIG. 3: Multiplace chamber for hyperbaric oxygen therapy.

- *Frequency*: One or two times daily depending on severity
- *Treatments*: Until clinical improvement
- *Review*: After 30–60 sessions, but only 1–2 in decompression sickness and gas embolism

INDICATIONS

Medical societies such as Undersea and Hyperbaric Medical Society (UHMS) and European Committee for Hyperbaric Medicine (ECHM) were established to address the shortcoming on HBOT and to reach on common consensus over indications of HBOT (**Fig. 4**).

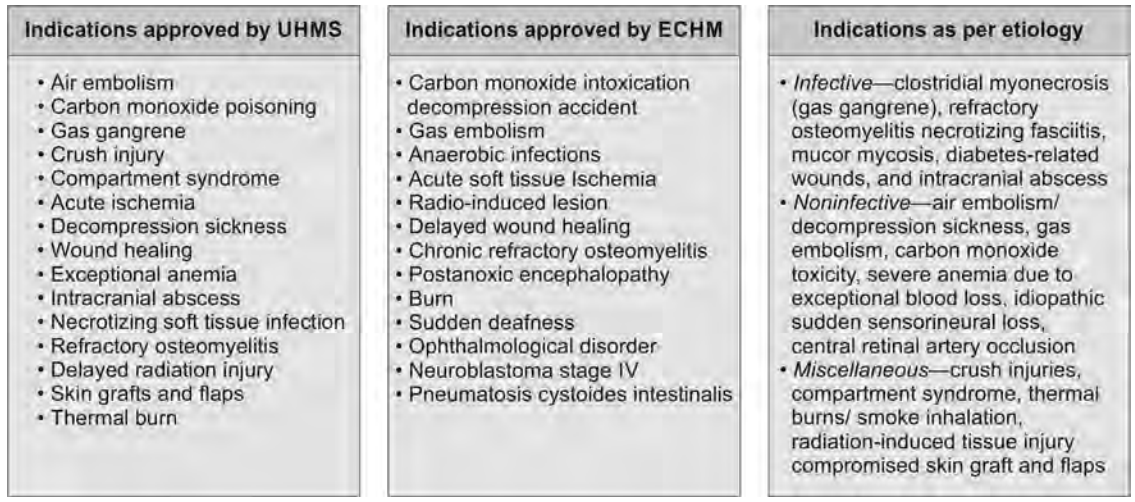
Indications approved by UHMS
• Air embolism
• Carbon monoxide poisoning
• Gas gangrene
• Crush injury
• Compartment syndrome
• Acute ischemia
• Decompression sickness
• Wound healing
• Exceptional anemia
• Intracranial abscess
• Necrotizing soft tissue infection
• Refractory osteomyelitis
• Delayed radiation injury
• Skin grafts and flaps
• Thermal burn
Indications approved by ECHM
• Carbon monoxide intoxication decompression accident
• Gas embolism
• Anaerobic infections
• Acute soft tissue Ischemia
• Radio-induced lesion
• Delayed wound healing
• Chronic refractory osteomyelitis
• Postanoxic encephalopathy
• Burn
• Sudden deafness
• Ophthalmological disorder
• Neuroblastoma stage IV
• Pneumatosis cystoides intestinalis
Indications as per etiology
• Infective—clostridial myonecrosis (gas gangrene), refractory osteomyelitis necrotizing fasciitis, mucor mycosis, diabetes-related wounds, and intracranial abscess
• Noninfective—air embolism/ decompression sickness, gas embolism, carbon monoxide toxicity, severe anemia due to exceptional blood loss, idiopathic sudden sensorineural loss, central retinal artery occlusion
• Miscellaneous—crush injuries, compartment syndrome, thermal burns/ smoke inhalation, radiation-induced tissue injury compromised skin graft and flaps

FIG. 4: Indications of hyperbaric oxygen therapy (HBOT).

CONTRAINDICATIONS

- *Absolute*: *Untreated pneumothorax*—can convert to tension pneumothorax, *use of cisplatin*—delayed wound healing, and *bleomycin*—significant lung injury or doxorubicin can lead to cardiac toxicity.
- *Relative*: *Cardiac instability*—do not use monoplace chamber but multiplace chamber with close monitoring, if benefits outweigh risks, *history of thoracic surgery, upper respiratory infections, seizure disorder, high fever, stapes implant, and chronic sinusitis.*

CLINICAL APPLICATION

- *Decompression sickness* occurs when atmospheric pressure decreases too rapidly as in scuba diving or rapid ascent while flying in unpressurised aircraft. Symptoms of this condition include joint pain (bends), headache, dizziness, fatigue, tingling or numbness, and sometimes, a skin rash. These symptoms are caused by blocked blood supply, damage from direct mechanical effects, or later biochemical actions from suspected bubbles evolving from inert gas dissolved in blood or tissues. The treatment of choice is recompression. Emergency treatment includes high-flow oxygen, positioning in left lateral position with head tilted down, and maintaining blood pressure. HBOT acts by decreasing the size of bubbles of nitrogen with increase in pressure as well as oxygen gradient thereby causing efflux of nitrogen from bubble into bloodstream.
- *Carbon monoxide (CO) poisoning* occurs accidentally due to inhalation of CO especially with the use of gas geysers in closed spaces. The binding affinity of CO to hemoglobin is around 200 times that of oxygen and it shifts oxygen dissociation curve to left thereby decreasing oxygen supply to the tissues. It also binds cytochrome oxidase and myoglobin. Symptoms of CO poisoning are nonspecific and include flu-like symptoms such as headache, nausea, dizziness, and visual changes. Serious manifestations include loss of consciousness, seizures, electrocardiogram (ECG) changes, and acidosis. The treatment is based on theory that oxygen competitively replaces CO from hemoglobin thereby reversing symptoms. However, at room air, this takes around 300 minutes. With 100% oxygen, this time is reduced to about 90 minutes and HBOT reduces it further to about 30 minutes only. HBOT in addition reduces cytochrome oxidase and also prevents delayed neurological sequel. HBOT is more effective if the treatment is initiated sooner. A total of 1–5 sessions may be needed depending on clinical situation at 2.5 ATA for 60–90 minutes.
- *Crush injuries and compartment syndrome* lead to acute peripheral ischemia and edema and have poor outcome even after surgical intervention due to reperfusion response. Symptoms include severe pain, swelling, weakness, pain with passive stretch, and tense compartment as compartment pressure exceeds capillary perfusion pressure. HBOT is beneficial in both impending stage when surgery is not indicated and after fasciotomy to decrease morbidity. HBOT causes hyperoxygenation, reduction in blood flow allowing capillaries to reabsorb extrafluid thereby decreasing edema, decreased neutrophilic adherence, and reducing reperfusion injury as it generates scavengers to destroy oxygen radicals. It should be started as soon as feasible, preferably within 4–6 hours of injury. Postsurgery, HBOT should continue at 2.5 ATA for 60–90 minutes two to three times daily until visible improvement.
- *Necrotizing soft tissue infections* are rapidly progressive, life-threatening, deep-seated infections involving fascia and subcutaneous tissues with mortality in range of 20–40%. The organisms involved include *Staphylococcus aureus, Escherichia coli, Bacteroides fragilis*, and various species *of Streptococci, Enterococci*, and *Clostridium*. These infections are named based on their clinical presentation and include necrotizing fasciitis, clostridial and nonclostridial myonecrosis, and Fournier gangrene. The primary treatment includes aggressive, early surgical debridement, often repeated, with broad spectrum antibiotic therapy. HBOT plays an adjunctive role but with significant reduction in mortality, avoiding amputations in selected cases and reduced number of debridement compared to surgical treatment alone. HBOT starts at 2.5 ATA for 60–90 minutes one to two times daily until maximum clinical improvement.

- *Gas gangrene,* also known as clostridial myonecrosis, is a rapid, progressive, and invasive clostridial infection of previously healthy muscle. The most common species implicated is *Clostridium perfringens*, a gram positive, spore forming, and anaerobic bacteria mainly in traumatic or postsurgical cases. Symptoms include pain out of proportion to size of infected area, low-grade fever, disproportionate tachycardia, anxiety, blebs, and bulla formation with crepitus felt during clinical examination mainly due to action of exotoxin production most notably alpha toxin which degrades cell membranes and produces a liquefactive necrosis, and in combination with other toxins, has a powerful myocardial depressant effect. The rationale for HBOT lies in the fact that hyperbaric oxygen at 3 ATA completely suppresses alpha toxin production and prevents any further damage. In addition, it has an antianaerobic organism effect which suppresses the growth of clostridia. However, the benefits of HBOT are best seen in combination with antibiotics and aggressive debridement.
- *Chronic refractory osteomyelitis* is an infection of the bone along with inflammation-induced bony destruction over months or even years and characterized by presence of organisms, low-grade inflammation, and even necrotic bone and fistulous tracts, which have not responded to conventional interventions including antibiotics and surgery. HBOT in these cases helps by having a direct suppressive effect on anaerobic organisms, augmenting the efficacy of antibiotics, osteogenesis by promoting fibroblast activity, and enhancing osteoclast activity. However, management of this condition requires a multidisciplinary approach including aggressive debridement, good local wound care, offloading (if on pressure point), appropriate antibiotics, nutritional support, and control of serum glucose in addition to HBOT.
- *Exceptional anemia* in patients who are unable to receive blood products due to medical or religious reasons can be candidates for HBOT. Tissues at rest extract 5–6 mL of oxygen per deciliter of blood, assuming normal perfusion. Administering 100% oxygen at normobaric pressure increases the amount of oxygen dissolved in the blood to 1.5 mL/dL; at 3 atmospheres, the dissolved-oxygen content is approximately 6 mL/dL, which is more than enough to meet resting cellular requirements without any contribution from hemoglobin. It is based on oxygen debt which is the difference between volume of oxygen consumed during and after the insult and baseline volume during same time interval. Since the central nervous system (CNS) and cardiovascular systems are the two most oxygen-sensitive systems in the body, patients with oxygen debt >33 L/m^2 do not survive, whereas patients with debt <9 usually recover. HBOT in these cases at 2–3 ATA is needed till patient can receive blood products, has no end-stage organ failure or no calculated oxygen debt.
- *Idiopathic sudden sensorineural hearing loss (SSHL)* is the predominant though relatively rare cause of SSHL which presents as unilateral tinnitus, vertigo or blocked ear in addition to hearing loss. The main etiology is related to inner ear hypoxia as cochlea requires a high oxygen supply and hence the role of HBOT in treating this condition. HBOT at 1.5–2.5 ATA for 90 min/day for 2–3 weeks is recommended for significant improvement in this condition.

POTENTIAL HARM, SAFETY, AND PRECAUTIONS

Hyperbaric oxygen therapy is considered safe. Adverse effects are generally mild and reversible. To avoid serious life-threatening adverse effect, it is important to take strict precaution, like proper installation and maintenance of facility with adequate staffing and their specific training. Sometime low risk of fire and explosion in monoplace chamber is present which is difficult to deal with presence of a patient. Claustrophobia is frequent problem seen in monoplace chamber and for successful therapy sedation is required. Sedation should be used cautiously

Barotrauma

Barotrauma is generally used when there is a tissue trauma due to differential pressure of the gas. The most common areas of the body affected are ear sinuses and the lungs. Most commonly reported adverse effect is middle ear barotrauma and patient complains of ear pain and discomfort which can be minimized by topical or systemic vasoconstrictors and myringotomy in special cases. Pulmonary barotrauma is a problem particularly during decompression phase of HBOT. Pulmonary barotrauma can be avoided by careful selection of patient (contraindicated in emphysema) and whenever it is suspected, therapy should be stopped immediately. Pneumothorax should be treated with chest tube insertion.

Oxygen Toxicity

As stated earlier, oxygen is considered as a drug and at high dose it generates free radicles which cause oxidation of chemical components of the tissue. Most common organs affected by oxygen toxicity are *lung*—pulmonary barotrauma during decompression phase, pulmonary toxicity can be reduced by intermittent inhalation of normal oxygen, *central nervous system*—seizure, muscular twitching, *eyes*—reversible myopia and cataract, prolonged oxygen therapy, and pressure affect the shape of the lens and refractory index, but these changes are reversible, one therapy is over. HBOT-induced cataract is usually not reversible.

SUMMARY

Hyperbaric oxygen therapy started as decompression illness therapy about 100 years ago, but since the last 50 years their role in various other illnesses is also proposed. HBOT is a therapy when 100% oxygen is administered intermittently at a pressure higher than the normal sea level pressure in the specified chamber. Scientific societies on hyperbaric medicine approved specific indications for use of HBOT. HBOT has certain specific indications in both infectious and noninfectious diseases that are often additive/adjunct to routine treatment and has been shown to be beneficial in most of the approved indications despite paucity of randomized controlled trials for its use. However, aggressive debridement, good local wound care, appropriate antimicrobial therapy, maximizing nutritional intake, and controlling serum glucose levels are the cornerstones to ensure the success of HBOT in approved indications.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Noninvasive Ventilation

Kishalay Datta

INTRODUCTION

In early nineties, increasing experience with positive-pressure ventilation led to development of a ventilatory strategy, where ventilation could be delivered through a well-fitted mask in patients of obstructive sleep apnea (OSA). Increasing success of noninvasive ventilation (NIV) in cases of OSA led to its adoption in ventilatory management of patients with chronic obstructive pulmonary disease (COPD). Finally, in the next ensuing 20 years, noninvasive positive-pressure ventilation (NIPPV) delivered via a mask widely became adopted as the first-line ventilatory management in many medical centers over the whole world.

Noninvasive ventilation/NIPPV refers to the administration of ventilatory support through the patient's upper airways using oronasal/nasal/similar masks without using an invasive artificial airway (endotracheal or tracheostomy tube). NIV has now become an integral tool in the management of both acute and chronic respiratory failure, in both hospital and home settings. NIV is being used as a replacement for invasive ventilation in many cases due to its advantages and flexibility.

The basic *concept of NIPPV* is the application of positive pressure during the respiratory cycle (inspiration and expiration). The simplest application of that is a continuous positive pressure throughout the respiratory cycle, which is named continuous positive airway pressure (CPAP). The next application is administration of two different levels of pressure, one for inspiratory phase and one for the expiratory phase, otherwise known as bilevel positive airway pressure (BiPAP). NIPPV operates with application of positive pressure to upper airway (via masks) either by using a conventional ventilator or specialized equipment such as BIPAP/CPAP machines. NIPPV can also be given by volume cycled or pressure cycled ventilators. CPAP/BIPAP/pressure support ventilation (PSV)/ other modes can all be used in NIV, as per ventilatory needs of the patient.

Evaluation and management of acute respiratory failure are a routine for emergency physician. It is important for emergency physician to be well aware about NIV/NIPPV, patient selection, modes of delivery, application of appropriate positive pressure, and appropriate monitoring methods. Patient on NIV should be monitored closely and signs and every hourly symptoms of patient should be evaluated to determine success or failure of therapy.

MODES OF NONINVASIVE VENTILATION

There are two *modes of NIV*—(1) CPAP and (2) BiPAP. In CPAP, same pressure is applied/set during inspiratory and expiratory phase of respiratory cycle. CPAP is comparable to positive end-expiratory pressure (PEEP) used in invasive mechanical ventilation. CPAP is most useful in hypoxic respiratory failure. In BiPAP, different pressure is applied/set in inspiratory and expiratory phase of respiratory cycle, these pressures known as inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). EPAP is the pressure which is comparable to the pressure of CPAP. BIPAP is useful in both hypercapnic as well as hypoxic respiratory failure. High-flow nasal cannula (HFNC) is a recent method of delivering NIV through nasal cannula instead of tight-fitting face mask.

Continuous Positive Airway Pressure

This mode can be used in patients, who are breathing spontaneously (a must). At end expiration, pressure in airways equals to pressure at mouth and both equates with normal atmospheric pressure. Surfactant prevents collapse of the alveoli which would have otherwise collapsed at this low end-expiratory pressure.

In diseased state, the alveoli collapse at low end-expiratory pressures due to lack of surfactant. So hypoxia occurs as a result of V/Q mismatch and shunting. Large number of alveoli collapses during disease process in lungs leading to decreased lung compliance. Once lung compliance decreases, more energy is needed to inflate the alveoli. So, higher inflation pressures are needed to open the diseased alveoli. Thus "WOB" (work of breathing) increases. Such high pressures needed to open diseased alveoli may also result in alveolar rupture leading to barotrauma.

Continuous positive airway pressure and PEEP both thus act as "internal splints" for unstable alveolar units. CPAP also elevates end expiratory pressure above atmospheric pressure thus keeping unstable alveolar units from collapsing and then finally "recruiting" them for useful ventilation. CPAP also helps

in the recruitment of collapsed alveoli thereby increasing functional residual capacity (FRC) of lung.

Continuous positive airway pressure thus decreases "WOB". CPAP can reverse hypoxia by restoration of ventilation to perfused areas (recruitment) thereby improving lung compliance. Stabilization of upper airways is also a purpose of this mode.

Bilevel Positive Airway Pressure

Continuous positive airway pressure does not provide support during inspiration as it only maintains positive pressure in airways. So, PSV was added to provide pressure support (PS) during inspiration in patients with poor respiratory effort. This resulted in creation of a new mode called BiPAP. So, BiPAP has two components providing pressures at two levels, i.e., inspiratory and expiratory level—(1) PSV, which provides inspiratory pressure and (2) PEEP, which provides expiratory pressure. BiPAP and CPAP both have disadvantage of propensity toward hyperinflation of lung.

PHYSIOLOGIC CHANGES WITH NIV: HOW DOES NIPPV WORKS?

While critically ill patient on NIV, this is very important that emergency physician should be aware about the physiologic changes on vital system (respiratory and cardiovascular). Primary goal of NIV is to decrease the WOB and improve gas exchange and oxygen saturation. Positive pressure application in NIV reduces the WOB by 60% through several mechanisms, similarly PS application also reduces the WOB by decreasing the inspiratory transpulmonary pressure. PEEP and PS help in improving ventilation perfusion mismatch, oxygenation, and removal of carbon dioxide removal. Positive pressure ventilation causes changes in circulatory system as well in the form of decrease in preload and afterload. This can help in cases of acute cardiogenic pulmonary edema. In preload-dependent patient, positive pressure alters the dynamics of intrathoracic pressure (decreases the negative intrathoracic pressure) and results in hypotension. So, the use of positive pressure cautiously in patient who is preload dependent. In brief *NIV, mechanism of action* is summarized here.

Noninvasive positive-pressure ventilation works by:

- Decreasing inspiratory WOB
- Decreasing inspiratory muscles work
- Decreasing "pressure time product" (PTP) of inspiratory muscle—an index for muscle O_2 consumption (PTP of diaphragm is reduced by 25% with PSV alone, while with PSV + PEEP, it goes down to 40%)

SELECTION CRITERIA FOR NIPPV

First and foremost, criteria are patient should be *conscious and spontaneously breathing*. Patient should have the ability to protect airway himself, be cooperative and also should be hemodynamically stable. Care should be taken that there are no excessive respiratory secretions present in such patients, undergoing a trial of NIPPV. Selecting patients for NIPPV requires careful consideration of its indications and contraindications. A trial of NIPPV is worthwhile in most patients who do not require emergent intubation and have a disease known to respond to NIPPV, assuming that they lack contraindications. The need for emergent intubation is an absolute contraindication to NIPPV. Further Indications and contraindications are discussed in **Table 1**.

TABLE 1: Indication and contraindications for noninvasive ventilation.

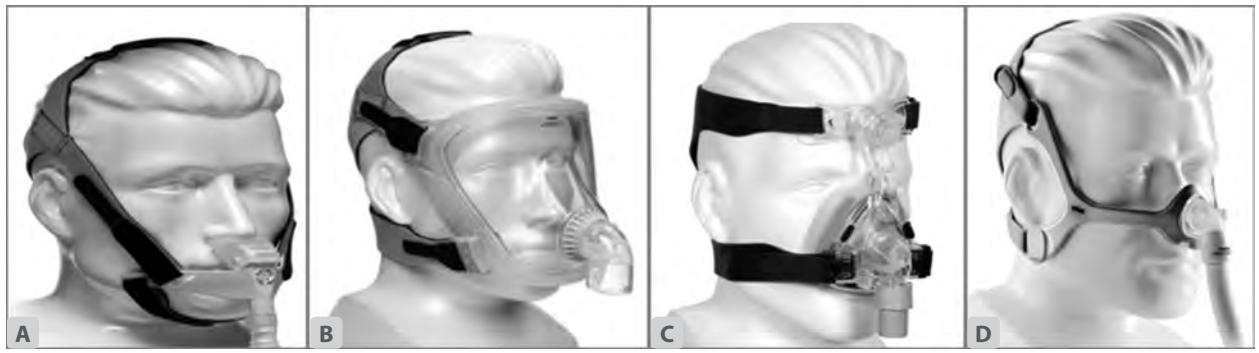
Indications	*Contraindication*
• Acute exacerbation of chronic obstructive pulmonary disease where $PaCO_2$ > 45 mm Hg or pH < 7.30 • Cardiogenic pulmonary edema • Acute hypoxemic respiratory failure • Obstructive sleep apnea–hypopnea syndrome • Congestive heart failure • Obesity hypoventilation syndrome • Immunocompromised host with acute respiratory failure • Postextubation and respiratory failure after extubation • Facilitate weaning • Asthma and status asthmaticus	• Patients having no spontaneous breathing • Unconscious patient • Severe hemodynamic instability of the patient • Upper airway obstruction • Facial trauma in a patient • Pneumothorax • Inability to cooperate, protect the airway, or clear secretions • High aspiration risk • Prolonged duration of mechanical ventilation anticipated • Recent esophageal anastomosis

INTERFACE OR MASK FOR NIPPV

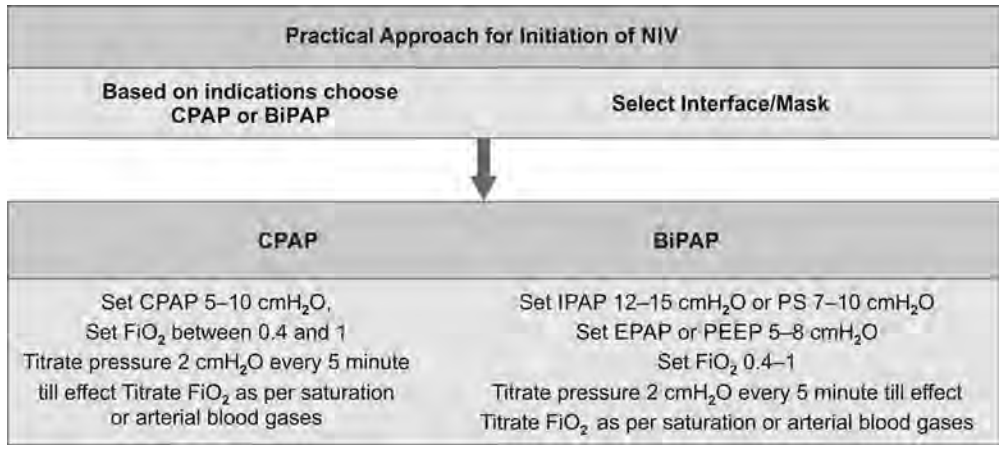
Interface or masks are devices, which connect ventilator tubing to facial region of the patient, during NIV. Patient-ventilator interfaces available for NIPPV include a full-face mask/oronasal mask/nasal mask/nasal prongs/helmets (**Figs. 1A** to **D**). The full-face mask includes the eyes, nose, and mouth, while the oronasal mask includes the nose and mouth, but not the eyes. A simple nasal mask is also available. Straps hold the interface in place and should be adjusted to avoid excess pressure on the nose or the face. The straps should be loose enough to allow one or two fingers to pass between the face and the strap. When a nasal mask is used, a chin strap is usually necessary to maintain closure of the mouth. The efficacy of the various interfaces has been debated over years. The face mask confers physiologic improvement, but the nasal mask is better tolerated. Whichever mask is selected, it is helpful to keep the following points in mind:

- Most patients with acute respiratory failure are mouth breathers; therefore, NIPPV delivered by a nasal mask may result in a larger air leak through the mouth thus leading to a bad outcome.
- The nasal air passages offer significant resistance to airflow, which can reduce the beneficial effects of NIPPV, if low positive pressure is used.
- The monitoring for aspiration in NIPPV patients is often difficult.
- Humidification of the inspired air is difficult through any form of masks.

The helmet interface has been used to improve patient tolerance in many cases. Moreover, the helmet interface allows patients to talk, read, and drink through a straw, while minimizing complications such as skin necrosis, gastric



FIGS. 1A TO D: Different types of interface/mask attachments.


Practical Approach for Initiation of NIV
Based on indications choose CPAP or BiPAP
Select Interface/Mask
CPAP
BiPAP
Set CPAP 5–10 cmH2O,
Set FiO2 between 0.4 and 1
Titrate pressure 2 cmH2O every 5 minute till effect Titrate FiO2 as per saturation or arterial blood gases
Set IPAP 12–15 cmH2O or PS 7–10 cmH2O
Set EPAP or PEEP 5–8 cmH2O
Set FiO2 0.4–1
Titrate pressure 2 cmH2O every 5 minute till effect
Titrate FiO2 as per saturation or arterial blood gases

(BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; NIV: noninvasive ventilation)

FIG. 2: Practical Approach for Initiation of NIV.

distension, and eye irritation. But this interface may cause accumulation of CO_2 within the helmet, may produce noise sufficiently high enough to cause hearing damage, and may also to lead to more patient-ventilator asynchrony, and less relief of inspiratory effort of the patient.

HOW TO INITIATE NIPPV IN PATIENTS?

As per medical condition, appropriate patient is selected for the NIV as per indications. Emergency physician should be able to choose the mode of ventilation, type of interface PEEP/CPAP level, IPAP/PS level, and FiO_2 level. While setting the CPAP/PEEP, start with 5 cmH_2O and increase the PEEP by 2 cmH_2O every 10–15 minutes with goal of improving the oxygen saturation. *Initiation of NIV* should be done through *graded steps* as given below, and practical approach for initiation of NIV is given in **Figure 2**.

- Selection of proper interface is foremost followed by acclimatization of the patient with the interface
- Start with low pressure/volume in spontaneous mode
- O_2 supplementation should be continued @ 3–5 L/min and adjusted as per pressure changes.
- Initial IPAP should be started at 8–10 cmH_2O while EPAP at 3–4 cmH_2O.
- An IPAP:EPAP ratio should be kept constant at 2.5:1.
- Gradual increase of both pressures at 1–3 cmH_2O increments can be done.
- Care should be taken that pressure should not exceed > 20 cmH_2O.

MONITORING OF PATIENTS ON NIPPV

After NIPPV is initiated, the patient should be observed closely for the first 4–6 hours to troubleshoot, provide reassurance, and look for deterioration of clinical condition of the patient. Improvement of the pH and arterial carbon dioxide tension ($PaCO_2$) within one and a half to two hours predicts success. In contrast, conditions such as worsening encephalopathy or agitation, inability to clear secretions, inability to tolerate any of the interfaces, hemodynamic instability, or decreased oxygenation may indicate toward failure. The use of sedatives and analgesics is sometimes employed by clinicians to increase tolerance and comfort of NIPPV as well as to treat comorbid anxiety or pain.

PREDICTORS OF SUCCESS OF NIPPV

One of the most consistent signs of favorable response to NIPPV is drop-in respiratory rate within 1st to 2nd hour of starting of NIPPV. The following parameters should be considered for successful NIPPV trial.

- Arterial carbon dioxide tension > 45 and < 90 mm Hg at initiation of NIPPV
- pH > 7.1 at initiation of NIPPV
- Less air-leakage via interface during NIPPV
- Ability of the patient to coordinate breathing with the ventilator
- Lower severity of illness (APACHE SCORES) and young age of the patient

Periodic assessment of clinical indication of the patient remains as a best predictor of success. This is very critical to predict which patients will fail NIV and require intubation. Frequent reassessment of clinical variables in patients on NIV is necessary, which indicate the likelihood of success or failure, should be assessed after 30–60 minutes of treatment.

- *Predictors of failure of NIPPV*: Sepsis as a cause of the respiratory failure, ARDS, and higher severity score (SAPS II)
- *Predictors of success of NIPPV*: Improving pH, improving $PaCO_2$, improving PaO_2/FiO_2 ratio

WHAT TYPE OF VENTILATORS CAN BE USED FOR NIPPV?

Noninvasive ventilation can be delivered via all standard type of ventilators found in most intensive care units of hospitals or by a portable ventilator. Nowadays *"hybrid ventilators"* offering both forms (invasive and noninvasive) of ventilatory support are also available. However, the standard invasive ICU ventilator has numerous advantages over the BIPAP/CPAP machines. The advantages are:

- A precise concentration of oxygen can be delivered, i.e., FiO_2 can be set.
- Separate inspiratory and expiratory tubing minimizes the rebreathing of carbon dioxide.
- Large mask leaks or patient's disconnection can be readily detected.
- Better monitoring and alarm features are present in standard ventilators.
- Higher inspiratory pressures (>20 cmH_2O) can be given if need arises.
- Backup ventilation is present when needed.

In addition, certain modes can only be delivered by a standard ICU ventilator (e.g., volume controlled, pressure controlled, and time-limited PSV, etc.)

WHAT MODES OF VENTILATOR CAN BE USED FOR NONINVASIVE VENTILATION?

Noninvasive positive-pressure ventilation can be delivered using the same modes that are used for invasive mechanical ventilation, although certain modes may be used more frequently:

- Assist control mode is the most common mode chosen by doctors who want a guaranteed minute ventilation.
- Pressure support ventilation is the most common mode chosen by doctors who focus on patient's comfort and synchrony.
- Continuous positive airway pressure/BiPAP is used for patients with acute respiratory failure.
- Proportional assist ventilation delivers an inspiratory pressure that is proportional to patient effort. This allows better patient-ventilator synchrony.

HOW TO SET THE VENTILATOR FOR NIPPV?

The selected mode determines which parameters need to be set during the initiation of NIV, e.g., assist control mode requires a tidal volume, respiratory rate, inspiratory flow rate, PEEP, and (FiO_2) to be set. BiPAP mode delivers both IPAP and EPAP like invasive ventilation. Patient of chronic obstructive lung disease and acute severe asthma commonly present to ED with acute dyspnea. Emergency physician must be aware about the initiation, adjustment, and weaning of NIPPV in these patient (**Table 2**).

WEANING

Weaning from NIPPV may be accomplished by progressively decreasing the amount of positive airway pressure, permitting the patient to be disconnected from the NIPPV for progressively longer durations, or a combination of both.

COMPLICATIONS OF NIPPV

These are common complications:

- Leakage via mask leading to multiple adjustments
- Intolerance of positive pressure by patient
- Gastric distention due to positive pressure
- Aspiration (rare)
- Facial skin breakdown (long-term use)
- Increased gastric pressure may lead to abdominal compartment syndrome
- Hypotension
- Barotrauma

TABLE 2: Managing COPD/asthma by noninvasive respiratory support.

	Noninvasive positive pressure ventilation (NIPPV)	***High-flow nasal cannula (HFNC)***
Initiation	*COPD*: EPAP 5–8, IPAP 5–10, FiO_2 80–100% *Asthma*: EPAP 0–5, IPAP 5–10, FiO_2 100%	*Start:* • Flow: 50% of maximum • FiO_2: 100%
Adjustment	• Titrate up IPAP (asthma and COPD) and EPAP (COPD) as tolerated to reduce work of breathing—monitor changes in tidal volume and minute ventilation • To increase ventilation, increase the gradient between IPAP: EPAP • Wean FiO_2 as tolerated to keep O_2 sat > 88%	*Adjust:* • Increase flow to reduce work of breathing and increase CO_2 clearance • Wean FiO_2 as tolerated to keep O_2 sat > 88%
Weaning	Wean: Reduce IPAP: EPAP gradient as work of breathing improves	Wean: Reduce flow as work of breathing improves

(COPD: chronic obstructive pulmonary disease; EPAP: expiratory positive airway pressure; IPAP: inspiratory positive airway pressure; FiO_2: fraction of inspired oxygen)

HIGH-FLOW NASAL CANNULA

Traditionally, we are using nasal cannula for providing supplemental oxygen for hypoxic patient. With this nasal cannula, 25–35% of supplemental oxygen can be delivered to the patient. Interest was developed regarding delivering the greater oxygen concentration with higher flow rates of oxygen by using HFNC. Since year 2000, HFCN was commercially available, which consists of specialized nasal cannula oxygen, delivery device, and humidification system. *Since the use of HFNC is becoming common, ability to produce positive airway pressure is questioned and various physiologic studies suggest the quality and quantity of positive pressure effect generated by HFNC are meager*. Mild-to-moderate hypoxic patient responds well to HFNC provides reliable improvement in oxygen saturation. HFNC is helpful for hypoxic respiratory failure and in patient after cardiac surgery. HFNC should not be used as first-line therapy for COPD and acute cardiogenic pulmonary edema, in these conditions traditional NIV is much beneficial.

SUMMARY

Emergency physician frequently manages acute respiratory failure in emergency department and selected patient can be managed successfully by NIV. Emergency physician should know their beneficial and detrimental physiologic changes associated with their use. NIV is delivery of the positive pressure ventilation through well-fitted nasal facial or oronasal mask in patient of hypoxic respiratory failure. NIV can be used in acute asthma COPD acute cardiogenic pulmonary edema traumatic respiratory failure community acquired pneumonia. CPAP or BiPAP modes can be used to deliver the positive pressure NIV. Patient should be monitored closely; hourly vital signs should be documented as physiologic changes occur in patient on NIV. Emergency physician should aware of failure of NIV which is common so require constant vigilance and reassessment of patient with acute respiratory failure.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Mechanical Ventilation

Mrinal Sircar, Saurabh Mehra, Devendra Richhariya

INTRODUCTION

Mechanical ventilation and intubation are an indispensable part of emergency room (ER) management. The indication for mechanical ventilation is either to provide assistance in breathing and/or airway protection. This applies to diverse conditions including trauma, sepsis, exacerbations of asthma and chronic obstructive airway disease (COPD), severe pneumonia, congestive cardiac failure, and neurological disorders associated with low Glasgow Coma Scale (GCS) or loss of protective airway reflexes, etc. All those working in ER need to be well versed in providing mechanical ventilation in ER as also during transport to ICU, operating theatres or for imaging or while transporting patients by ambulance.

PHYSIOLOGY OF BREATHING

Spontaneous breathing involves contraction of diaphragm and intercostal muscles to cause expansion of thorax and movement of air into lungs. Physiologically, development of a pressure gradient between the alveoli and the atmosphere causes air movement into lungs. Since this involves generation of a negative pressure, spontaneous ventilation is negative pressure ventilation. The expiration is a passive phenomenon, however; in diseased states it may require active contraction of accessory muscles. The ventilation involves four pressures *(mentioned below)* and four pressure gradients (**Table 1**) which must be understood to know the physiology of breathing (**Fig. 1**).

1. *Airway opening pressure (P_{awo}) (or airway pressure or mouth pressure)*: It is zero or atmospheric pressure unless a positive pressure is applied.
2. *Pressure at body surface (P_{bs})*: It is zero or atmospheric pressure.
3. *Intrapleural pressure (P_{pl})*: It is the pressure in the pleural space, i.e., space between the parietal and visceral pleurae. It is negative as there is no air in the pleural space. At the end of expiration in a spontaneously breathing person, it is about –5 cmH_2O. However, in an upright lung it varies depending upon where it is measured. P_{pl} increases by 0.3 cmH_2O/cm vertical distance of lung. The cause of this vertical gradient is the weight of the lung itself. So it is around –3 cmH_2O at the lung base and –7 cmH_2O at the lung apex.
4. *Alveolar pressure ($P_{A\ or}P_{alv}$) (or Intrapulmonary pressure or lung pressure)*: It also varies with the phase of ventilation. P_A is –1 cmH_2O during spontaneous inspiration and becomes positive during expiration (+1 cmH_2O).

TABLE 1: Pressure gradients during spontaneous breathing.

Transairway pressure (P_{ta})	Airway pressure – alveolar pressure ($P_{aw} - P_{alv}$)
Transpulmonary pressure (P_{TP} or P_L) or transalveolar pressure	Alveolar pressure – pleural pressure ($P_{alv} - P_{pl}$)
Transthoracic pressure (P_w)	Alveolar pressure – body surface pressure ($P_{alv} - P_{bs}$)
Transrespiratory pressure (P_{tr})	Airway opening pressure – body surface pressure ($P_{awo} - P_{bs}$)

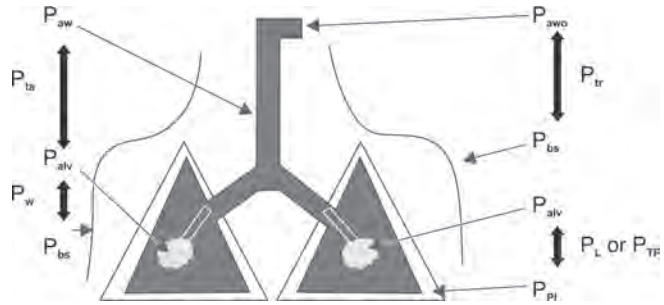
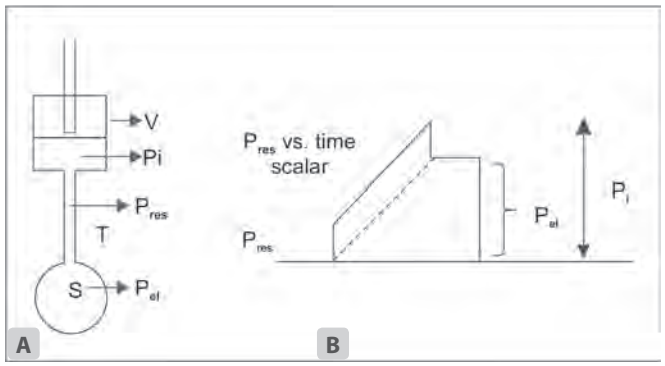


FIG. 1: Various pressures and pressure gradients of the respiratory system.

MECHANICAL DETERMINANTS OF "PATIENT–VENTILATOR" INTERACTIONS

To *understand the interaction between a ventilator and a patient*, we assume that lung may be represented as a simplified linear model with a tube (T) and a balloon or hollow sphere (S). The sphere is inflated by applying a pressure (Pi) near the tube inlet (**Figs. 2A** and **B**).



FIGS. 2A AND B: Figure A shows a simple linear system with a ventilator (V) applying a pressure (Pi) to the inlet of tube (T) leading to inflation of hollow sphere (S); Figure B shows the resulting pressure versus time waveform.

The pressure applied to the tube inlet Pi, is equal to the sum of two pressures, an elastic pressure of the sphere (P_{el}) and a resistive pressure of the tube (P_{res}).

$$\mathbf{Pi = P_{el} + P_{res}} \qquad \textbf{(}\textit{Equation 1}\textbf{)}$$

P_{el} reflects the elastic properties of lungs and chest wall, whereas P_{res} reflects the resistive properties of endotracheal tube and airways. We know from principles of physics that,

Elastic recoil pressure (P_{el}) = Elastance × Volume = E × V and

Flow resistance pressure (P_{res}) = Resistance × Flow = R × $\dot{V}$ (Ohm's Law) So, Equation 1 can be stated as:

$$\mathbf{Pi = EV + RV\dot{}} \qquad \textbf{(}\textit{Equation 2}\textbf{)}$$

For a patient on ventilator, Pi has two components, i.e., P_{mus} (pressure generated by the respiratory muscles) and P_{vent} (pressure delivered by the ventilator)

So, Equation 2 can be written as:

$$\mathbf{P_{mus} + P_{vent} = EV + RV\dot{}} \qquad \textit{(Equation 3)}$$

Compliance (C) of the respiratory system is determined by measuring the change of volume (ΔV) that occurs when pressure gradient (ΔP) is applied to the system: Normal values of compliance and resistance is shown in **Table 2**.

$$\text{Compliance (C)} = \Delta V/\Delta P$$

It is inversely proportional to elastance.

Resistance of respiratory system includes resistance to the flow of gases in airways (airway resistance) or resistance offered by the lung tissue and the chest wall (tissue resistance).

$$\text{Airway resistance } (R_{aw}) = \text{Transairway pressure/Flow}$$

Time constant: It tells us the time lung units or the acini take to fill and empty. It is the product of the compliance and resistance.

One time constant = 0.1 L/cmH_2O (C) × 1 cmH_2O/L/s (R)

Normally, one time constant is 0.1 second. One time constant means the time to exhale 63% of volume, similarly two-, three-, four- and five-time constants are the time to exhale 86, 95, 98, and 100% volume.

Because lung is a heterogeneous structure, time constants can vary in different regions of lungs. This is exacerbated in diseased states such acute severe asthma or acute respiratory distress syndrome (ARDS).

TABLE 2: Normal values of compliance and resistance.

	Compliance (mL/cmH_2O)	*Resistance (cmH_2O/L/s)*
Spontaneously breathing	100 (range 50–170)	0.6–2.4 (at 0.5 L/s flow)
Intubated and mechanically ventilated	• 40–50 (males) • 35–45 (females) • Can vary up to 100 in either gender	• 5–7 • Can be higher depending on patients clinical condition or circuit determinants

BOX 1: Common indications of mechanical ventilation.

- Cardiopulmonary arrest
- Neurological problems (stroke, myasthenia gravis, meningitis, encephalitis, tumors, high intracranial pressure, drug overdoses causing unconsciousness, etc.)
- Pulmonary problems—asthma, COPD, ARDS, and pneumonia
- Trauma
- Congestive cardiac failure
- *Shock*: Septic shock, cardiogenic shock, hemorrhagic shock, etc.

(ARDS: acute respiratory distress syndrome; COPD: chronic obstructive airway disease)

The clinical importance of time constant lies in the fact that inspiratory time less than three-time constants will lead to incomplete delivery of tidal volume. Similarly, if the expiratory time is less than three-time constants it will lead to incomplete exhalation.

INDICATIONS OF MECHANICAL VENTILATION

Tracheal intubation with cuffed endotracheal/tracheostomy tubes protects from aspiration and ventilation supports the breathing. Patients who have diminished airway reflexes or have respiratory insufficiency as evident by hypoxemia, hypercarbia, or severe respiratory distress are the likely candidates to receive mechanical ventilation. Common indications are shown in **Box 1**.

TYPES OF MECHANICAL VENTILATION

Mechanical ventilation can be categorized as (1) invasive or noninvasive, (2) positive pressure or negative pressure, and pressure control or volume control or dual mode. Positive pressure ventilators are the ones used in clinical practice. A positive (higher than the atmospheric) pressure is applied to the patient's airway which creates a flow of gases into the lungs. Such a pressure can be applied to endotracheal tube, tracheostomy tube, or noninvasively to the face of the patient. However, in this chapter we will limit our discussion to the invasive mechanical ventilation only. *Volume control ventilation* is the one in which

volume is set and pressure is the independent variable, while in pressure control ventilation, pressure is set and volume is an independent variable. Before moving on we will discuss about the *"variables"* in the ventilation.

- *Control variables*: Control variables are the main variables the ventilator adjusts to produce inspiration. They include pressure, volume, flow, and time.
- *Phase variables*: Phase variables control the four phases of a breath (i.e., beginning of inspiration, inspiration, end inspiration, and expiration). *Types of phase variables include:*
  - *Trigger variable*: It is a preset variable which decides the beginning of inspiration. It can be pressure (pressure triggering), flow (flow triggering), volume (volume triggering), or time (time triggering). Traditionally, pressure has been used, but modern ventilators have flow triggering which is now considered better for patients. Patients who have a spontaneous effort should generate the set amount of pressure or flow or volume that can be sensed by ventilator as a patient effort and then it can be supported by a positive pressure breath. When the ventilator starts inspiration according to the set rate and the I:E ratio, it is called time triggering.
  - *Target variable (limit variable)*: A target variable is one that can reach and maintain a preset level before inspiration ends. It can be flow, volume, or pressure. Achieving the target of limit does not mean end of inspiration. Some use the term limit variable; however, limit is a term which is generally used in reference to alarm settings.
  - *Cycle variable*: It decides the cycling (termination of the inspiration and beginning of the expiration). It can be time, flow, pressure, or volume cycled, e.g., decrease in flow to a particular proportion of the peak flow will cause the ventilator to cycle to expiration.
  - *Baseline variable*: It is the parameter controlled during exhalation. The pressure level from which a ventilator breath begins is called the baseline pressure. Baseline pressure can be zero (atmospheric), which is also called zero end-expiratory pressure (ZEEP), or it can be positive if the baseline pressure is above zero [positive end-expiratory pressure (PEEP)].

Types of Breaths during Mechanical Ventilation

- *Mandatory breaths*: They are time triggered, volume or pressure limited, and time cycled.
- *Assisted breaths*: They are patient triggered, limited by the ventilator (volume or pressure limiting), and cycled by ventilator (time cycling).
- *Spontaneous breaths*: They are triggered limited and cycled by the patient. The variables, however, can be pressure, flow, or volume.

MODES OF VENTILATION

The relationship between various possible types of breath and the inspiratory phase variables is called a mode of ventilation. Mode can be volume targeted, pressure targeted, or combined.

Volume-targeted Mode

In this mode, the machine delivers a volume set on the control panel by the physician irrespective of the pressure generated within the system. There are several inspiratory flow profiles, e.g., square wave, sine wave, ascending ramp, and descending ramp (decelerating) patterns (**Fig. 3**). Descending ramp pattern is associated with lower peak airway pressure and higher mean airway pressure. Expiratory flow is always decelerating in a mechanical breath irrespective of the inspiratory flow pattern. **Figure 4** shows a complete mechanical breath with a square wave flow inspiratory pattern. Changes in the mechanical properties of the lungs from atelectasis, edema, or bronchoconstriction may cause high inflation pressures (increasing the risk of barotrauma).

Pressure-targeted Mode

A predefined target pressure is set on the control panel of the ventilator. The ventilator generates flow to achieve the same pressure during the inspiration; the volume, however, is an independent variable which will depend on the impedance of the respiratory system. The underlying reason for mechanical ventilation guides the selection of the mode of ventilation. Volume-targeted ventilation should be used when strict control of tidal volume is required, e.g., ARDS. Conversely, in patients with asthma and COPD, strict control of airway pressure is desired so pressure-targeted ventilation is preferred.

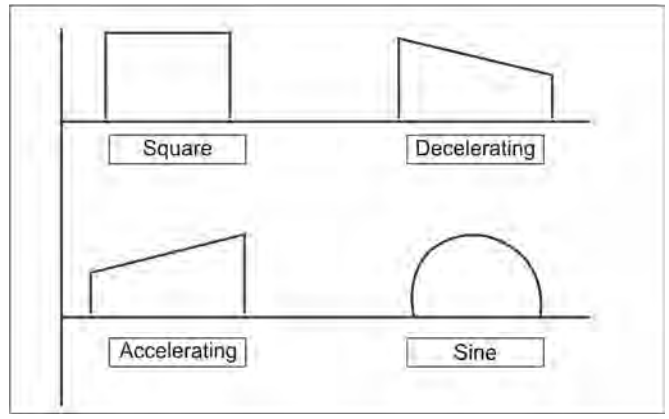


FIG. 3: Four different types of inspiratory flow patterns.

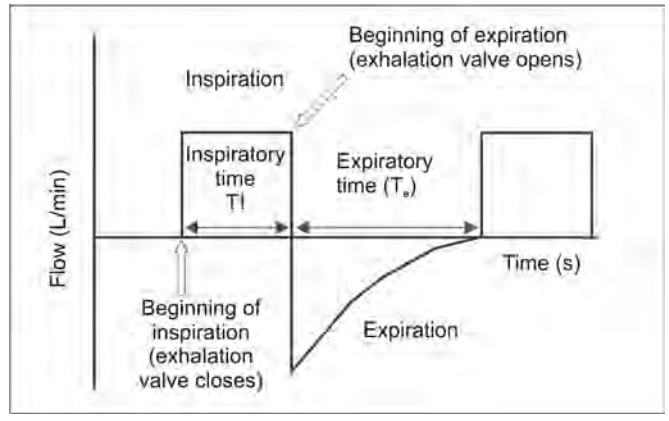


FIG. 4: Flow time scalar with constant flow waveform.

Control Mode or Controlled Mandatory Ventilation

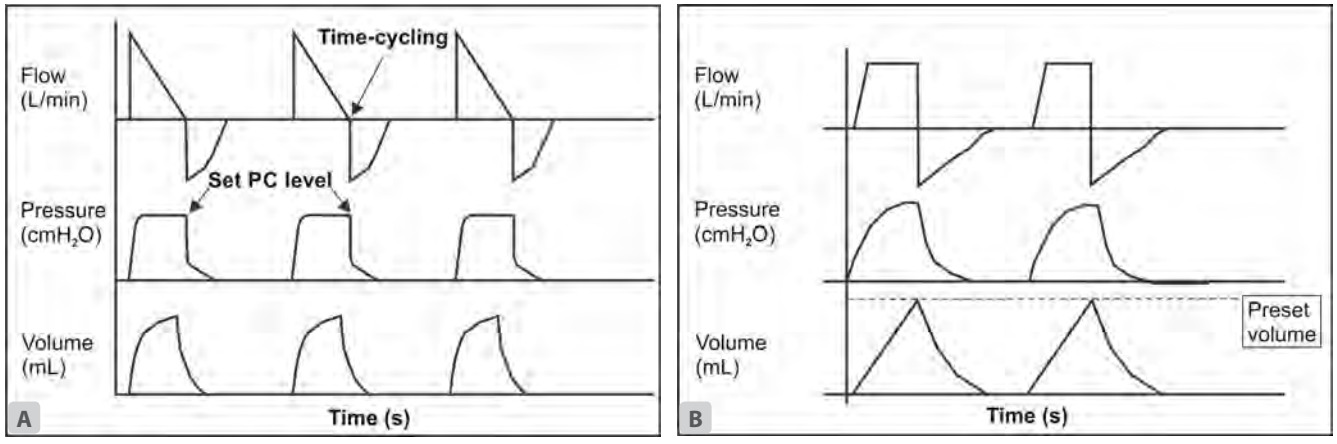
Controlled mandatory ventilation (CMV) mode is appropriate for the patients who are either deeply sedated, paralyzed or have no spontaneous efforts of their own. The breaths delivered are time triggered. No matter how strong is the patient's breathing effort, the ventilator does not deliver gas flow unless it is time triggered. **Figures 5A** and **B** respectively show ventilator waveforms for pressure and volume control CMV. It is used when the aim is to provide complete rest to the patient or in cases such as chest trauma where paradoxical movements of chest due to flail segment impede the ventilation.

Assist-control (AC) Ventilation

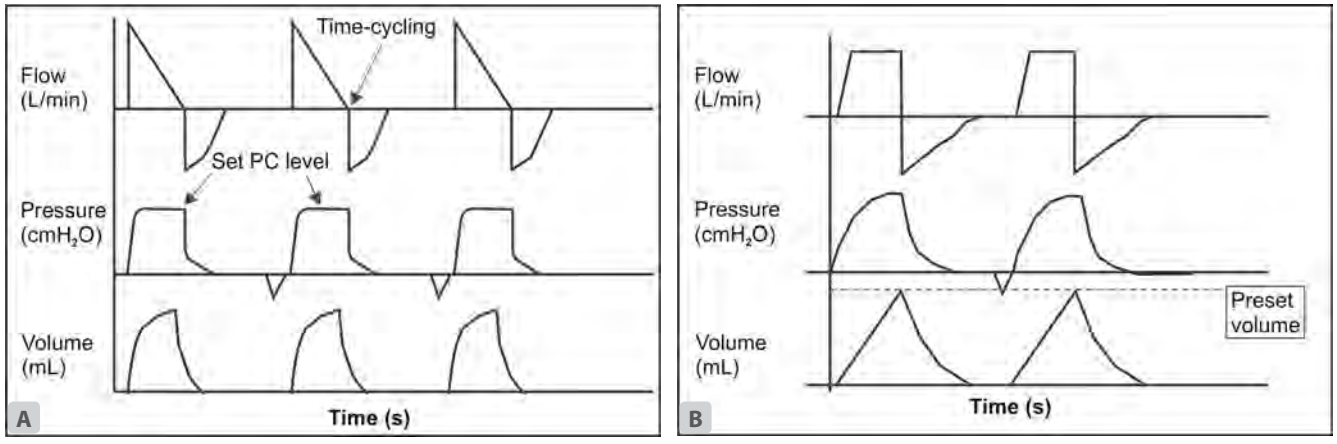
It is a time-triggered or patient triggered CMV mode. It is the appropriate mode of ventilation, when we want to provide full support to the patient, but patient has spontaneous efforts. *There are two types of breaths: (1) controlled, and (2) assisted*. Control breaths are time triggered, pressure or volume targeted, and time cycled. Assisted breaths are patient triggered, volume or pressure targeted and time cycled. The sensitivity level is set in the ventilator and when the ventilator senses a spontaneous effort, mechanical breath is delivered to achieve the same target as the control breaths. The major problem with this mode is that all the appropriately sensed efforts are converted to a mechanical breath which may lead to hyperventilation and respiratory alkalosis when the patient's respiratory rate (RR) is high. Also because it involves assisted breaths there may be inappropriate sensing if the trigger sensitivity is not correctly set leading to wasted efforts or there may be a delayed response time of the ventilator which can cause a patient-ventilator dyssynchrony. AC ventilation can be either a pressure controlled (**Fig. 6A**) or volume controlled (**Fig. 6B**). In volume control mode, setting of adequate gas flow is very important. If flow is less then patient will have flow hunger and dyssynchrony will result. Patients may not stop breathing even when the flow ceases and this may cause dyssynchrony. We may need to adjust the sensitivity. Several studies have shown that the decelerating ramp flow curve associated with PC mode may improve gas distribution and allows the patient to vary inspiratory gas flow during spontaneous breathing efforts.

Intermittent Mandatory Ventilation and Synchronized Intermittent Mandatory Ventilation

Intermittent mandatory ventilation (IMV) involves delivery of breaths (volume or pressure targeted) at set intervals (according to the set RR). However, the patient can breathe spontaneously between mandatory breaths at any desired baseline pressure without receiving a mandatory breath



FIGS. 5A AND B: Control mode ventilation: (A) Pressure control; (B) Volume control.



FIGS. 6A AND B: Assist-control ventilation: (A) Pressure control; (B) Volume control.

(contrast from AC mode). Synchronized intermittent mandatory ventilation (SIMV) is similar to IMV except that the mandatory breaths may be either patient triggered or time triggered (**Fig. 7**). IMV has an inherent drawback of stacking of breaths, which happens when patient takes a breath at the time of a mandatory breath. To overcome this, SIMV was developed in which ventilator waits for the patient to take a spontaneous breath. If it does not sense patient effort, then it delivers time-triggered breath. *Advantage of IMV and SIMV over AC mode* is that patient can breathe spontaneously to his own tidal volume, thus avoiding hyperventilation which may be seen in AC mode. Both IMV and SIMV have been used to wean patients from mechanical ventilation. As the mandatory rate is lowered, the patient gradually assumes a greater part of the work of breathing (WOB). However, IMV or SIMV can significantly increase WOB for spontaneous breaths. The spontaneous breaths can be supported with pressure support [SIMV + PSV (pressure support ventilation)], if we want to reduce the WOB. Both IMV and SIMV were used as a weaning mode, however, studies have shown that they do not fasten the weaning process rather can delay it.

Dual Modes of Ventilation

Newer ventilators offer many dual modes of ventilation. For the ER physician, all of them are not important; however, we will discuss one of such modes in brief. *Pressure-regulated volume control (PRVC)*—problem with regular volume control is high airway pressures which can cause barotrauma. PRVC was developed with purpose to deliver set tidal volumes at minimum pressure level. It is a volume targeted, pressure limited, and time-cycled mode. The ventilator automatically adjusts inspiratory pressure control level according to the changes in the properties of lung on a breath to breath basis. However, it has inherent limitations. If patient demand and effort increase higher tidal volumes are generated and the pressure support level is decreased. It means patient is getting less support when he actually requires more.

Pressure Support Ventilation

It is a patient-triggered, pressure-limited, and flow-cycled ventilation (**Fig. 8**). The ventilator provides a constant pressure during inspiration once it senses that the patient has made an inspiratory effort. Inspiratory pressure, PEEP, flow-cycle criteria, and the sensitivity level are set. Rise time is the time taken to reach the target pressure. It can be changed according to the comfort of the patient. High rise time and inadequate flows can result in patient ventilator asynchrony. Inspiratory flow in PSV ends when the ventilator senses that the flow has dropped to a certain level (flow cycling). Breathing through endotracheal tube increases the WOB. PSV overcomes WOB for spontaneously breathing patients breathing through a ventilator circuit. Patients who have a high respiratory drive and flow requirements may benefit by PSV compared to VC-CMV. High pressure settings than required by patient and air leaks may cause patient-ventilator dyssynchrony.

Continuous Positive Airway Pressure (CPAP)

Ventilators can also provide CPAP for spontaneously breathing patients. It helps in preventing atelectasis and treating and preventing hypoxemia.

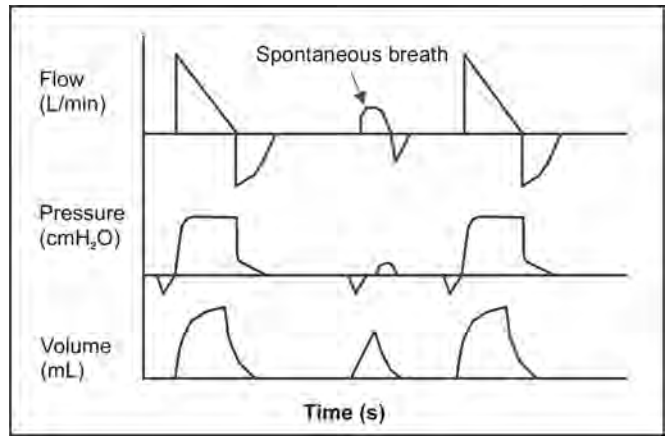


FIG. 7: Synchronized intermittent mandatory ventilation mode.

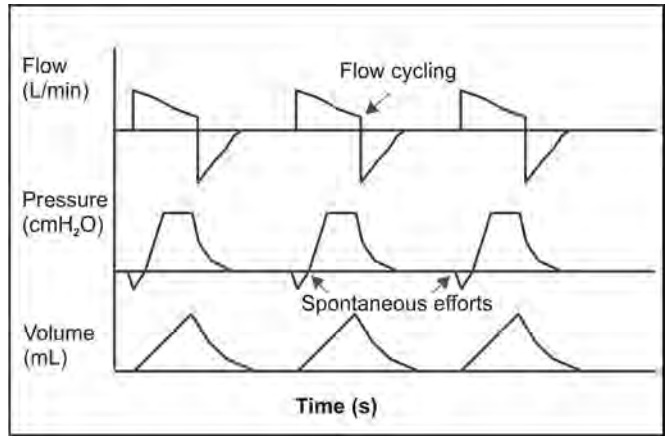


FIG. 8: Pressure support ventilation mode.

INITIATION OF VENTILATION

Initially, a controlled or assist-control mode is selected to decrease the WOB and provide complete relaxation to the respiratory muscles. Later, mode can be changed to either a SIMV or a PSV.

- *Fraction of inspired oxygen (FiO_2)*: For patients with severe hypoxemia, the initial FiO_2 should be set at 100%. ABG should be done to see the PaO_2, which should be targeted at 80 and 100 mm Hg for most patients, except those with COPD and ARDS where lower targets may be allowed. FiO_2 should be titrated and brought down to <50%, if feasible.
- *Respiratory rate*: It refers to the number of breaths per minute intended to maintain pCO_2 in normal range or patient's normal. It varies from 12 to 20 depending upon the clinical condition.
- *Minute ventilation (V_E)*: In resting patients with healthy lungs and metabolic rates, a V_E setting between 80 and 100 mL/kg usually results in normocapnia. However, most of the patients presenting to ER have a different from normal metabolic rate. V_E varies directly with the metabolic rate. Metabolic rate is estimated on the basis of an individual's gender and body surface area (BSA). BSA can be calculated using the Du Bois BSA formula:

$$BSA = 0.007184 \times Ht^{0.725} \times W^{0.425}$$

where BSA = body surface area in square meters, Ht = body height in centimeters, and W = body weight in kilograms.

$V_E = 4 \times BSA$ (men) $V_E = 3.5 \times BSA$ (women)

Minute ventilation requirements change in many pathological conditions. Example, V_E increases by 5% for every degree F above 99°F or 9% per degree C above 37°C. Metabolic acidosis causes a 20% rise in V_E.

- *Tidal volume*: The normal spontaneous tidal volume (V_T) for a healthy adult is about 5–7 mL per kg body weight. Earlier total body weight was used to derive the tidal volume. But now ideal or the predicted body weight (PBW) is used. PBW (in kg) may be derived as:

  Men = 50 + 2.3 × (height in inches – 60)
  Women = 45.5 + 2.3 × (height in inches – 60)

  For patients presenting to ER with apparently normal lungs, such as patients with a drug overdose an initial V_T of 5–7 mL/kg and a rate of 10–20 breaths/min are generally accepted. A V_T of >9–10 mL/kg is not recommended because of the risk of high pressures.
- *Pressure control setting*: It should be selected to achieve the target tidal volume as mentioned above. Care should be taken that the pressure should not be too high so as to avoid barotrauma. It will vary according to the compliance of lung and chest wall and airway resistance. Those with compliant lungs and low airway resistance will require less pressure to deliver the same tidal volume.
- *I:E ratio*: It refers to the ratio of the inspiratory to the expiratory time. Different ventilators have different settings. Some will allow to directly set I:E ratio, some however; will allow setting of inspiratory time and rate only and will decide I:E ratio from the set values. Usually, I:E ratio is kept at 1:2, however, it may be required to change the I:E ratio in certain situations. It will be discussed under the section "ventilation in special conditions."
- *Total cycle time (TCT)*: It is the time of one cycle of inspiration and expiration. If RR is kept at 10 breaths/min, then one cycle of inspiration and expiration will be 6 seconds, i.e., TCT will be 6 seconds. Now either we can set I:E ratio as 1:2 which will make T_i as 2 seconds and T_E as 4 seconds. Some ventilators do not have I:E setting, but require setting T_i. Setting T_i as 2 seconds will set I:E ratio as 1:2.

  Some ventilators use gas flow rate to decide the I:E ratio. Increasing the flow rate will cause Ti to decrease and T_E to increase. In the above example, Ti is 2 second. If the tidal volume set is 500 mL, then this 500 mL volume needs to be delivered to the patient in a time of 2 seconds which will equal to a flow of 250 mL/s or 15 L/m. Flow rate affects RR and tidal volume of a spontaneously breathing patient.
- *Positive end-expiratory pressure*: PEEP is defined as positive pressure at the end of exhalation during either spontaneous breathing or mechanical ventilation. **Figure 9** shows pressure time scalar in which the baseline pressure is elevated (PEEP). Usually, clinicians set a minimum PEEP of 5 cmH_2O. The explanation behind this practice is that the glottis usually provides a physiological PEEP of around 5 cmH_2O in spontaneously breathing nonintubated patients. Intubation of trachea removes this PEEP. So PEEP may be applied through the ventilator to prevent the atelectasis. However, some patients may require higher PEEP, e.g., pulmonary edema and ARDS.

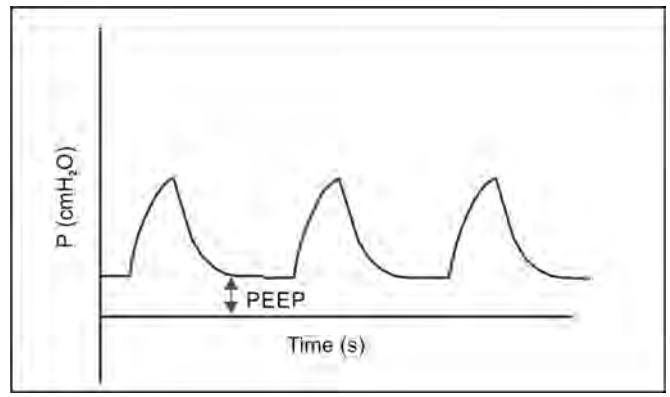


FIG. 9: Pressure time scalar showing elevated baseline pressure.

- *Trigger or sensitivity*: It can be set as pressure (1–5 cmH_2O) or flow (1–5 L/m). High trigger will mean that ventilator will ignore those spontaneous efforts of the patient which produce a pressure or flow less than that which is set in ventilator. These spontaneous breaths will not be supported by the ventilator.

MONITORING AFTER INITIATING VENTILATION

- Constant vigilance is required after intubation and setting ventilator. Optimum delivery of breaths needs to be ensured.
- Monitor vitals and oxygen saturation after intubation.
- Monitor the parameters on the ventilator screen, e.g., if PC mode is used, see how much volume is being delivered to the patient. It may be grossly inadequate if lung compliance is poor. In VC mode, peak airway pressure is influenced greatly by airway resistance and therefore is not reflective of end-inspiratory alveolar pressure. Alveolar pressure at end inspiration in VC mode is approximated by the P_{plat}, which can be measured with the ventilator at the end of inspiration by means of an inspiratory hold maneuver.
- Check alarm limits in the ventilator. The ventilator may be cutting off the delivery of gases in inspiration if the pressure limit gets exceeded (too low-pressure limit).
- Do arterial blood gas (ABG) after 15 minutes. Adjust the parameters (if required) according to the ABG report**.**
- Do a chest X-ray to check for endotracheal tube and nasogastric tube position and to rule out complications such as tube malposition, lung collapse or pneumothorax, etc.
- After ensuring effective ventilation, the most important goal is to provide comfort to the patient. Initiate sedation infusion according to your institutional protocol.
- Avoid neuromuscular blockers. However, they may be necessary in some cases such as ARDS.
- Periodic reevaluation of patient is needed. Initiate liaison with the intensive care unit (ICU) team for further management and shifting to ICU and anesthetist if patient is due to go to operating room or with radiology team if an imaging procedure such as computed tomography (CT) scan is planned.

COMPLICATIONS OF INTUBATION AND VENTILATION

The complications of intubation are depending on the patient airway anatomy, the urgency of the procedure, and the skill of the emergency physician. Mechanical ventilation is always known to save lives of critically ill patients, but also associated with multiple complications. Some of them are temporary and unrelated to ventilatory support but many are a direct result of positive-pressure ventilation, e.g., barotrauma. Infection, nosocomial pneumonia associated with various clinical factors, and concurrent intubation are one of them. Further complications of intubation and mechanical ventilation are summarized in **Table 3**.

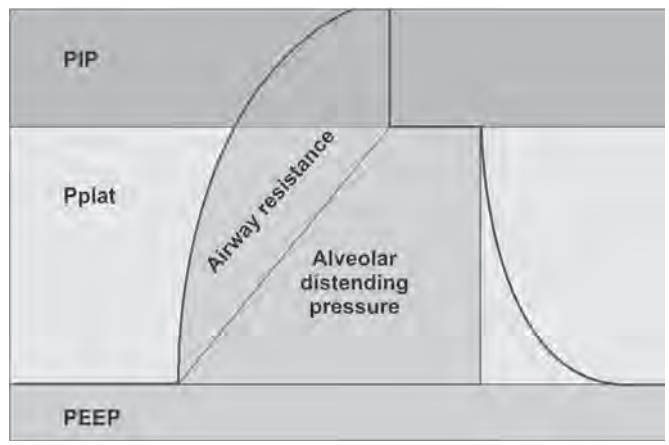
AIRWAY PRESSURES, ALARMS, AND TROUBLESHOOTING

In a volume-targeted mode, the ventilator delivers a set tidal volume with airway pressures being dependent on the resistance and compliance of the pulmonary system. Pressure-targeted modes can be successfully used but require significantly greater vigilance. The pressure measured at the airway opening can be divided into the pressure to overcome resistance in the airways and the pressure to overcome the elasticity of the lung and chest wall (**Fig. 10**). With few exceptions, the peak pressure represents the total pressure required to overcome both resistive (e.g., bronchospasm and airway edema) and elastic forces (e.g., stiff lungs or chest wall), whereas the *plateau pressure represents only the contribution of elastic forces*, as it is measured in the absence of gas flow. Patients with obstructive lung disease often have high peak pressures due to the resistance from bronchospasm and airflow obstruction. The peak inspiratory pressure (PIP) is evaluated continuously without any maneuvers on the ventilator, as it is the pressure read at the airway opening at the end of inspiration.

- *The plateau pressure* is determined by performing an inspiratory hold on the ventilator that closes the inspiratory valve at end-inspiration and allows the pressure to equilibrate with the alveoli in the absence of gas flow. Patients who have dynamic hyperinflation and significant auto-PEEP will have both high peak and plateau pressures and are at risk of pneumothorax, which is why mechanical ventilation in asthmatics can be dangerous. Although peak pressure >50 and plateau pressure >30 have been associated with barotrauma, it is unlikely that these represent threshold values and risk likely increases with increasing pressure. Elevated peak pressure should only confer risk of barotrauma when it is symptomatic of elevated plateau pressure. When the plateau pressure is elevated, one must evaluate factors reducing respiratory system compliance, often auto-PEEP and air trapping in the context of obstructive lung disease. When auto-PEEP (intrinsic PEEP) is suspected the flow waveforms should be examined, as air trapping it is the most likely culprit.
- *Auto-PEEP* is measured by performing an expiratory hold on the ventilator, which closes the expiratory valve and allows pressure to equilibrate with the alveoli at rest. The total pressure measured will be higher than the set PEEP (**Fig. 11**) in the presence of auto-PEEP. Auto-PEEP may be grossly underestimated due to regional obstruction, which is most pronounced in patients with the fixed bronchospasm and mucous plugs with normal to decreased lung compliance as seen in asthma as opposed to dynamic airway collapse and increased lung compliance as seen in patients with emphysema and COPD. If a lung unit has an auto-PEEP that exceeds the pressure required to obstruct the efflux of gas, the pressure will not be reflected at the airway opening, underestimating the total PEEP. In cases of obstructive lung disease with significant auto-PEEP, externally applied PEEP may reduce WOB by lowering the threshold pressure needed to trigger the ventilator but it is a double-edged sword. Externally applied PEEP greater than this threshold will worsen dynamic hyperinflation and increase the risk of pneumothorax. This is the risk of PEEP both invasively and noninvasively in patients with respiratory failure secondary to obstructive lung disease.

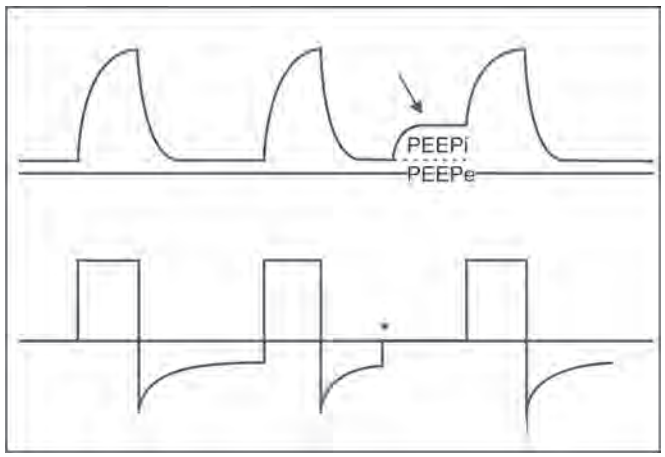
TABLE 3: Complication of intubation and mechanical ventilation.

Intubation	*Mechanical ventilation*
Hypoxemia during intubation	Hemodynamic collapse—decreased venous return
Failed intubation, esophageal intubation, and unilateral intubation	Inability to ventilate—difficult to ventilate situations, e.g., severe exacerbations of asthma and COPD and ARDS
Injury to teeth	Air trapping, auto-PEEP
Hemodynamic response to intubation—hypertension and tachycardia	Pneumothorax
Hemodynamic collapse—secondary to sedatives and positive pressure ventilation	Atelectasis
Injury to trachea, vocal cords	Tube blockage, lung collapse
Bleeding	Accidental extubation
	Decreased renal blood flow



(PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; Pplat: plateau pressure)

FIG. 10: *Airway pressures*. This pressure waveform on the ventilator shows time on the X-axis and pressure on the Y-axis. The ventilator must overcome two pressures to deliver a breath, the airway resistive pressure, and the alveolar distending pressure. The starting and ending pressure for each breath will be from the set PEEP.



(PEEP: positive end-expiratory pressure)

FIG. 11: *Air trapping and auto-PEEP*. Air trapping and auto-PEEP can be evaluated with an expiratory hold maneuver. If the expiratory limb of the flow waveform (bottom green) does not return to baseline before the subsequent breath that volume of gas is "trapped" in the lung while the next volume-targeted breath is delivered as seen here. Holding the expiratory valve closed with an expiratory hold maneuver on the ventilator (asterisk) will allow the pressures to equilibrate between the alveoli and the airway opening. This will demonstrate a total PEEP (arrow), with the components being extrinsically set PEEP and the difference between the total PEEP and set PEEP being the intrinsic, or auto-PEEP.

TABLE 4: Causes of high peak pressure.

High peak pressure but normal of low plateau pressure (mechanism involved—increased respiratory system resistance to flow)	*High peak pressure but high plateau pressure*: Mechanism involved (decreased respiratory compliance—increased stiffness of ling)
Causes: • Bronchospasm • Mucous plugging • Obstructed (secretions) or kinked tracheal tube or ventilator tubing • Endobronchial tumors • Extrinsic compression • Foreign body aspiration	*Causes*: • Lung overdistension—dynamic hyperinflation—"breath stacking," auto-PEEP, and right mainstem intubation • Decreased lung compliance—ARDS, edema, fibrosis, collapse, and consolidation • Pleural factors—effusion, tension pneumothorax • External factors—obesity, ascites, burn eschar, supine positioning, and abdominal hypertension

- *Peak pressure alarms* are frequently encountered in patients undergoing mechanical ventilation for obstructive lung disease. These alarms occur when the ventilator senses the peak pressure during a breath going over a preset maximum. In the setting of a high peak pressure with a normal plateau pressure, one might reasonably assume that the alarm is of little consequence, as they are a consequence of airways resistance and not transmitted to the lung parenchyma. However, this is not the case and "alarm" is a bit of a misnomer, as when the pressure threshold is reached for the alarm, the ventilator acts as a pop-off valve and stops delivering the breath, which results in tidal volumes less than the set volume even in volume control modes, sometimes severely decreasing V_E. Peak pressure alarms in an unstable patient should result in disconnection of the ventilator and hand ventilation of the patient. Troubleshooting stable patients is done on the ventilator by first observing the actual delivered tidal volume and then measuring the plateau pressure to develop a differential. Causes of both high peak and plateau pressures are factors that reduce the compliance of the respiratory system, whereas factors that cause increased resistance to airflow elevate only the peak pressure (**Table 4**). If peak pressure alarming persists despite considering this differential and treating the modifiable causes, most importantly auto-PEEP, then the peak pressure alarm setting may be increased, accepting that this may be associated with an increased risk of barotrauma, particularly in cases where respiratory system compliance is reduced. Increasing the peak pressure alarm can be helpful but risks patient harm when done incorrectly, namely when decreased compliance is the cause of the elevated peak pressure (plateau pressure is elevated). All patients on mechanical ventilation should be monitored with continuous waveform capnography. Common ventilator-associated problem and their solution (troubleshooting) is summarized in **Box 2**.

MECHANICAL VENTILATION IN SPECIAL CONDITIONS

Bronchial Asthma

Severe bronchospasm causes longer time constant and severe inhomogeneity of time constant of lung units leading to air trapping. This is also called auto-PEEP. In other words, there is insufficient time for complete inspired air to flow out of the lungs before the next inspiration occurs. This can cause increased intrathoracic pressure and decreased venous return resulting in hemodynamic collapse. So the target of ventilation in such patients should be to minimize air trapping and achieve hemodynamic stability. It can be achieved by providing long expiratory times which can be achieved by the following settings:

f = 8–10 breaths/min;
VT = 4–8 mL/kg;
T_I = ≤1 sec
I:E ratio – 1:4–1:5
Gas flow = 80–100 LPM
PEEP 0–5 cmH_2O (in case severe asthma it should be kept at zero)
Descending flow waveform pattern
P_{plat} <30 cmH_2O

Permissive hypercapnia refers to the strategy of accepting a higher PCO_2 while maintaining a pH > 7.2. It aims to avoid air trapping. If Pplat > 30 cmH_2O and pCO_2 > 90 mm Hg—deeper sedation and/or paralysis should be considered.

Chronic Obstructive Airway Disease

Pressure control-CMV may be ideal for such patients as it provides flow on demand to meet the patient's needs. Basic principle of ventilation is same as in asthma. Aim is to minimize

BOX 2: Troubleshooting in patient on mechanical ventilation.

- *Not able to achieve patient-ventilator synchrony?*
  - Ensure patient is under adequate analgesics and sedation
  - Evaluate ventilator waveforms
  - Administer a neuromuscular blocking agent (NMBA)
  - Consider a pressure-targeted mode
- *Not able to achieve a respiratory rate?*
  - Reduce tidal volume
  - Deepen sedation
  - Consider NMBA
  - Rescue maneuvers—extracorporeal CO_2 removal with ECMO or induced hypothermia
  - Increase inspiratory flow rate/increase peak pressure alarm setting
- *Not able to maintain an adequate pH despite required ventilator settings?*
  - If hemodynamically stable, may consider allowing a lower pH if closely monitored
  - Rescue maneuvers—infusion of a buffer (sodium bicarbonate), extracorporeal CO_2 removal with venovenous ECMO, or induced hypothermia
- *Venous blood gas is not improving, and patient is on noninvasive support*
  - *Increase IPAP*: EPAP gradient if on BiPAP
  - Increase flow if on HFNC
  - Invasive mechanical ventilation (exception: asthmatics)
- *Patient becomes suddenly hypotensive?*
  - Disconnect ventilator and decompress the chest
  - Evaluate for pneumothorax
- *The peak pressure continues to alarm?*
  - Evaluate plateau pressure
  - Low plateau pressure—bronchodilators, pulmonary toilette, eliminate endotracheal tube biting, or obstruction
  - High plateau pressure—evaluate and treat causes of decreased respiratory compliance, particularly dynamic hyperinflation in the context of obstructive lung disease
  - Reduce inspiratory flow if patient factors allow, consider expert consultation, consider increasing peak pressure alarm setting as a last resort

(BiPAP: bi-level positive airway pressure; ECMO: extracorporeal membrane oxygenation; EPAP: expiratory positive airway pressure; HFNC: high-flow nasal cannula; IPAP: inspiratory positive airway pressure)

auto-PEEP or air trapping which occurs because of expiratory flow limitation. Ventilator settings will be similar to those for asthma. Controlled hypoventilation refers to the strategy of ventilation in which we aim a normal pH by targeting patient's baseline PCO_2. When patients are spontaneously breathing and having trouble triggering breaths due to air trapping and auto-PEEP, setting the PEEP at about 75–80% of intrinsic PEEP may make triggering easier.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome patients can be one of the most difficult ones to intubate and ventilate in ER. Intubation has a high risk of hypoxemia during the procedure and ventilating the lungs even after a successful intubation can be a nightmare.

Acute respiratory distress syndrome lungs are poorly compliant and need higher PEEP levels. A lung protective ventilation strategy gives a higher priority to the lung protection compared to the traditional goals of acid base balance. It minimizes mechanical over inflation of lung and lung inflammation or biotrauma. Open lung approach should be followed, which includes using maneuvers to open the collapsed lung, to maintain them in the same state without causing over distension.

Initiate ventilation with FiO_2 100%, RR—15–25 breaths/min, tidal volume 6–8 mL/kg of PBW and a PEEP of 10–15 cmH_2O. TV should be gradually brought down to 6 mL/kg. P_{plat} should be targeted to <30 cmH_2O. I:E ratio should be kept between 1: 2 and 1: 1.5.

Later the PEEP may need to be titrated to find the optimum PEEP. It is the PEEP level which optimizes oxygenation while having the least detrimental effect on hemodynamics, oxygen delivery, and airway pressures. It has also been defined as the level of PEEP at which the static compliance is highest. There are a number of strategies to find optimum PEEP. These methods most commonly consist of using a $PEEP/FiO_2$ table aimed at providing acceptable oxygenation, titrating PEEP to reach a maximal compliance using stress index, or a decremental PEEP approach. Recruitment maneuvers refer to a strategy of ventilation which involves transient application higher transpulmonary pressures to open previously atelectatic alveoli. Several methods have been described, the most commonly used of which is a sustained inflation breath; e.g., CPAP of 40 cmH_2O for 40 seconds. Another method is a stepwise increase in PEEP accompanied by low levels of pressure control ventilation. The best recruitment technique is still unknown and may be according to specific circumstance. It is worth remembering although P_{plat} target of <30 cmH_2O is accepted as a rule, but patients who are obese or have ascites or abdominal distension may need higher P_{plat}.

Severe Acute Respiratory Syndrome (SARS-CoV-2 COVID-19)

Once the decision is taken to intubate the patient, full personal protective equipment (PPE that at minimum includes an N95 mask, protective eye wear, fluid impervious gowns, and gloves) should be used to perform the intubation by most experienced physician. Preferably use video laryngoscopy if available. Surviving Sepsis Campaign recommendation and ventilator strategy for ARDS (tidal volumes of 4–8 mL/kg of predicted body weight; higher PEEP strategy), are used in SARS-CoV-2 COVID-19 patient also. Gattinoni et al., have observed on the basis of small cohort of patients that there are two primary groups of patient in this scenario—(1) L-type with low elastance (normal compliance), low lung weight, and low lung recruitability; and (2) H-type with high elastance (low compliance), high lung weight, and high lung recruitability. Thus, the respiratory management and ventilatory strategies in these two patient types will be different. L-type patients are more likely to respond to nasal cannula (NC), high-flow nasal cannula (HFNC), and noninvasive positive pressure ventilation (NIPPV) than H-type patients. H-type patients should be approached as in a traditional severe ARDS scenario where one would be treated with an escalating PEEP strategy. It

is important to note that the observations from Gattinoni et al., are based on small studies thus larger studies are required for better understanding of heterogeneous COVID-19 pulmonary syndrome (**Flowchart 1**).

Head Trauma

Head trauma patients may have an increased intracranial blood volume or elevated intracranial pressure (ICP). Such patients need intubation and mechanical ventilation for either poor sensorium or decreased respiratory drive. The aim is to provide sufficient ventilation to keep pCO_2 in normal range. Higher pCO_2 can cause cerebral vasodilatation leading to increase in ICP. However, higher intrathoracic pressure must be avoided as they may be transmitted to the brain causing elevation of ICP. So PEEP should be judiciously used.

Pregnant Patient

Pregnancy results in a number of physiologic changes that have a direct bearing on the ventilatory strategy. Important changes which must be remembered are:

- Increased metabolic rate
- Increased V_E
- Respiratory alkalosis (pCO_2 about 30 mm Hg)
- Reduced chest wall compliance
- Mucosal edema and increased vascularity
- Increased intra-abdominal pressure

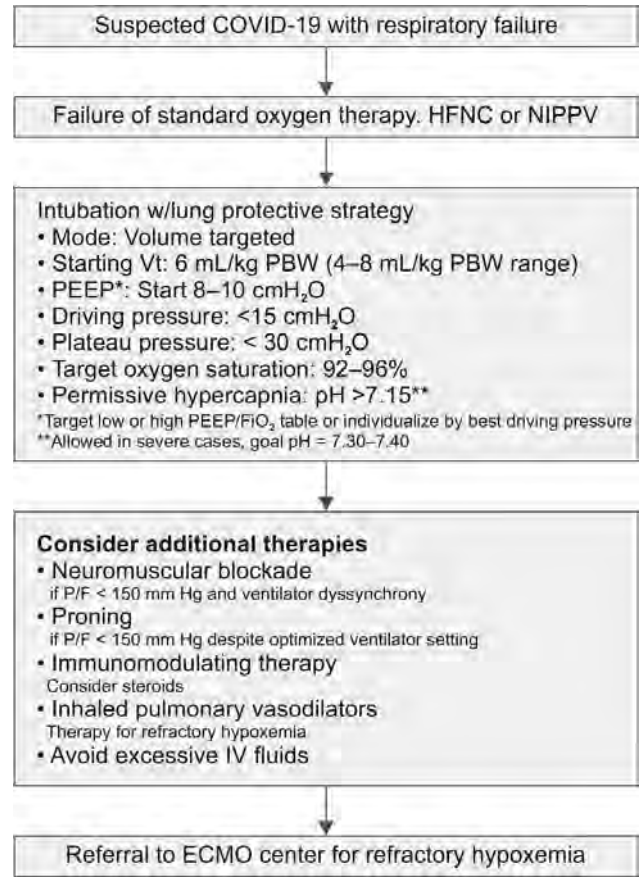
Therefore, in the pregnant mechanically ventilated patient, the minute volume setting should be adjusted to a pCO_2 target between 28 and 32 mm Hg. Higher peak airway pressures may be acceptable due to reduced chest wall compliance. Smaller diameter endotracheal tubes should be used. A rapid sequence intubation is mandatory in view of apparent full stomach and high risk of pulmonary aspiration. Long-acting sedative agents should not be used if delivery is imminent, as they may depress the fetus.

Transporting Intubated Patients

Patients need to be shifted to ICU after initial resuscitation. Some patients may be directly shifted to the operating room; some may require a radiologic procedure such as CT scan or MRI before shifting to ICU. Although transporting any critically ill patient involves risk, but patients on vasopressors, ARDS patients and those who have difficult airway have a much higher risk of adverse events.

Manual resuscitators are still used frequently in the transport of patients from ER. However, alteration in patient's respiratory status occurs frequently when manual resuscitators are used for transportation as compared to the transport ventilators. So a transport ventilator is recommended in such a case because it provides stable V_E and also frees the caregiver to perform other tasks. Adverse events include but are not limited to incorrect measurement of vitals, arrhythmias, hypotension, hypertension, increased ICP, endotracheal tube blockage, loss of airway, and cardiac arrest. Following points should be remembered:

- There should be a written protocol and a dedicated transport team.


Suspected COVID-19 with respiratory failure
Failure of standard oxygen therapy. HFNC or NIPPV
Intubation w/lung protective strategy
• Mode: Volume targeted
• Starting Vt: 6 mL/kg PBW (4–8 mL/kg PBW range)
• PEEP*: Start 8–10 cmH2O
• Driving pressure: <15 cmH2O
• Plateau pressure: < 30 cmH2O
• Target oxygen saturation: 92–96%
• Permissive hypercapnia: pH >7.15**
*Target low or high PEEP/FiO2 table or individualize by best driving pressure
**Allowed in severe cases, goal pH = 7.30–7.40
Consider additional therapies
• Neuromuscular blockade
if P/F < 150 mm Hg and ventilator dyssynchrony
• Proning
if P/F < 150 mm Hg despite optimized ventilator setting
• Immunomodulating therapy
Consider steroids
• Inhaled pulmonary vasodilators
Therapy for refractory hypoxemia
• Avoid excessive IV fluids
Referral to ECMO center for refractory hypoxemia

FLOWCHART 1: Ventilatory support strategy for COVID-19 patient.

- Transport ventilator should be preferred to a manual resuscitator.
- Monitoring during transport should include cardiac monitor [including electrocardiogram (ECG), blood pressure (BP) monitoring, pulse oximetry, and end-tidal CO_2 ($etCO_2$) monitoring] with defibrillating capacity. Other equipment should include airway management equipment, oxygen supplies, resuscitation drugs, and intravenous fluids.
- If patient is to be shifted to MRI suite, it must be ensured that the ventilator, gas hoses that plug into wall outlets and syringe pumps are MRI compatible.

SUMMARY

Prompt evaluation of patients presenting to ER should identify those who may need intubation and mechanical ventilation. Ensure patient comfort and safety. Constant vigilance is required after intubation and setting ventilator. Blood gas analysis should be performed to confirm effective ventilation. Avoid fall in blood pressure and immediately treat if occurs. Sudden drastic change in measured ventilatory or hemodynamic parameters should prompt evaluation for life-threatening conditions and assessment of the ventilator settings.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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40 CHAPTER

Sedation and Analgesics for Mechanically Ventilated Patients

Manish Garg, Devendra Richhariya

INTRODUCTION

Patients are now spending more and more time in emergency department (ED) due to nonavailability critical care bed. Emergency physicians are now taking care of mechanically ventilated patients more often for and longer periods of time. Problem such as pain, agitation, and anxiety is commonly associated with mechanically ventilated patient. A systematic approach is required for delivering sedation and analgesia in mechanically ventilated patient including goals, specific medication target, specific situation, and other methods such as retrain other than pharmacological management.

After the rapid sequence intubation (RSI), pharmacologic management avoids discomfort during paralysis. Pain is treated aggressively with objective scoring system is used for its assessment. If possible, lighter sedation is the first choice over the deep sedation. As mechanically ventilated patients are being managed in emergency for longer period of time, standard assessment and medication protocol are best practices for ED.

GOALS AND PRINCIPLES

Significant discomfort and anxiety related to their care is prime concern in critically ill-ventilated patient. Initially goal should be mild sedation with lowest possible dose to address any specific need with patient safety. Deep sedation is independent factor for mortality in mechanically ventilated patient in ED and critical care unit. Various painful procedures are required to perform in critically ill patient such as endotracheal intubation, invasive procedures such as central and arterial line insertion, and routine care of decubitus ulcer. Adequate pharmacologic management for analgosedation (prophylactic analgesia) is instituted before performing the procedure. Patients are also in discomfort and agitated because not able to communicate, and posttraumatic disorder. "Analgesia first or only analgesia "is the best policy to start with, further analgesia dose is titrated according to pain assessment tool. In spite of the adequate analgesic, if patient remains agitated or anxious, sedation is used.

Timing of Medications

The short-acting sedative medications are used for RSI. Therefore, management of symptom starts immediately with adequate sedation following intubation. Then administering *fentanyl,* a *minimum of a 50–100 μg bolus intravenous (IV)* immediately after intubation is recommended who receives longer-acting paralytics (**Flowchart 1**).

Qualities of Ideal Medications

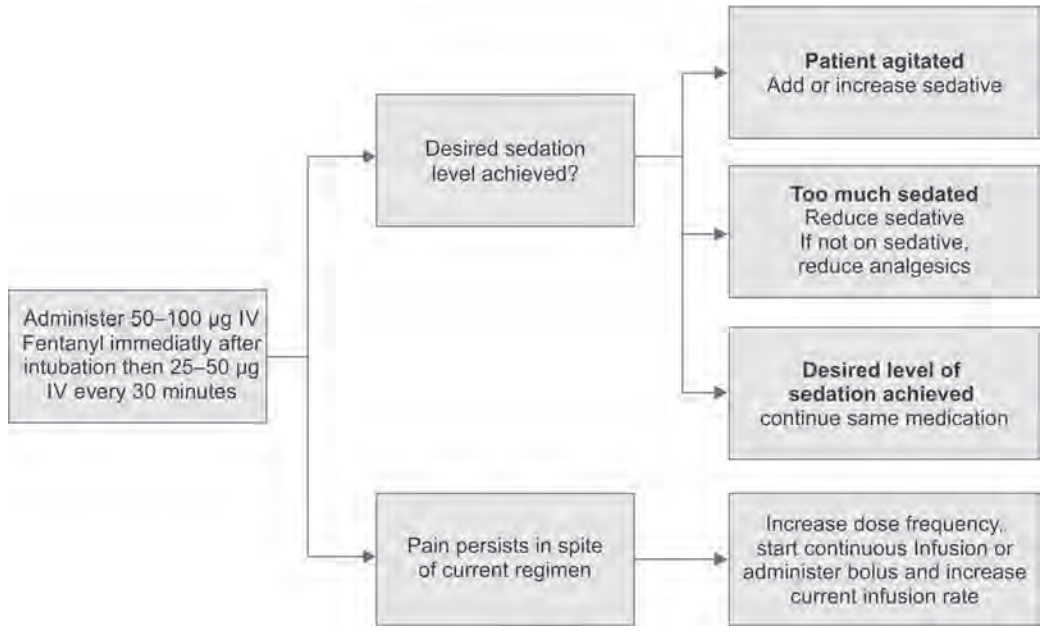
- Rapid onset
- Short-acting
- Adequately controls the symptoms
- No immediate or late adverse effects

Unfortunately, no ideal medication presents. Medications are typically divided into two classes first for analgesia and second those for sedation, as discussed earlier in this chapter our goal is to control the pain first to address agitation and anxiety.

MEDICATIONS

Analgesia

For mechanically ventilated patients, opiates remain the first choice of pain management. Fentanyl, hydromorphone, morphine, and remifentanil are common intravenous agents. Fentanyl or hydromorphone is well tolerated but other factors such as patient factors, pharmacokinetic profile, cost, and institutional availability play an important role while choosing the agent**.** Various analgesic agents and their doses are summarized in **Table 1**. Intermittent dosing or infusion dosing is depending on the patient's need and requirement and based on validated pain assessment score. But general policy is to start analgesics with intermittent doses and then escalating it to a continuous infusion. Opiates are important as pain management therapy in mechanically ventilated patient but because of side-effect profile other common adjuncts can also be used to reduce the opioids requirement,


Administer 50–100 µg IV Fentanyl immediatly after intubation then 25–50 µg IV every 30 minutes
Desired sedation level achieved?
Patient agitated
Add or increase sedative
Too much sedated
Reduce sedative
If not on sedative, reduce analgesics
Desired level of sedation achieved
continue same medication
Pain persists in spite of current regimen
Increase dose frequency, start continuous Infusion or administer bolus and increase current infusion rate

FLOWCHART 1: Basic algorithm for management of sedation and analgesia in a mechanically ventilated patient in emergency department.

TABLE 1: Common opioids analgesic for mechanically ventilated patients.

Medication	*Bolus/intermittent dose*	*Infusion dose*	*Comments*
Fentanyl	0.35–0.5 µg/kg intravenous every 0.5–1 h (50–100 mg boluses are typically well tolerated)	0.7–10 µg/kg/h (infusions >200–300 mg/h are generally not required)	*Onset of action*: 1–2 min, half-life 2–4 h, consider as first-line agent. Relatively hemodynamically stable Accumulates if hepatic impairment
Remifentanil	–	*Loading dose*: 1.5 µg/kg IV Maintenance dose: 0.5–15 µg/kg/h IV	Onset of action 1–3 min Half-life 3–10 min, does not accumulate with renal or hepatic impairment
Morphine	2–4 mg IV every 1–2 h	2–30 mg/h	Onset of action 5–10 min, half-life 3–4 h Not recommended in patients with renal impairment or as first-line agent
Hydromorphone	0.2–0.6 mg IV every 1–2 h	0.5–3 mg/h	Onset of action 5–15 min, half-life 2–3 h Consider as first-line agent, can accumulate with renal/hepatic impairment

e.g., acetaminophen, ketamine, and neuropathic agents (gabapentin, pregabalin and carbamazepine).

Sedation

In most of the patients, pain can be controlled by analgesic alone and few patients require sedative medication because they experience anxiety and agitation despite adequate pain medication. There are various sedatives available for acute episodes of anxiety and agitation and can be used as bolus as well as continuous infusion (**Table 2**). Benzodiazepines (e.g., lorazepam or midazolam) is used as infusion but associated with prolonged effects of delirium and adverse outcome in critically ill patient so benzodiazepine is not a first choice of agent. Propofol or dexmedetomidine is used as first-line agents in critically ill and mechanically ventilated patients according to recommendations. Recommendations are based on literature which concludes that propofol takes shorter times to achieve light sedation and shorter times to extubation in comparison to benzodiazepines, and shorter times to extubation and reduced delirium with dexmedetomidine in comparison to benzodiazepines. Comparison of the clinical outcomes of propofol with dexmedetomidine is limited and superiority to one another need to be further investigated. Dexmedetomidine poses lower risk of delirium and may be more cost-effective when compared with other sedatives.

In mechanically ventilated critically ill patients, ketamine is not commonly used as a continuous sedative but is an option for use as an adjunct or as single agent for symptoms that are difficult to control. On the basis of clinical scenario, desired level of sedation is achieved.As discussed earlier, deep sedation is directly related to prolonged mechanical ventilation and increased mortality, but in some clinical scenario such as acute respiratory distress syndrome, deeper levels of sedation are achieved during pharmacologic paralysis.

TABLE 2: Common medications for sedation in mechanically ventilated patient.

Medications	*Bolus dose*	*Infusion dose*	*Comments*
Propofol	5 µg/kg/min over 5 min	5–50 µg/kg/min	Onset of action in 1–2 min, half-life 3–12 h Consider as first-line agent Can cause respiratory depression, hypotension, hypertriglyceridemia, and propofol infusion syndrome
Midazolam	0.01–0.05 mg/kg loading over several minutes	0.02–0.1 mg/kg/h	Onset of action in 2–5 min, half-life 3–12 h Can cause respiratory depression and hypotension
Ketamine	0.5–1 mg/kg over 1–2 min	1–2 µg/kg/min titrating up as needed to 10–20 µg/kg/min	Onset of action <5 min Half-life α-15 min β-300 min Also has analgesic effect
Dexmedetomidine	1 µg/kg over 10 min	0.2–1.5 µg/kg/h	Onset of action 5–10 min Half-life 2–3 h Can cause bradycardia and hypotension Should not be used for deep sedation or continuous paralysis is needed Otherwise consider as first-line agent

TABLE 3: Pain-scoring scales for intubated patients.

Critical Care Pain Observation Tools (CPOT)			*Behavioral Pain Scale (BPS)*		
Facial expression	Neutral	0	Facial expression	Relaxed	1
	Tense	1		Partially tight	2
	Grimacing	2		Fully tight	3
				Grimacing	4
Body movement	Absent	0	Upper limb movement	No movement	1
	Protective	1		Partially bent	2
	Restless	2		Fully bent	3
				Permanently retracted	4
Muscle tension	Relaxed	0	Compliance with mechanical ventilation	Tolerating	1
	Tense	1		Coughing but tolerating	2
	Very Rigid	2		Fighting	3
				Unable to control	4
CPOT- Evaluation of pain in patients who are unable to report it. *CPOT score ≤ 2 minimal/no pain* *CPOT score ≥ 2 unacceptable pain, add analgesic sedation*			BPS is used to assess pain in intubated patient		

ASSESSMENT

Frequent reassessment of patient is required of mechanically ventilated patient on continuous analgesic and sedative infusion. During ED stay, their requirement of doses may change and doses need to be adjusted because under-dose or overuse of these medications can adversely affect the outcome of the patient. The tools used for monitoring the patient on analgesics and sedation are pain-scoring scale and sedation-scoring scales. These tools are vital to managing critically ill patients.

Pain-scoring Scales

Pain scales which are used to assess the mechanically ventilated critically ill patient are based on nonverbal factors such as body movement, facial expressions, and compliance with the ventilator because these patients are unable to communicate effectively and cannot self-report pain. The *Critical Care Pain Observation Tool (CPOT*) and the *Behavioral Pain Scale (BPS)* are two most commonly recommended scores, are used for this challenging task (**Table 3**). These scales use nonverbal parameters to determine the need for analgesia, are simple to use, widely recommended in current guidelines.

Sedation Scoring

In most critically ill mechanically ventilated patients, the goal for sedation is to achieve a state whereby the patient is spontaneously alert and arousable or can be aroused with verbal stimuli. *Richmond Agitation–Sedation Scale (RASS)* (**Table 4**) *and the Riker Sedation–Agitation Scale* are most

TABLE 4: Richmond Agitation–Sedation Scale (RASS).		
Description of patient	Combative	+ 4
	Very agitative	+ 3
	Agitative	+ 2
	Restless	+ 1
	Alert and calm	0
	Drowsy	– 1
	Mild sedation	– 2
	Moderate sedation	– 3
	Deep sedation	– 4
	Unarousable sedation	– 5
Patients with a RASS of -3 or less should have their sedation decreased or modified in order to achieve a RASS of -2–0. Patients with a RASS of 2–4 are not sedated enough and should be assessed for pain, anxiety, or delirium. The underlying etiology of the agitation should be investigated and appropriately treated to achieve a RASS of -2–0. A RASS score should be obtained on all hospitalized patients and at regular interval in all mechanically ventilated patients. Unless a patient meets indication for deep sedation, a protocol for minimal sedation (RASS -2–0) should be used		

commonly used and helpful to standardize the level of a patient's consciousness. Sedation-scoring scales are also helpful to standardize communication between healthcare workers and specify targets for medication titration.

Protocol for Minimizing the Sedation and Analgesia

There are no prospectively validated protocols specifically for analgesics and sedation administration for ED. Therefore, multidisciplinary approach is adopted in which ED team, nursing team, and critical care team should formulate a uniform protocol for ED, similar to ICU which promotes simplicity and uniformity in the sedation and analgesia goals for critically ill patients.

Many strategies can be applied to minimize the risk of over-sedation, commonly used strategy is the daily interruption of sedation in which turning off continuous infusions of analgesia and sedatives at specific times and allowing the patient to wake up, as soon as patient becomes uncomfortable, these infusions can be restarted at the lower rates. Daily interruption of sedation and patient assessment enable us to know lowest possible doses of medications are required for a desired level of sedation. Careful observation by nurses and staff is required with daily interruption of because there is an increased risk of self-extubation and self-harm by the patient. In another strategy, nurses are allowed to administer medications intermittently and keep the patients at specific sedation preferably targeting the light sedation without the need to fully wake.

Light sedation can be achieved for patients who are mechanically ventilated by either method**.** As in many ED settings, awakening trials are unlikely to be practical, use of a nurse-driven protocol targeting light sedation on mechanically ventilated patients in the ED can recommended.

SPECIAL SITUATIONS

Hypotension with Sedation

Common problem in mechanically ventilated patients is hypotension. Hypotension can be due to various reasons such as patient pathology, positive pressure ventilation, and medications. Many medications commonly used for pain and sedation also contribute to exaggerate hypotension. A stepwise approach is recommended for patient on mechanical ventilation and on sedation. Before evaluating and addressing other life-threatening causes do not assume that a patient's hemodynamic insult is medication related.

- First step is to check whether the patient is fully resuscitated or management is fully instituted for original pathology. If patients need further escalation of therapy of the original condition (e.g., additional blood product resuscitation in hemorrhagic shock), it needs to be corrected.
- Reduce dose or discontinue sedative/or analgesic, if the patient's level of sedation is achieved or no clinical evidence of pain. Patients who are in pain or agitated continue appropriate analgesic and sedation and support hemodynamic further resuscitation.

Persistently Agitated Patient

A few patients create danger to both to themselves and to staff and are challenging to manage because they remain continuously agitated despite adequate pain management and sedation. The causes for these situations can be high medication tolerance (opioid dependence), delirium, acute substance use or withdrawal, psychiatric illness, and preexisting cognitive impairment.

Underlying cause of the patient's agitation (e.g., persistent pain, alcohol withdrawal, and head injury) needs aggressive treatment. Acute severe symptoms can be treated with one-time bolus dose before titrating the infusion rate**.** Adding an additional sedative agent or alternative agent is an option if required (e.g., ketamine). In severely agitated patients who are not intubated, adding an antipsychotic can be considered. Benzodiazepines should be avoided, as it can worsen agitation.

Paralyzed Patient

For initiation of deep sedation boluses of 250 μg/kg propofol and 1 mg of hydromorphone followed by continuous infusion rates of 20 μ/kg/min and 1 mg/h, respectively. Once a patient is no longer paralyzed, light sedation should again be targeted whenever possible. Analgesic and sedative drugs should be continuously administered with the goal of deep sedation until the paralytic is withdrawn and an assessment can be made as traditional pain-scoring systems cannot be performed in these patients.

Status Epilepticus

Status epilepticus (SE) patient is often intubated and deeply sedated for airway protection and additional antiepileptic therapy is started, if refractory to existing antiepileptic medi-

cations. Neurocritical Care Society (NCS) suggests continuous infusion of antiepileptic drugs such as midazolam, propofol, or pentobarbital till clinical or electroencephalograph (EEG) evidence of cessation of seizures (titrating to continuous EEG).

Physical Restraints

The decision to use physical restraint (PR) is debatable and varies, mostly depends on patient and staff-specific factors and only be used as a bridge to adequate chemical restraints. PRs are often used to prevent patients from removing essential devices, inflicting self-harm, unplanned extubation, musculoskeletal injuries, psychological trauma, and also preventing staff from injuries. The need for their use should be continuously reassessed and they should be removed once it is safe to do so.

SUMMARY

Significant pain and anxiety are associated with mechanically ventilated patients and associated various procedures with their care. A systematic approach is applied to treat these symptoms in aggressive manner. Appropriate analgesics and sedation started immediately following intubation. Aggressive treatment is required for pain, use medications for sedation as a supplement to achieve adequate analgesia, not as a substitute for it. Use objective scoring systems to frequently assess patients' levels of pain and sedation and adjust medications based on these assessments. Whenever possible, target lighter levels of sedation over deep sedation aim to standardize patient assessment and medication protocols across the ED and ICU.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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ONLINE REFERENCES

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Extubation in Emergency Department

41 CHAPTER

Joanne Hng Mei Hwa, Ahmad Zulkarnain Ahmad Zahedi

INTRODUCTION

Emergency medicine specialty has been managing airway and becoming adept at inserting an endotracheal tube for definitive airway. The common goal is to safely protect the airway while maintaining adequate oxygenation and ventilation until the underlying disease process is reversed. Most guidelines have focused on intubation, with little to guide the process of weaning from mechanical ventilation and extubation. The rate of critically ill patients requiring intubation in emergency department (ED) is rising and limited intensive care unit (ICU) resources prolong their stay in ED. Some patients' clinical conditions improve during their extended stay in ED and emergency physicians infrequently encounter a dynamic clinical decision-making as a result. Nevertheless, there are no available studies which published algorithms or guidelines in assessing patients for possible extubation in ED. Moreover, the extubation protocols may vary according to local settings and needs. This chapter aims to provide an understanding in depth, safe and practical approach on extubation in ED and resuscitation unit.

PATIENT SELECTION AND THE "ABC" PROCEDURAL CONSIDERATION

Patient Selection

Resolution of the initial indication for intubation and its process is important. The first consideration for ED extubation is complete resolution of underlying conditions for which the invasive mechanical ventilation is started. Clinician should be aware of initial indication of the mechanical ventilation otherwise extubation failure may occur. There should be no documented airway trauma, challenging airway, or complicated at initial intubation. Clinician has to make sure that no other anticipated factors which will require continuous mechanical ventilation, e.g., intracranial pathologies (severe brain injury and brainstem stroke), cervical spine instability or injury**,** acute airway trauma**,** acute lung injury, plan for imminent emergency procedure, surgery, or interfacility transfer and transport**.** Intoxication, drug overdose, clinical emergency procedure requiring procedural sedation analgesia (i.e. endoscopy), traumatic brain injury with improving mental status, and a negative CT and palliative extubation are the common indications in which extubation can be considered (**Fig. 1**).

Airway Patency Assessment: Ability to Maintain Airway Patency

The paramount of maintaining a patent airway is the ability to cough with the clearance of secretions adequately and effectively. One of the independent clinical variables, predicted reintubation is copious amount of endotracheal secretion. The patient should be assessed by the ability to lift his or her head off the bed and produce a strong cough before extubation is conducted. Moreover, the patient should not have any known or documented glottic swelling, upper airway obstruction, or any difficult laryngoscopic intubation at the initial ED or prehospital care (PHC) airway management.

Pulmonary and Breathing Assessment: Patient Able to Maintain on a Minimal Ventilator Setting

The clinical respiratory parameters of adequate oxygenation are defined as oxygen saturation > 92% and PaO_2 > 70 mm Hg, with adequate ventilation defined as $PaCO_2$ 38–42 mm Hg. A patient is stratified as low risk for extubation failure, if he or she could oxygenate and ventilate on low ventilatory settings, either with continuous positive airway pressure (CPAP) alone or with minimal pressure support (PS). As a guide, a patient with spontaneous breathing should generally be able to produce a ≥5 mL/kg ideal body weight of tidal volume on CPAP or minimal PS, as well as an adequate oxygenation with a fraction of inspired oxygen (FiO_2) <40% with a positive end-expiratory pressure (PEEP) ≤8. Precise critical decision on the timeliness of extubation is important owing to the complications of a failed extubation.

Spontaneous Breathing Trial

Spontaneous breathing trial (SBT) can be a very helpful approach to early and successful ventilator liberation, in

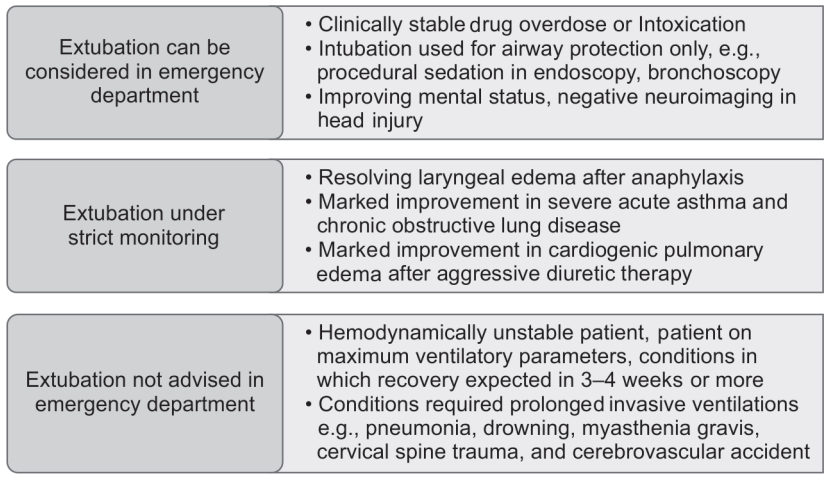
Extubation can be considered in emergency department
• Clinically stable drug overdose or Intoxication
• Intubation used for airway protection only, e.g., procedural sedation in endoscopy, bronchoscopy
• Improving mental status, negative neuroimaging in head injury
Extubation under strict monitoring
• Resolving laryngeal edema after anaphylaxis
• Marked improvement in severe acute asthma and chronic obstructive lung disease
• Marked improvement in cardiogenic pulmonary edema after aggressive diuretic therapy
Extubation not advised in emergency department
• Hemodynamically unstable patient, patient on maximum ventilatory parameters, conditions in which recovery expected in 3–4 weeks or more
• Conditions required prolonged invasive ventilations e.g., pneumonia, drowning, myasthenia gravis, cervical spine trauma, and cerebrovascular accident

FIG. 1: Indications/contraindications for emergency department extubation.

patients intubated initially for underlying cardiopulmonary pathologies. There are three potential ventilator setting (**Box 1**) options for SBT described as follows:

Pressure support SBT is the recommended screening method for extubation readiness in current extubation guidelines by the CHEST and American Thoracic Society, comparing to the other two options which are less sensitive, especially in patients who have been mechanically ventilated for >24 hours.

Nwakanma and colleagues advocated the use of a low PS or CPAP—only approaches for ED extubation and the duration of the trial between 30 and 120 minutes. In addition to, a set of predictors of a successful SBT was extracted from the study conducted in ED by *Weingart and colleagues as below* (**Box 2**).

Another dynamic assessment that can be measured during an SBT to determine extubation preparedness is known as the *rapid shallow breathing index (RSBI*). RSBI is defined as respiratory rate (breaths per minutes) divided by tidal volume (L). A high RSBI indicates the patient's inability to tolerate independent breathing. Whereas a lower RSBI cut-off indicates an optimal breathing and the latter is more specific inpatient selection, hence potentially reduces the risk of extubating patient with borderline parameters. In ED setting, an RSBI of <75 breaths/min/L using the PS or CPAP SBT only approach is recommended.

Reintubation represents a major setback that is not only psychologically discouraging to patients, but also associated with morbidity and mortality. Therefore, extubation evaluation should be a holistic assessment which consists of patient's general clinical conditions, ability to manage secretions, respiratory effort, work of breathing, and hemodynamic and neurological status. Arterial blood gas may be a helpful adjunct, but it should not be solely relied on. Whenever there is hindrance, extubation should not be done in ED but deferred to ICU.

BOX 1: Suggested ventilator setting for spontaneous breathing trial.

- Pressure support spontaneous breathing trial with 5 cmH_2O pressure support and a positive end-expiratory pressure (PEEP) of ≤5 cmH_2O to overcome the resistance of the endotracheal tube
- Only continuous positive airway pressure with PEEP ≤ 5cmH_2O
- T-piece trial with supplemental oxygen only via the endotracheal tube

BOX 2: Parameters suggestive of successful spontaneous breathing trial.

- Respiratory rate between 8 and 30 breaths/min
- Oxygen saturation >92%, PaO_2 > 70 mm Hg (on FiO_2 <0.4 and PEEP ≤8 cmH_2O)
- Heart rate between 60 and 140 beats/min
- Systolic blood pressure between 90 and 200 mm Hg, or <20% change from baseline systolic blood pressure
- Spontaneous tidal volume >5 mL/kg ideal body weight
- No signs of increased work of breathing, severe anxiety, or altered mental status

(FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen; PEEP: positive end-expiratory pressure)

Cardiovascular Assessment: Stability of Circulatory/Hemodynamic Parameters

Weaning-induced pulmonary edema is a well-recognized cause for extubation failure. Main risk factors include chronic obstructive lung disease, structural cardiomyopathy (dilated/hypertrophied cardiomyopathy and valvular heart disease), reduced ejection fraction left ventricular failure, and obesity.

The readiness for extubation is crucially determined by the hemodynamic stability of the patient. The patient should be liberated from the administration of inotropes or vasopressors prior to extubation. The following are proposed criteria for hemodynamic stability (**Box 3**).

Neurological Assessment: Ability to Follow Commands with Full Consciousness

It is important to ensure that the patient is fully awake and is breathing independently before an extubation is done. Patient should be allowed adequate time to regain full conscious level, while sedation is slowly weaned or tapered down. The patient

BOX 3: Hemodynamic parameter (stable) suggestive for extubation.

- Oxygen saturation > 92% (on FiO_2 < 0.4)
- Respiratory rate < 30 breaths/min
- Heart rate < 100 bpm
- Systolic blood pressure > 90 mm Hg unsupported by vasopressors
- No ongoing cardiac ischemia or unstable cardiac arrhythmia

may experience discomfort, anxiety, agitation, or restlessness when sedation is discontinued. Dexmedetomidine (DMT) may be used to ease the patient and facilitate the extubation process. It is an excellent anxiolytic agent which has an onset of therapeutic effect in 15–40 minutes, without affecting the patient's respiratory drive and effort. Nevertheless, it is crucial for the attending physician to be certain that the patient's agitation is not due to hypoxic respiratory distress or cardiovascular derangement. This can be done either by a spontaneous achieved normal or high tidal volume in a patient, or a point of care arterial blood gas. A clinically tachypneic patient with ventilatory insufficiency will have a normal or high PCO_2, whereas a low PCO_2 and respiratory alkalosis may be associated with agitation. A neurological examination should be done and documented once the patient is fully awake and follows commands. The patient should always be asked to lift his or her head during neurological assessment, or to raise his or her arm in the air for 15 seconds to elicit strength and to ensure the remaining effect of neuromuscular blocking agents is not present.

POSTEXTUBATION COMPLICATIONS AND MANAGEMENT

Postextubation Cardiopulmonary Dysfunction

Postextubation cardiopulmonary dysfunction is a known complication occurred during the transition from positive pressure to negative pressure of ventilation, resulting in an increased left ventricular transmural pressure, afterload, postextubation hypoxemia, myocardial ischemia, life-threatening arrhythmias, subsequent risk of reintubation, and poor outcome. Clinical presentations are similar to acute cardiogenic pulmonary edema, which include tachypnea, increased work of breathing, hyperdynamic responses, and progressive hypoxemic respiratory failure. Point-of-care lung ultrasound will demonstrate new B-lines to suggest "wet lungs". Noninvasive ventilation (NIV) and intravenous nitroglycerine remain the mainstays of acute management. Diuretics may also be helpful in fluid removal. Critical decision to reintubate a patient who has failed to tolerate NIV or rapidly deteriorates despite aggressive medical interventions, should be prompt.

Postextubation Hypoxemia

Further ventilation-perfusion mismatch and impaired gas exchange are contributed by increased airway resistance, shunt, derecruitment and atelectasis, and worsen postextubation hypoxemia. A prospective study conducted by Soummer and colleagues had demonstrated the use of lung ultrasound as a predictive tool for postextubation distress after a successful SBT. A higher incidence of development of B-lines or consolidation on lung ultrasound was found in >30% of the studied cohort who developed postextubation respiratory distress.

Additionally, two randomized clinical trials on post-extubation high-flow nasal cannula (HFNC) had demonstrated its potential benefits in reducing reintubation rate in patients with postextubation hypoxemic respiratory failure safely and effectively.

Postextubation Stridor

Postextubation stridor is defined as the presence of inspiratory noise following extubation and it indicates >50% narrowing of the airway passage, which commonly occurs at the glottic and infraglottic anatomical sites. Laryngeal edema is frequently caused by endotracheal intubation where the endotracheal tube abuts the trachea, and it usually occurs after 36 hours postintubation. This can then result in postextubation stridor and respiratory failure with subsequent reintubation that is associated with high morbidity and mortality. Therefore, the documentation of preexisting laryngeal edema, airway trauma, difficult, or multiple intubation attempts is crucial before an extubation is proceeded. Several tests have been evaluated for the assessment of airway patency before extubation and the identification of patients at potential risks for postextubation laryngeal edema. These tests include the cuff leak test (CLT) and airway ultrasonography.

The CLT is a noninvasive and easy to perform method to predict postextubation stridor. The measurement of the cuff leak volume in a mechanical-ventilated patient is the difference between the inspiratory tidal volume before the endotracheal tube cuff is deflated and the averaged expiratory tidal volume, on volume control intermittent mandatory ventilation (IMV). The tidal volume should temporarily be titrated up to 8–10 mL/kg ideal body weight when the patient is on volume control IMV, in order to correctly demonstrate the presence of a cuff leak. The measured cuff leak can be either an audible leak or volume loss >24% tidal volume by approximation, and this volume of air leak should be >110 mL. The associated risk of postextubation stridor and respiratory distress secondary to laryngeal edema is increased with small (volume <110 mL) or absent cuff leak. Hence, the administration of intravenous glucocorticoid treatment (intravenous methylprednisolone 40–125 mg every 6–8 h; or intravenous dexamethasone 5 mg every 6 h) and nebulized epinephrine (5–10 mL of undiluted 1:10,000 0.1 mg/mL; or 0.5 mL of a 2.25% racemic epinephrine diluted in a 2–4 mL volume) may help to reduce the laryngeal swelling and subsequent postextubation stridor. It is also important to note that a negative CLT can occur with a relatively oversized endotracheal tube to patient's trachea, or the secretion around the deflated endotracheal tube cuff. Unfortunately, even patients with low-risk factors for postextubation laryngeal edema which include absence of traumatic or difficult intubation, use of small endotracheal tube size, low cuff pressure, and duration of intubation of <6 days, may still experience severe respiratory distress or postextubation stridor and hence potential reintubation.

The airway patency may also be assessed using ultrasonography. The difference of air column width at the level of the vocal cords between pre- and postendotracheal cuff deflation can be measured. A lower air column width difference and air column width during endotracheal cuff deflation were

found in patients who developed postextubation stridor in the studies by Ding et al., and Sutherasan et al., respectively.

Postextubation Agitation and Delirium

Agitation and delirium are two common entities in critically ill patients and the causes can either be an underlying pathological condition or secondary to intubation or sedative agents, occur during weaning process. Delirium is an organic dysfunction with complex pathophysiology, including inflammatory response to neuronal injury, hormonal influences, alterations in neurotransmission, and neural network connectivity. The hallmark of delirium is alteration of mental status and its course of fluctuation, with impaired cognitive function. The patient mostly presents as hypoactive and infrequently hyperactive or mixed delirium. In the ICU, patients with delirium are often associated with prolonged mechanical ventilation, prolonged length of hospitalization, and increased risk of mortality. Whereas in the ED, acute delirium is often due to the underlying presenting illness. Therefore, the decision for extubation should be carefully considered.

PALLIATIVE EXTUBATION IN EMERGENCY DEPARTMENT

Palliative extubation is an intentional withdrawal of mechanical ventilation support to liberate patient and patient's families from prolonged suffering. It is performed on the patient who is unknowingly intubated against his or her prior expressed will, or diagnosed with a nonsurvivable medical condition after intubation that would not be consistent with a favorable quality of life. These patients are ideal candidates for palliative ED extubation. The act of withdrawal of life support can be emotionally and ethically challenging. It is important to effectively communicate in a compassionate but a direct manner with the patient's family. The discussion should include details regarding the patient's current clinical status, prognosis, expected outcome, and postextubation care. Once extubation is decided collectively, it ought to be accomplished to offer comfort. Medications such as opioid infusion and benzodiazepines should be part of a standard care. They also help to reduce postextubation dyspnea and pain.

SUMMARY

Emergency department extubation is feasible. It can be safely performed after a careful and logical consideration, as well as patient selection. The application of available guidelines or protocols, understanding, preparing to intervene any potentially life-threatening complications and subsequent disposition, is cornerstones. **Figure 2** provides a proposed ED extubation pathway.

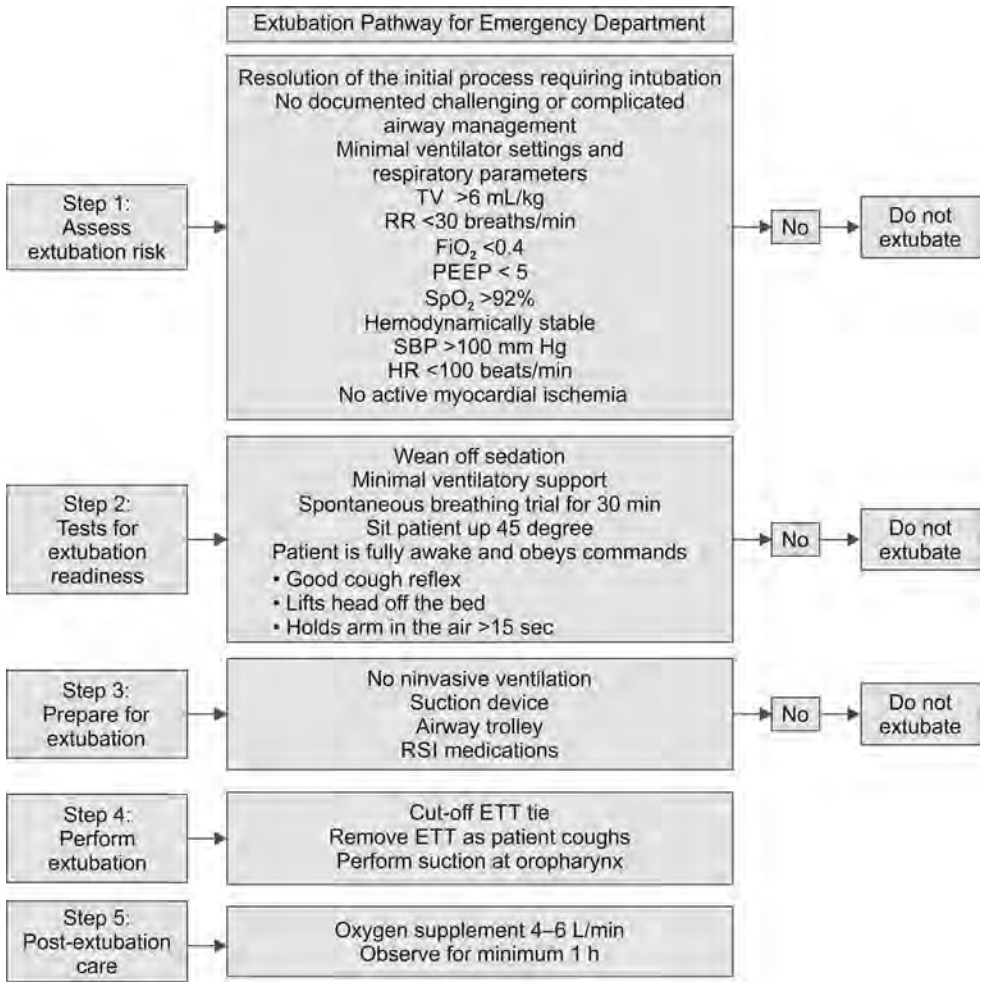

FIG. 2: Extubation pathway for emergency department.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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42 CHAPTER

Vascular Access

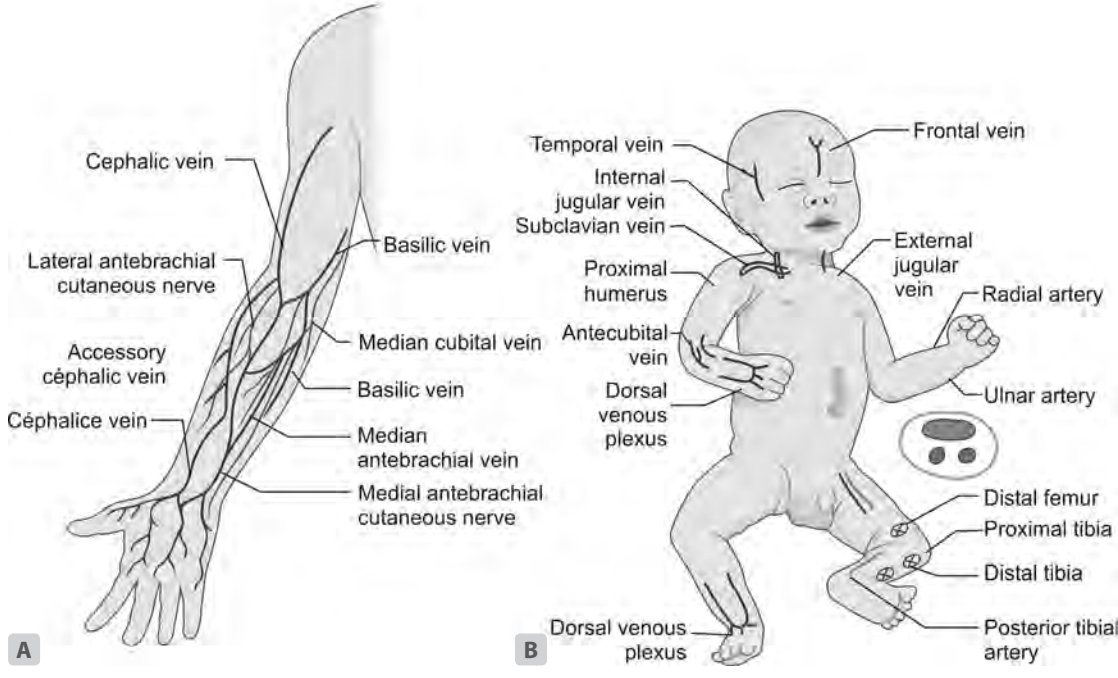
Eric Revue

INTRODUCTION

Vascular access is a necessary component of the delivery of medical treatment in emergency situations. The main principles of vascular access need knowledge of the basic anatomy, techniques, ultrasound, indications, and contraindications are essential to emergency care. More than 60% of patients in acute care worldwide require a vascular access device (VAD). Multiple factors determine the site for vascular access and knowledge of infusion rate is a key in the resuscitation of patients with severe hypovolemia or hemorrhage situations. Vascular access site for adult and pediatric age is shown in **Figures 1A** and **B**. Over a 30% of adults, > 50% of children who require a peripheral intravenous catheter (PIVC), are reported to have difficult venous access (DiVA). DiVA is defined by nonvisible and nonpalpable veins where a highly experienced operator is required with the use of technological help to insert a vascular device. Patients with chronic and complex disease, chemotherapy, who have a history of intravenous drug use, are obese, malnutrition, are known to suffer from DiVA.

BASIC KNOWLEDGE OF PATHOPHYSIOLOGY

According to Poiseuille's law, the rate of flow is directly proportional to the catheter radius and the pressure gradient, and inversely proportional to the dynamic fluid viscosity and catheter length. Flow rates are maximized by using the largest internal diameter catheter possible. Flow rates increase with larger catheter radius, use of more pressure, decreasing viscosity (co-administration of crystalloid with viscous blood products), or decreasing catheter length (peripheral angiocatheter vs. triple-lumen catheter).



FIGS. 1A AND B: Vascular access site for adult and pediatric age.

HOW TO CHOOSE APPROPRIATE VASCULAR DEVICE?

The placement of any device except the short peripheral catheter must be made by a trained or supervised operator, in a dust-controlled room under conditions surgical asepsis, under local anesthesia (buffered lidocaine with molar bicarbonate) with or without sedation or even hypnosis in adults. The use of a checklist is highly recommended. Various catheters used in general practice are shown in **Table 1**. Emergency physician should choose the appropriate catheter (depending on the total duration) as shown in **Table 2**. Multiple factors are involved and are deciding factors for choosing the appropriate VAD (**Fig. 2**), e.g., patient clinical conditions, treatment plan risk factors involved, vein conditions, and medications involved

PERIPHERAL ACCESS

Peripheral catheters are considered appropriate for treatment of peripherally compatible medications and solutions (<900 mOsm/L, not vesicant or irritant) and duration of treatment < 6 days with transition to midline or PICC when duration is extended. Peripheral catheters need access into the veins and arteries of the arms and legs for pediatric or neonatal applications. Peripheral access has a lower risk of infection (0.5/1,000 catheter days). Prescribed therapy and patient need to determine the type of peripheral cannula for the use. Various peripheral cannulae are available commercially for different clinical situations with different dimensions (external catheter diameters, length, and water flow rates) (**Table 3**). Other factors which could influence the fluid flow rates are type of fluid, viscosity and temperature of fluid, height of the container, and the use of connectors.

Peripheral Catheter Indications

Peripheral catheters are the preferred access for all patients where no indication is present for central venous access. Short PIVCs are the most frequently used invasive medical devices in for urgent procedures. PIVC treatment involves the infusion of peripherally compatible solutions for 5 days or less. Patient has adequate veins to accommodate catheter size and length. Emergent use with placement in the external jugular or foot veins (emergent or <4 days) (**Figs. 3A** to **D**). For those requiring multiple attempts such as obese patients, diabetes or other chronic conditions, difficult intravenous access (DIVA), and the VAD the needs of the treatment plan with the lowest risk selection of a VAD should be based on specific indications. When multiple peripheral catheter attempts fail, the designation of DIVA may lead to assessment with a greater success with ultrasound-guided peripheral catheter access after training and reduced need and avoidance of central venous access devices (CVADs).

TABLE 1: Catheter used for venous and arterial access.

Catheters	*Entry*	*Length*	*Comments*
Short peripheral venous catheters	Forearm and hands veins	<3 inches	Prolonged use phlebitis
Peripheral arterial catheters	Radial artery (preferred), femoral axillary, brachial	<3 inches	Infection risk is low
Midline catheters	Inserted through antecubital fossa to basilic or cephalic veins but does not enter central veins	3–8 inches	Low rate of infections
Central venous catheters (nontunneled)	Percutaneously inserted to subclavian internal jugular femoral veins	>8 cm, depends on patient size	Infection (most of CRBSI)
Central venous catheters (tunneled)	Implanted into subclavian, internal jugular and femoral	>8 cm, depends on patient size	Lower rate of infection than nontunneled
Peripherally inserted central venous catheter (PICC)	Inserted into the basilic cephalic and enters the superior vena cava	>20 cm, depending on patient size	Lower rate of infection than nontunneled
Pulmonary artery catheters	Inserted to subclavian internal jugular or femoral through Teflon introducer	>30 cm, depending on patient size	Infection similar to central venous catheters
Totally implantable catheters	Tunneled beneath the skin and have subcutaneous port-subclavian and internal jugular	>8 cm, depending on patient size	Lower risk of CRBSI

TABLE 2: How to choose the catheter?

Duration	*< 5 days*	*6–14 days*	*< 14 days*	*>14 days*
Catheter	Peripheral venous catheter	Peripheral catheter especially if bad venous	Midline or PICC	Peripheral venous catheter
ICU, and if hemodynamic monitoring, or high infusion rate		Preferred nontunneled central venous catheter		PICC line preferred to midline
Cancer patient's chemotherapy parenteral nutrition	Central venous access			

(ICU: intensive care unit; PICC: peripherally inserted central venous catheter)

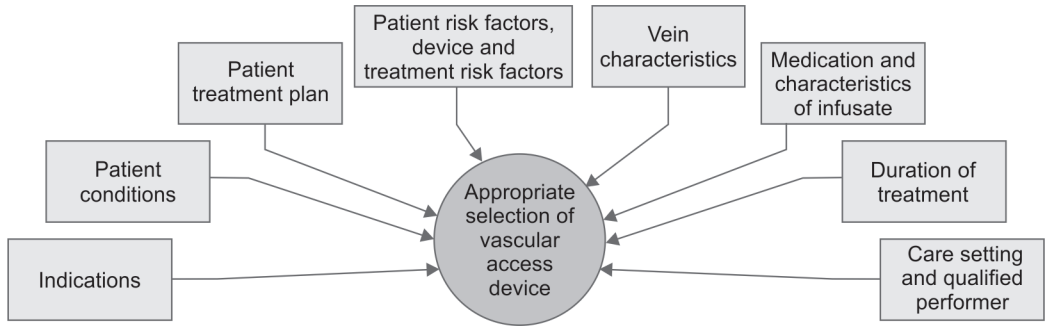
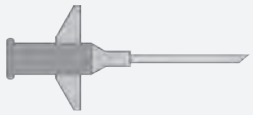
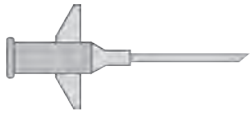
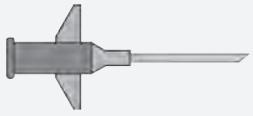
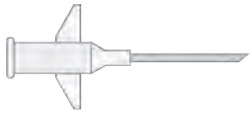
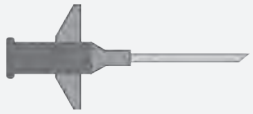


FIG. 2: Important factors while choosing appropriate vascular access device (VAD).

TABLE 3: Selection of peripheral cannula as per prescribed therapy. ***(For color version, see plate 2)***

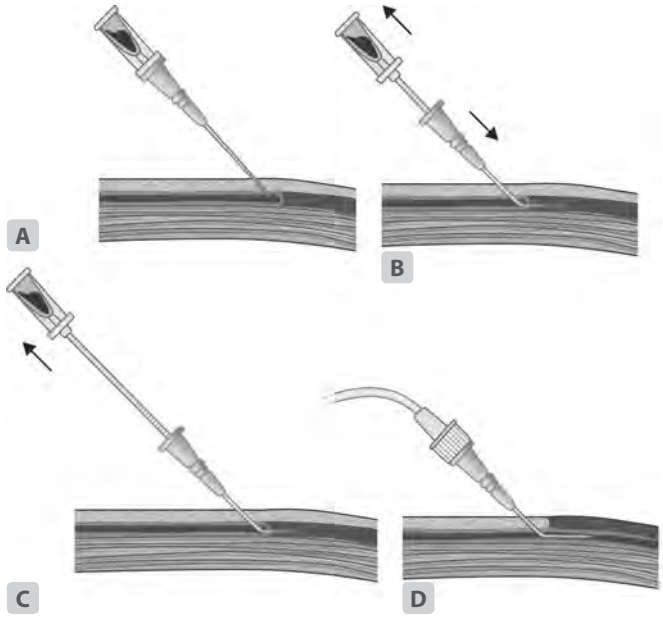
Color	*Gauge size*	*External diameter (mm)*	*Length (mm)*	*Water flow rate (mL/min)*	*Recommended uses*
Orange	14G	2.1 mm	45 mm	~240 mL/min	Trauma, Rapid blood transfusion, Surgery[1]
Gray	16G	1.8 mm	45 mm	~180 mL/min	Rapid fluid replacement, Trauma, Rapid blood transfusion[1]
 Green	18G	1.3 mm	32 mm	~90 mL/min	Rapid fluid replacement, Trauma, Rapid blood transfusion[1]
 Pink	20G	1.1 mm	32 mm	~60 mL/min	Most infusions, Rapid fluid replacement, Trauma, Routine blood transfusion[1]
 Blue	22G	0.9 mm	25 mm	~36 mL/min	Most infusions neonate, pediatric, older adults, Routine blood transfusion[1]
 Yellow	24G	0.7 mm	19 mm	~20 mL/min	Most infusions neonate, pediatric, older adults, Routine blood transfusion, Neonate or Pediatric blood transfusion[1]
 Purple	26G	0.6 mm	19 mm	~13 mL/min	Pediatrics, Neonate[1]

Source: Infusion Therapy Standards of Practice Jan/Feb 20161 https://www.bd.com/infusion/products/ivcatheters/iagbc/videos/pdfs/iagbc_wp3.pdf

Ultrasound-guided Peripheral Catheter Indications

Use visualization technology to establish peripheral access using longer catheters for the purpose of intravenous treatment less than 5 days or more than 15 days (with transition to midline or PICC).

For patients with one or more failed attempts, inability to identify veins visually or those identified as DIVA commonly



FIGS. 3A TO D: Peripheral venous access technique—(A) insertion of needle, (B) Proceed needle further as blood seen on the top, (C) Remove the needle and catheter is advanced further, (D) Catheter is attached to tubing and secured.

inserted in the forearm, antecubital fossa or upper arm. For contrast based radiological studies requiring upper extremity access in larger veins with 20-, 18- or 16-gauge catheter (where visible veins to accommodate catheter size are not present)

CENTRAL VENOUS CATHETERS

Central venous access devices exceed >10 million worldwide, with significant risk to the patient. Vascular access has great importance in the treatment of patients submitted to prolonged chemotherapy. The central veins are the target for placement of the internal section of central venous catheters (CVCs) and their tips.

Large numbers of CVADs are performed yearly, the majority via the upper body for short-and long-term access. Ultrasound and electrocardiogram (ECG) guidance increase the successful placement of needles, guidewires, and catheters, but significant number of catheter misplacements can still occur, particularly if operators are not fully proficient in such techniques.

Indications for a Central Venous Catheter

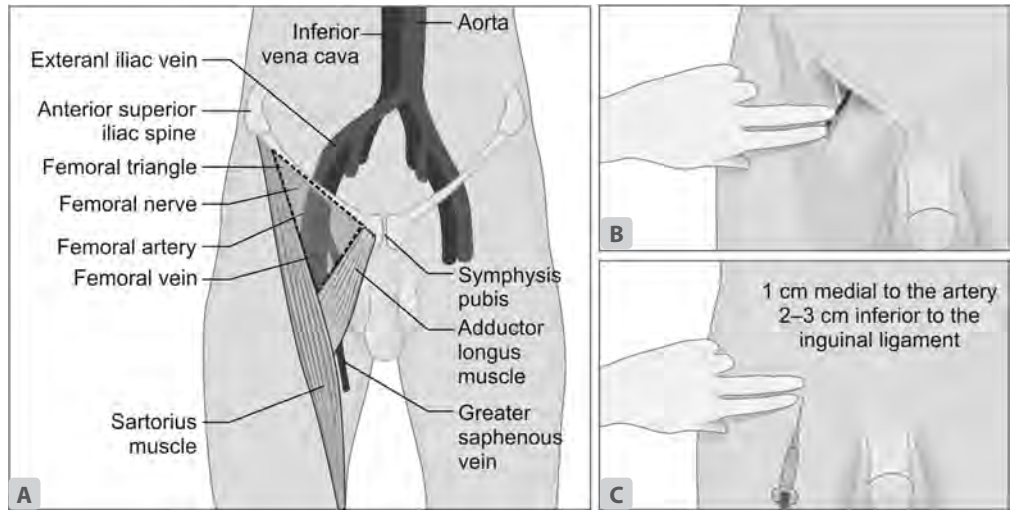
In the emergency department, CVCs are inserted for a large number of different indications: administering drugs (vasopressors/inotropes and antibiotics), monitoring central venous pressure (CVP), measurement of central venous oxygen saturation ($ScvO_2$), poor peripheral venous access, cardiac catheterization, and transvenous cardiac pacing. Many different types of catheters exist, for example, tunneled or nontunneled, monolumen or multilumen, dialysis catheters, and peripherally inserted central catheters (PICCS). In intensive care unit (ICU), in recent studies, the use of the central catheter subclavicle way should have less complications than the jugular or femoral access. In this trial, subclavian-vein catheterization was associated with a lower risk of bloodstream infection and symptomatic thrombosis and a higher risk of pneumothorax than jugular-vein or femoral-vein catheterization. There is a lack of standard minimal requirements for the training of insertion techniques and maintenance of CVADs. The insertion method and site selected affect the amount of risk involved related to trauma, colonization. The decision to choose a particular type or size of the device contributes to the risk for infection or thrombosis. Emergency physicians, anesthetics, intensivists, and nurses are also involved in the placement of CVADs using ultrasound guidance need appropriate training to ensure patient safety and avoid major complications with the insertion of CVADs. Basic knowledge of anatomy, ultrasound physics, and imaging, and infection prevention strategies are necessary for adequate understanding and safety of the insertion procedure.

Femoral Vein Catheter Insertion—Technique

Employ the *"landmark technique"* to isolate the location of the femoral vein for puncture (**Figs. 4A** to **C**). Use your index finger to locate the arterial pulsation along the inguinal ligament at the midpoint between the anterior superior iliac spine and the pubic symphysis. Then move 1–2 cm inferior to this position as the needle puncture must be performed below the inguinal ligament. Next, move 1–2 cm medially as the vein lies medial to the artery. Use your index and middle fingers to locate the distal and proximal pulsations of the femoral artery, respectively. Just medial to your fingertips should be the general course of the femoral vein. Hence, you should puncture just medial to your index finger in a direction just medial to your middle finger.

Internal Jugular Vein Catheter Insertion—Technique

If an ultrasound machine is not immediately available and central venous access via the right jugular vein is required, a simple three-finger technique for insertion of a central venous access line into the right internal jugular vein has proven to be a reliable method for accomplishing this task. Basic anatomy of neck area is shown in **Figure 5**. Place the patients supine with their head turned gently to the left. This technique of the central venous access via the right jugular vein will be successful no matter how much or how little the head can or cannot be turned. The practitioner's left ring finger is placed in the patient's sternal notch, and the adjoining middle and index fingertips are brought together such that they are in the midline over the trachea. This group of fingers is then rolled over the trachea and down into the space between the trachea and medial head of the medial sternocleidomastoid muscle. The pads of the three fingers must stay in contact with the trachea. When done properly, the left ring finger is now in contact with the sternoclavicular joint and the medial head of the sternocleidomastoid muscle is bunched into a mound lateral to the fingers. In the middle of the mound and at the level of the left index finger insert the finder needle at a 45° angle to the skin aiming toward the patient's ipsilateral nipple with gentle suction applied to the syringe. Once the vein has been entered and venous blood positively identified in the syringe, the larger introducer needle is inserted directly over the top of the smaller finder needle at the same angle and direction of the finder needle (**Fig. 6**). Proceed to place a catheter with the Seldinger technique. This completes the central venous access via the right jugular vein procedure. Check the postprocedure chest radiograph, by using mammography or blood gas for proper central venous line catheter placement.



FIGS. 4A TO C: Landmark technique for insertion of central venous catheter at femoral vein site.

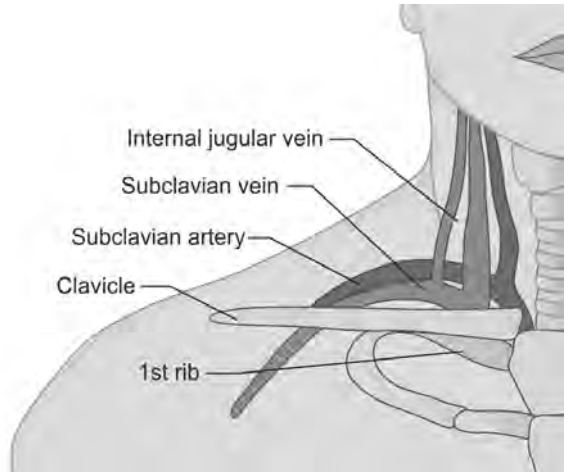


FIG. 5: Anatomy of neck area.

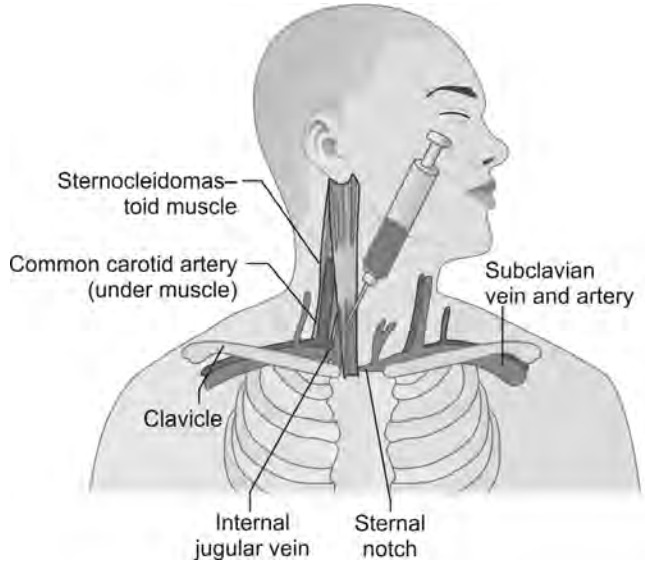


FIG. 6: Internal jugular vein catheter insertion technique.

Subclavian Vein Catheter Insertion—Technique

Subclavian vein catheter insertion is good choice for long term as this allows the patient to move the neck freely. Supraclavicular and infraclavicular approaches (**Figs. 7A** and **B**) are the two traditional approach used for subclavian vein catheterization. Supraclavicular approach provides good sonographic visualization. Both approaches are associated with risk of developing the pneumothorax. Insertion of a central venous access, whether it is being used for a short or a long period of time, is a common procedure, which is often undertaken by emergency physicians, intensivists, and anesthetists. The associated morbidities include punctured arteries for almost 10% of cases and hemothorax or pneumothorax for about 3%. These complications can be serious or even fatal.

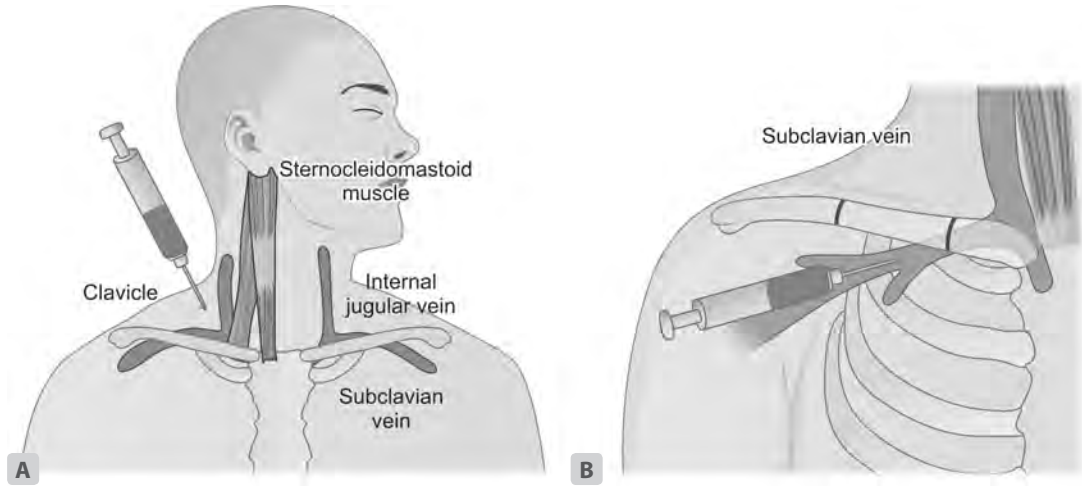
Nontunneled Central Venous Catheters

Nontunneled CVCs are commonly used for internal jugular access with acute care patients who are unstable and who require hemodynamic monitoring or large fluid infusions.

Nontunneled catheter indications—unstable patients requiring hemodynamic monitoring, multiple medications, large fluid infusions, blood or blood products or continuous parenteral nutrition, and short-term critical access. Nontunneled CVCs are preferred over PICCs for access up to 14 days. Chemotherapy treatment anticipated for >3 months. Antimicrobial nontunneled catheters are often used for these critical patients to reduce the risk of infection by approximately 40%.

Tunneled Central Venous Catheters

Tunneled CVCs are inserted into internal jugular or subclavian veins with a subcutaneous tunnel are indicated for use with intravenous treatment >31 days or for patients not considered candidates for a PICC due to vein size or thrombosis risk. *Tunneled catheter indications*—patients receiving treatment exceeding 31 days. Infusion of vesicant, irritant, parenteral nutrition, or chemotherapeutic agents regardless of duration; patients likely to receive cyclic or intermittent ongoing therapy



FIGS. 7A AND B: (A) Supraclavicular approach; (B) infraclavicular approach to subclavian vein.

exceeding 31 days; and- -Patients with >6 hospitalizations annually with expected duration of therapy > 15 days per hospitalization.

Totally Implanted Catheter with Subcutaneous Ports

Patients with expected treatment > 6 months [neutral rating for 3–6 months (duration of treatment)]. Patients requiring intermittent or cyclic infusion treatment, rather than continuous, for >6 months.

MIDLINE CATHETERS

Midlines are appropriate for patients with peripherally compatible solutions or medications for duration of treatment > 6 days. Midlines are preferred for patients requiring infusions up to 14 days, but may be used in a manner consistent with the clinically indicated removal of peripheral catheters. *Midline catheter indications*—treatment involves peripherally appropriate solutions that will likely exceed 6 days. It is preferred for patients requiring infusions of up to 14 days and in patients with DIVA despite ultrasound-guided peripheral catheter attempts. Single-lumen midline is placed unless specific indication for dual lumen with compatible infusions.

PERIPHERALLY INSERTED CENTRAL CATHETERS

This long-term intravenous device is a central catheter. It is inserted under ultrasound by a peripheral vein deep in the arm and can be tunneled. There are PICC authorizing injections at 5 mL/s.

Technique of Peripherally Inserted Central Catheters

The size of the catheter must be adapted to the vein as the risk of thrombosis increases with the diameter of the catheter. The Trendelenburg technique and the Valsalva maneuver can increase the diameter of the chin strap and prevent collapse (up to 50%). Single-lumen PICCs preferred unless specific indication for additional lumen. Use smaller gauge PICC with fewer lumen to reduce risk of deep vein thrombosis (DVT) (Grove and Pevec, 2000; Evans et al., 2013). Measure vein size to establish appropriate catheter size of >45% of vein diameter (Sharp et al., 2015). Position of terminal tip of PICC in lower third of the superior vena cava, cavoatrial junction, or right atrium.

Peripherally Inserted Central Catheter Indications

- Patient requires intravenous access for >14 days. For proposed treatment of 6 or more days ultrasound-guided or midline catheter preferred over PICC.
- Clinically stable patient requiring intravenous therapy with peripherally incompatible solutions. Hemodynamically unstable patients where cardiac monitoring or use of vasopressors is necessary in cases <14 days and >15 days (CVCs favored over PICCs).
- For use with continuous infusions of vesicant, parenteral nutrition, chemically irritating, or nonperipherally compatible solutions for any duration
- For cyclic chemotherapy with active cancer where treatment is >3 months. Consideration given to discontinuation of PICC when each cycle complete (peripheral catheter preferred when >3 months).
- Use with patients receiving frequent phlebotomy of every 8 hours or more often with duration of 6 days or more
- For burn patients where early implementation of PICC decreases risk of bacteremia.
- For use in patients in palliative treatment, actively dying or in hospice requiring intravenous solutions

Peripherally Inserted Central Catheter Contraindications

Do not insert the peripheral catheter near skin or infected lesions, on the side of an axillary dissection, lymphedema, and hemiplegia. No PICC in renal failure insufficiency who may need an arteriovenous fistula.

USE OF ULTRASOUND FOR CENTRAL VENOUS CATHETER INSERTION

Ultrasound guidance for the insertion of CVADs has become standard practice, and mitigates serious procedural complications such as pneumothorax and accidental arterial puncture. There is an emerging trend for the use of this technology to aid in the insertion of PIVCs for patients with DiVA guidelines on the use of ultrasound guidance for vascular access (**Table 4**). The spread of ultrasound scanners in emergency departments and ICUs has made ultrasound-guided catheterization possible.

TABLE 4: Recommendation for use of ultrasound for central venous access

Guidelines	*Strong recommendation*	*Weak recommendation*
Guideline 1: Internal jugular vein in adults	X	
Guideline 2: Subclavian vein in adults	X	
Guideline 3: Femoral vein in adults	X	
Guideline 4: Radial artery in adults		X
Guideline 5: Peripheral veins in adults		X
Guideline 6: Internal jugular vein in children	X	
Guideline 7: Subclavian vein in children		
Guideline 8: Femoral vein in children	X	
Guideline 9: Radial artery in children		X
Guideline 10: Peripheral veins in children		X

REMOVAL OF CATHETER

Removal of a CVC (PICC, CVC, and tunneled catheter) after notification of physician and when catheter has not been used for any clinical purpose for 48 hours or longer. Removal of catheter when patient no longer has a clinical indication for use or the original use has been met.

Removal of catheter when used only for blood samples in stable patient when peripheral veins available. Removal of catheter only by clinician trained for removal of specific device.

ARTERIAL ACCESS

Peripheral arterial catheters are widely used in the care of critically ill patients. They are a vital component of contemporary management of patients in ICU and are usually inserted into a peripheral artery for continuous blood pressure (BP) monitoring and blood sampling for frequent blood gas analysis. Arterial cannulation provides easy and convenient access, allowing multiple blood samplings.

High Indications

- Cardiac surgery with extracorporeal circulation
- Pheochromocytoma surgery
- Neurosurgery with high risk deep decrease BP (hypotension)
- Hepatic and pulmonary transplants

Strong Recommendation

- Surgery with sudden and/or significant variations in blood volume
- Major vascular surgery with aortic clamping
- Risk hemorrhagic surgery (spine surgery)
- Cardiovascular conditions require precise intraoperative control of BP:
  - Coronary insufficiency
  - Severe high blood pressure (HBP)
  - Heart failure and cardiac insufficiency
  - Hemorrhagic and hypovolemic shock

Technique

The radial artery is preferred for securing arterial blood and for cannulation to provide continuous BP monitoring and arterial blood sampling. If the radial artery cannot be cannulated, the femoral artery offers a viable alternative. Arterial line placement can be performed via multiple methods. The choice of methods is determined by location, operator preference, and available equipment.

- *Step 1*: Use a prepackaged radial artery catheterization kit, include iodine or chlorhexidine solution, dorsal wrist extensor splint, 1% lidocaine for local anesthesia, 4 × 4 gauze squares, adhesive tape, nylon suture (3-0 or 4-0), needle driver, catheter-over-the-needle, and compatible spring-wire guide.
- *Step 2*: Extend the patient's wrist to identify the radial artery insertion site. Secure arm and hand with tape if needed. Palpate the radial artery to determine its location. Clean the skin with antiseptic solution, arrange sterile drape, and inject anesthetic.
- *Step 3*: With a one-piece catheter-over-the-wire, puncture the artery and insert the cannula in a continuous motion at an approximately 45° angle (**Fig. 8**). After noting a flash of blood in the needle hub, stabilize the catheter-over-the-needle.

Allen's Testing

Appreciate the vascularization of the hand by the radial artery and the ulnar artery, respectively.

- The patient flexes his wrist strongly. Apply pressure on both arteries at the wrist. The patient then reopens his hand.
- Relieve the pressure on the radial artery. The color of the skin did not return after 30 seconds, the pressure was released on the ulnar side.
- Then repeat the test, first releasing the pressure on the ulnar artery.
- This test allows to know what is the predominant vascular supply radial or ulnar.

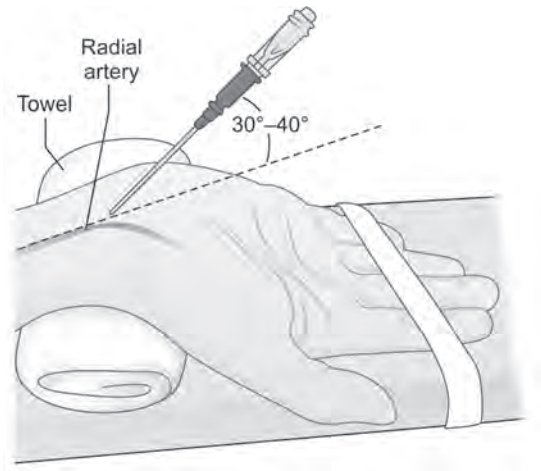


FIG. 8: The radial artery catheterization needs a control by the Allen's Test. If the patient suffers from a Raynaud's disease, the catheter is not indicated.

Source: Ramsey L. (2018). Arterial line placement: Basics for medical students. [online] Available from https://www.emra.org/emresident/article/arterial-line-placement/ [Last accessed July, 2021].

Other Sites

- *Femoral artery*: Preferred in emergency conditions. Large diameter and deep anatomical situation. Disadvantages—limited intraoperative accessibility risks of kinking and disconnection.
- *Foot artery:* Superficial artery with a collateral vascular network not detectable in 20% of cases not very accessible during the intraoperative phase.
- *Humeral artery:* To be avoided. Use only if no substitution is possible.

ARTERIAL BLOOD PRESSURE

Arterial blood pressure (ABP) is the pressure generated by the interaction of cardiac output with the arterial wall resistance. As the cardiac output is ejected from left ventricle, it travels downstream from aorta to different arterial branches, arterioles, and meta-arterioles perfusing different organs. Hence, ABP has been used traditionally as a marker of global tissue perfusion. During resuscitation in emergency room usually we target mean ABP of >65–70 mm Hg. In certain condition due to altered physiology and hemodynamics, different MAP is targeted (**Table 5**). *ABP measurement:* Routinely, noninvasive BP is measured in patients but in shock state they are unreliable; hence direct BP measurement by placing indwelling arterial catheter in a peripheral artery is preferable during shock resuscitation. It provides beat-to-beat display of characteristic arterial pressure waveforms and values. The arterial catheter is commonly placed in radial or femoral artery. Femoral artery catheter is recommended when noninvasive cardiac output measurement is planned. The indwelling catheter is connected to monitor through tubing and transducer assembly (**Fig. 9**). Transducer is the mainstay of the system and should be calibrated ("zeroing") to the ambient pressure at the ipsilateral mid-axillary line fourth intercostal space. Transducer converts mechanical energy of the pulse wave into electrical waves which are transmitted to and displayed on the monitor. The waves must be interpreted with corresponding ECG display.

TABLE 5: Mean blood pressure targets during resuscitation in special clinical conditions.

Higher MAP target (85–90 mm Hg)	*Lower MAP target (55–60 mm Hg)*
Traumatic brain injury	Polytrauma (damage-controlled resuscitation)
Cerebrovascular accident	Hemorrhagic shock
Chronic hypertension	
Hypertensive nephropathy	
Eclampsia	

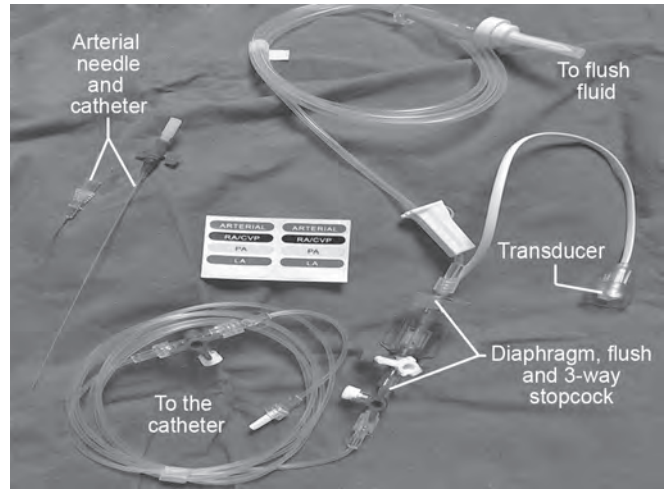


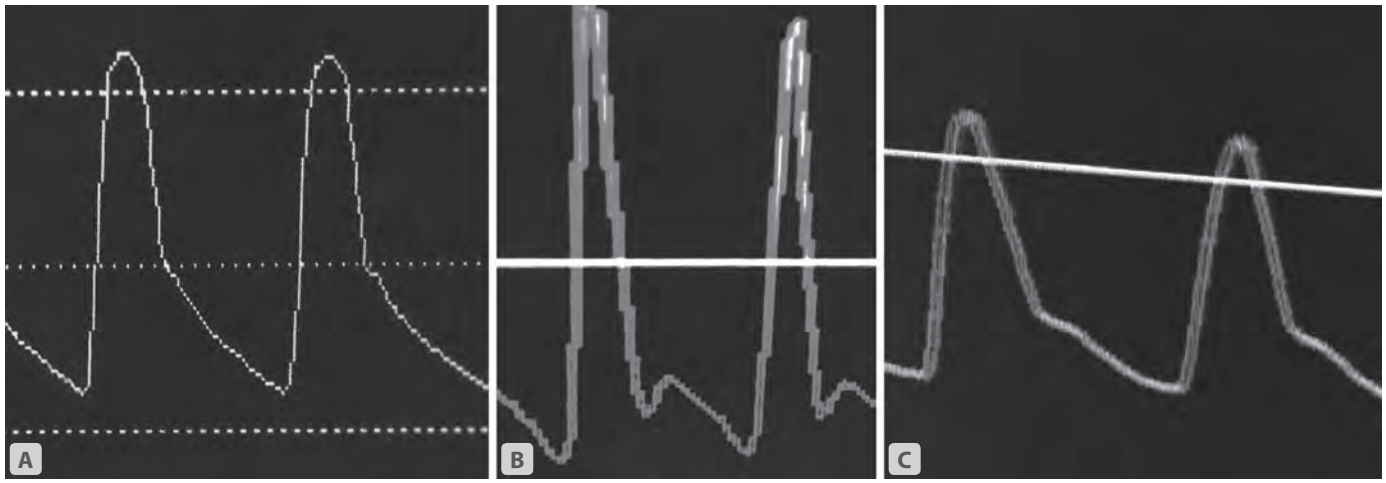
FIG. 9: Pressure line components of invasive pressure monitoring.

Interpretations

- The arterial wave may be displayed underdamped/overdamped (**Figs. 10A** to **C**) due to erroneous system. This will display incorrect systolic/diastolic pressure value but mean pressure will be correct. Common causes of erroneous direct arterial BP display are given in **Table 6**
- The beat-to-beat variation in ABP plethysmography with breathing phases happens due to heart lung interaction. In a spontaneously breathing patient at end inspiration, there is decrease in left ventricular stroke volume which is displayed as decreased SBP while during positive pressure ventilation, there is increased SBP value in plethysmograph at end inspiration. Any exacerbation of these variations in display usually indicates hypovolemic state and fluid challenge must be given. In monitors displaying dynamic parameters, it is possible to measure these variations and these are termed systolic pressure variation (SPV) and pulse pressure variation (PPV). SPV variation of 15% and PPV variation of >12% again signify hypovolemia.

EMERGENCY CONDITIONS WHERE FEMORAL ARTERY ACCESS IS RECOMMENDED

- For intraaortic balloon pump/tandem heart/ECMO/Impella device placement for hemodynamic support
- For percutaneous structural heart procedures (balloon valvuloplasty, percutaneous valves, etc.)



FIGS. 10A TO C: Invasive arterial waveforms (A) normal wave form with smooth pick and dicrotic notch. (B) Underdamped wave with sharp tall picked systolic wave. (C) Damped wave pattern with nondiscernible dicrotic notch.

TABLE 6: Common causes of erroneous direct arterial BP display.

Causes of overdamped	*Causes of underdamped*
Air bubble in tubing	Long tubing
Clot/Kink of tube/catheter	Increased vascular resistance (e.g., very high vasopressor dose)
Low flush bag pressure	

- Peripheral vascular angiography and intervention (transradial access can be used with the use of longer length catheters)
- For invasive hemodynamic monitoring (radial access preferred)
- Coronary angiography and intervention (preferred over radial for procedures requiring larger sheath size)

Femoral access should be strongly considered in situations where larger sheath size (8 Fr or higher) is required or in patients with prior difficult radial access. The ideal site of femoral arterial puncture (not skin puncture) is at the common femoral artery (CFA) at a point approximately 1 cm lateral to the most medial aspect of the femoral head, midway between its superior and inferior borders *(Rupp's rule)*.

Procedure

- Prepare the femoral artery site using antiseptic solution and dry it using a dry gauge.
- Cover the site with a sterile drape, with an opening at the site of the femoral access site.
- Prepare the patient prior to a potentially painful step of the procedure (e.g., administering local anesthesia) by informing him or her of the next step to ensure adequate patient cooperation.
- Identify the ideal femoral artery puncture site.
- Feel the femoral arterial pulsation at the site of skin entry with the tips of the middle and index fingers, and parallel to the course of the femoral artery.
- Make a 2–4 mm nick parallel to the skin crease at the identified site of the femoral artery puncture. The nick can be enlarged and deepened using the tip of a small curved forceps. The nick and tunnel approach may not be necessary for smaller size sheaths.
- Puncture the artery using an 18-gauge arterial cannulation needle using a modified Seldinger technique with an anterior wall puncture. Enter the skin at a 30–45° degree angle so as to cannulate the artery 2 cm superior to the skin incision.
- Ensure pulsatile blood flow before wire advancement.
- Remove the dilator leaving behind the J-tipped guidewire and flush the side port of the sheath.

Complications

- Bleeding at the puncture site (hematoma)
- Thrombosis and occlusion of the radial artery (1.5–35%)
- Local or general infection from the catheter
- Pseudoaneurysm (mean incidence 0.09%)
- Injury of a nerve causing pain or transient functional impairment
- Obstruction of the arterial catheter with a clot
- Atheroma thrombus with arterial ischemia
- Arterial spasm

INTRAOSSEOUS DEVICE

In an out-of-hospital emergency setting, rapid vascular access is often needed to infuse fluids and administer drugs. In some urgent situations, the conventional procedure by peripheral venous cannulation cannot be performed rapidly due to difficult conditions like an out-of-hospital cardiac arrest. In difficult or impossible cases, central venous access or intraosseous (IO) access (**Fig. 11**) may be used in emergency situations, especially in children. IO vascular access is an effective first alternative to failed or delayed peripheral or central IV access in emergent situations. The technique involves the placement of a vascular device with the tip of the IO catheter in the bone matrix with a dwell time of 24 hours. Delivery of crystalloids, colloids, or medications through this catheter immediately infuses into the systemic circulation via the bone marrow cavity.

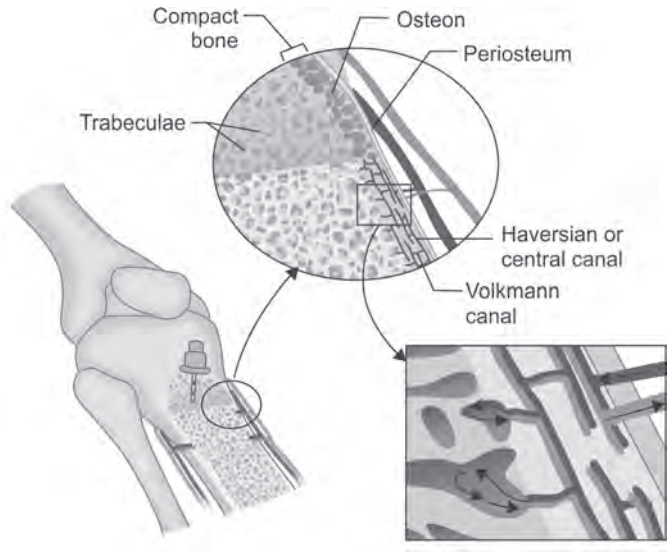


FIG. 11: Intraosseous vascular access.

Source: Tintinalli JE, Ma OJ, Yealy DM, Meckler GD, Stapczynski JS, Cline DM, et al. Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th edition. United States: McGraw-Hill Education; 2015.

Clinical Situations in which IO Access may be Considered

The following clinical situations represent patient groups in whom vascular access is notably difficult or who need access repeatedly but characteristically have limited vascular access.

Intraosseous access can be considered clinically appropriate on the basis of a short-term need for patients:

- With chronic disease who have been admitted to the hospital for treatment of a medical event, for example, the deteriorating patient with chronic obstructive pulmonary disease.
- With limited vascular access due to aggressive treatment modalities, for example, fistulas, grafts, shunts, mastectomies, or multiple central line placements
- For whom, rapid response teams are called to prevent an emergent situation and in whom obtaining peripheral or central IV access is difficult.
- Who experience an unexpected medical event that causes their peripheral or central IV device to become nonfunctional, for example, infiltration or occlusion, and difficult to reestablish.
- Who have limited peripheral access due to morbid obesity.
- Who experience intractable pain.
- Who are in the early stages of sepsis.
- Who are receiving palliative or hospice care.
- Who are undergoing anesthesia and experience prolonged, difficult, or failed IV access

Contraindications to IO Access

Intraosseous access should be avoided in the following situations:

- Fractures in the same extremity as the targeted bone
- Previous surgery involving hardware in the bone targeted for IO access
- Infection at the insertion site or within the targeted bone
- Local vascular compromise
- Previous failed IO insertion within 24 hours in the targeted bone
- Inability to locate the landmarks

TABLE 7: Complications of indwelling vascular catheters.

Common	*Arterial catheter*	*Central venous Catheter*
Hemorrhage **Hematoma** **Infection**	Arterial thrombosis AV fistula pseudoaneurysm Distal limb ischemia and gangrene	Deep vein thrombosis Limb swelling Thrombotic venous occlusion Pneumothorax

Complications of IO Access

Few complications are reported in connection with IO access. Most are avoidable with proper education and training.

Complications associated with IO access include extravasation from dislodgement, iatrogenic fracture, growth plate injury, infection, fat emboli, compartment syndrome, and osteomyelitis

COMPLICATIONS

Intravascular catheters use puts patients at risk for local and systemic infectious complications, including local site infection, septic thrombophlebitis, endocarditis, and other metastatic infections (e.g., lung or brain abscess, and osteomyelitis). Serious complications of infection and thrombosis require applying evidence-based indications and avoiding potential overuse of PICCs. Due to low insertion-related complications, reduced cost, and placement primarily by vascular access teams, the use of PICCs is popular. Mechanical complications include occlusion, infiltration, and accidental removal. Vascular complications include venous thrombotic occlusion and phlebitis. Infectious complications may be bacterial or fungal, and local or systemic bloodstream infections [catheter-related bloodstream infections (CR-BSIs)]. PICC venous thrombosis is known to also impact the risk of lower-extremity thrombosis and potentially contribute to incidence of pulmonary emboli. Selecting the intravenous device with the lowest risk that most effectively supports, the patient's treatment plan should be performed based on available evidence and specified indications (**Table 7**).

SUMMARY

Choosing the right catheter in urgent situations depends on many factors due to the patient's anatomy, comorbidities, hemostasis disorders, expected duration and type of treatments, and the infusion rate required. The ability to preserve vessel health for future medical needs requires clinical education and training in three areas—(1) device selection, (2) placement, and (3) daily device care. Selection of the most appropriate VAD is necessary to avoid the potentially serious complications of infection and/or thrombosis. Selection of a central VAD (CVAD) should be based on indications for that specific device rather than the inability to gain peripheral access. The use of 2% alcoholic chlorhexidine without predetergent on clean

and healthy skin is strongly recommended for skin antisepsis. Ultrasound-guided punctures are recommended in case percutaneous punctures. The position of the distal end of the catheter is fundamental to reduce the risk of thrombosis of CVCs. Extravasation complication is essential to recognize. All VADs have a risk of infection and other complications for the patient and should be removed as soon as no longer medically necessary. Prevention is crucial. Always consider patient's safety. *Mnemonic of what an Emergency Physician needs to think before access: "POCUS" Prevention*: anticipation is the key *O*rganize *C*lean and use 2% Alcoholic chlorhexidine Ultrasound are recommended *Sa*fety first.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Intravenous Fluids

Ripenmeet Salhotra, Supradip Ghosh

INTRODUCTION

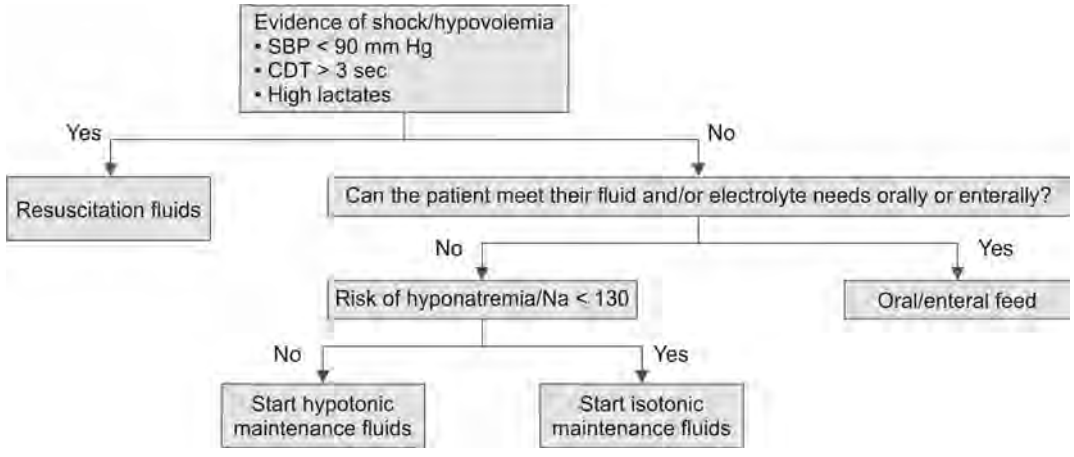
Intravenous (IV) fluid therapy is one of the most commonly provided treatments in both the emergency department (ED) and in-patients. Common indications for its use are resuscitation of a patient in shock and providing maintenance fluids to a patient who cannot take orally. Several types of IV fluids are available and each possesses specific benefits and disadvantages in a given clinical scenario. IV fluids can be divided into two broad categories—(1) crystalloids and (2) colloids. Colloids can further be classified as natural (albumin) or synthetic. Resuscitation fluids are frequently administered in ED to a patient with hypoperfusion with an aim to increase the stroke volume. Isotonic crystalloids and colloids are used for fluid resuscitation. IV fluid therapy is unnecessary and even harmful in the absence of signs of hypoperfusion such as hypotension, raised capillary refill time (CRT), high lactates, etc. Maintenance fluids should be provided to such well-perfused patients in case they are unable to accept oral or enteral feeding (**Flowchart 1**).

CRYSTALLOIDS

Crystalloids are the oldest forms of IV fluids. They are basically are simple solutions of electrolytes and/or sugars in water. They include isotonic solutions primarily used in resuscitation and hypotonic solutions used as maintenance fluid therapy. Electrolyte composition of some popular commercially available crystalloids is shown in **Table 1**.

Normal Saline (0.9% Saline)

The most popular crystalloid in clinical practice, 0.9% saline, contains 154 mmol/L of sodium and chloride each. Thus, concentration of both sodium (plasma sodium ~140 mmol/L) and chloride (plasma chloride ~100 mmol/L) are much higher than in plasma, resulting in a strong ion difference (SID) of 0. SID is the difference between the predominantly positive charge (sodium) and negative charge (chloride) in plasma. Normal SID of plasma is about 40. Any decrease in SID produces acidosis and conversely any increase produces alkalosis.



(SBP: spontaneous bacterial peritonitis; CRT: catheter-related thrombosis)

FLOWCHART 1: Approach to intravenous fluids administration in ED.

Infusion of large volumes of 0.9% saline leads to higher chloride concentrations in plasma and a decrease in SID. This decrease in SID (and hence bicarbonate) leads to hyperchloremic acidosis (**Fig. 1**). Several observational studies correlate resuscitation with saline and subsequent hyperchloremic acidosis with worse outcomes including acute kidney injury and mortality. Notably increased chloride concentrations in renal tubules lead to arteriolar vasoconstriction and reduce glomerular filtration. Despite these adverse effects, it remains the most used crystalloid in the world because it is relatively cheap, widely available, familiarity, and compatibility with blood and most medications. On its own, it should be the crystalloid of choice in patients with raised intracranial pressure (because of high osmolality of ~308) and in patients with metabolic alkalosis especially following vomiting and nasogastric aspiration.

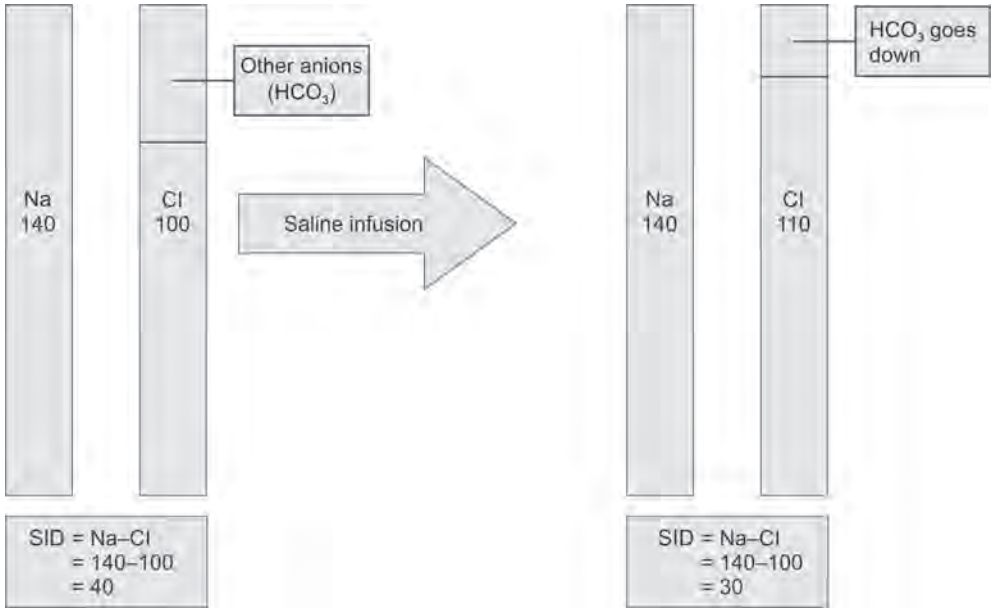
TABLE 1: Electrolyte composition of commonly available crystalloids.

Contents (mmol/L)	*Plasma*	*Normal saline*	*Ringer's lactate*	*Plas-malyte*	*Stero-fundin*
Osmolality	275–295	308	280	295	304
Sodium	135–145	154	130	140	140
Chloride	95–105	154	109	98	127
Potassium	4–5	0	4.5	5	4
Bicarbonate	24	0	0	0	0
Calcium	2.2–2.6	0	2.7	0	2.5
Magnesium	0.8–1.2	0	0	1.5	1
Lactate	0.8–1.8	0	28	0	0
Acetate	0	0	0	27	24
Gluconate	0	0	0	23	0
Maleate	0	0	0	0	5
pH	7.35–7.45	4.5–7.0	5.0–7.0	4.0–6.5	5.1–5.9

BALANCED SALT SOLUTIONS

Balanced crystalloids which are also known as *"physiological solutions"* have a chemical composition approximating that of extracellular fluid. These solutions employ metabolizable anions such as lactate, acetate, gluconate, or maleate to maintain electroneutrality, as bicarbonate is unstable in plastic. They have concentrations of chloride similar to plasma and hence devoid of harmful hyperchloremic metabolic acidosis. They may be somewhat hypotonic to plasma and should be avoided in patients with raised intracranial pressure. Besides, calcium in some of these fluids can bind to certain medications and citrated blood and should not be coadministered with these agents. In the SALT-ED trial, there was no difference in primary outcome of hospital free days when saline was compared to balanced crystalloids in non-critically ill ED patients. However, patients receiving saline had higher increase in creatinine. In another recent SMART trial, critically ill patients were randomized to receive saline or balanced crystalloids. The primary outcome which was a composite of death, new RRT and rise in creatinine favored balanced crystalloids. This difference was more pronounced in patients with sepsis.

Most commonly used balanced solution, the lactated Ringer's solution contains lactate which can raise plasma lactate making it harder to use trends in lactate to guide fluid management. Concerns also have been raised regarding the presence of potassium in the solution and theoretical risk hyperkalemia in vulnerable patients (e.g., renal failure). However, this has been refuted by a number of studies, which showed that in reality rise in potassium is more common with 0.9% saline than Ringer's lactate.



(Na: sodium; Cl: chloride)

FIG. 1: Effect of 0.9% saline transfusion on strong ion difference (SID).

Another newer balanced solution named plasmalyte containing acetate and gluconate as buffers and claims to eliminate the problems with the use of lactate. Unlike lactate predominantly getting metabolized in liver, metabolism of acetate happens in most cells of body. Also metabolism of acetate is faster compared to lactate. At least theoretically, acetate has been known to produce vasodilatation and hypotension; however, this has not been substantiated in several clinical studies. Plasmalyte contains higher sodium and lower chloride and thus resembles the electrolyte composition of plasma more closely than Ringer's Lactate. In spite of these, no studies have proven it to be superior to much cheaper Ringer's lactate in terms of clinical outcomes.

COLLOIDS

Colloids unlike crystalloids consist of large molecules and are believed to stay in the intravascular space for longer duration before leaking into the interstitium. They are used as resuscitation fluids in ED, critically ill, and during surgery (**Table 2**). In the past, it was thought that colloids are three to four times more effective than crystalloids in restoring the intravascular volume. This, however, was not substantiated in several recent trials, which suggested that only marginally lesser volume of colloids is required to produce similar hemodynamic effect when compared to crystalloids.

Albumin

The natural colloid albumin is available in iso-oncotic (4% and 5%) or hyperoncotic (20% and 25%) concentrations. Use of albumin in resuscitation of critically ill patients is safe and even showed a trend toward improved outcomes as compared to crystalloids in patients with sepsis. However, harm was seen when albumin was used in patients with traumatic brain injury and one must be careful to avoid it in this group of patients. Nevertheless, cost and availability remain an important hurdle in use of albumin that led to the development of synthetic colloids.

Synthetic Colloids

Hydroxyethyl starch (HES) is polydisperse solutions of hydroxylated carbohydrate molecules of various sizes. They are a group of synthetic colloids which differ in their concentration, molecular weight, molecular substitution, and carrier solution. For example, a product labeled 6% HES 140/0.4 contains a 6% solution of HES of mean molecular weight 140 kDa and a molecular substitution of 0.4. Newer or third generation HES solutions have lower molecular weight and substitutions resulting in more rapid metabolism and clearance and fewer adverse effects without loss of efficacy.

Several large multicenter randomized controlled trials have suggested that use of HES is associated with increased incidence of acute kidney injury and probably mortality in critically ill patients in general and septic patients in particular. Its use remains contraindicated in critically ill patients with sepsis. Though evidence for harm caused by HES in noncritically ill patients in ED or undergoing surgery is not so obvious neither is there any evidence of its usefulness in these patients. The case is more or less similar for other synthetic colloids such as Gelatins. Besides, synthetic colloids are also associated with other important adverse effects such as coagulopathy, anaphylactoid reactions, and pruritus. The routine use of synthetic colloids is currently not recommended.

Specific clinical situations sometimes warrant particular type of resuscitation fluid. Also, patient's acid-base status and electrolyte requirement must be considered before selecting appropriate type of fluid. For example, 0.9% saline is preferred if metabolic alkalosis is present due to its acidosis causing properties. Some fluids must also be avoided in certain conditions. For example, balanced crystalloids and albumin should be avoided in traumatic brain injury and synthetic colloids in sepsis (**Table 3**).

MAINTENANCE FLUIDS

The goal of maintenance fluid therapy is to sustain normal water and electrolyte balance and volume status. It should only

TABLE 2: Properties of colloids.

Colloid	*Types available*	*Used for*	*Adverse effects*
HES	• 6% and 10% • Molecular weight (MW): 130–670 • Molecular substitution (MS): 0.4–0.7	Resuscitation fluid	• Renal injury • Pruritus • Coagulopathy • Anaphylactoid reactions
Gelatins	• Urea cross-linked (e.g., Haemaccel) • Succinylated (e.g., Gelofusine)	Resuscitation fluid	• Renal injury • Coagulopathy • Anaphylactoid reactions
Dextrans	• 10% dextran-40 • 6% dextran-70	• Rarely used in resuscitation • Used to improve microcirculatory flow	• Renal injury • Coagulopathy • Anaphylactoid reactions
Albumin	• Iso-oncotic 4% and 5% • Hyperoncotic 20% and 25%	Resuscitation fluid (septic shock)	Increased mortality in traumatic brain injury

(HES: hydroxyethyl starch)

be undertaken if oral or enteral feeding is not possible and must be distinguished from fluid resuscitation. This must consider sensible losses from urine and stool and insensible losses from respiratory tract and skin. Routine prescription constitutes 25–30 mL/kg/day of water and approximately 1 mmol/kg/day of potassium, sodium, and chloride and approximately 50–100 g/day of glucose to limit starvation ketosis (e.g., glucose 5% contains 5 g/100 mL) (**Box 1**). Additional fluid and electrolyte supplements may be needed to replace the extra ongoing losses, such as nasogastric drainage, polyuria, or diarrhea. For example, water requirements increase by 100–150 mL/day for each degree of body temperature elevation above 37°C. Hypotonic fluids with dextrose and potassium are suitable maintenance fluids. Examples of commonly used hypotonic fluid formulations for maintenance include 0.18% saline +4% dextrose with added potassium and isolyte M (**Table 4**). Acutely ill patients are sometimes susceptible to hyponatremia resulting from impaired free-water excretion due to nonosmotic release of antidiuretic hormone. This will be worsened if hypotonic fluids are used as maintenance fluids. Serum sodium concentration must be monitored and maintenance fluids must be switched to isotonic crystalloids, if possibility of hyponatremia exists. Besides dextrose containing fluids must be avoided in patients with uncontrolled diabetes mellitus or hypokalemia.

Battery operated infusion devices or the IV pump is used for accurate precise and safe administration of fluid as well as various drugs also. Sometimes when infusion pumps are not available and healthcare worker uses "dial-a-flow" in which number of drops/minutes are infused to achieve the desired hourly infusion rate. A healthcare provider should have knowledge about the drop/minute reference guide (**Table 5**) so they can infuse desired level of fluid even in the absence of infusion pumps.

TABLE 3: Preferred resuscitation fluids in specific clinical situations.

Clinical situation	*Preferred resuscitation fluid*
Burns resuscitation	Balanced crystalloids, albumin
Hemorrhagic shock	Blood and blood products, limited crystalloids till blood is available
Metabolic alkalosis	0.9% saline
Septic shock	Balanced crystalloid, consider adding albumin, avoid HES
Traumatic brain injury	0.9% saline (avoid albumin)

(HES: hydroxyethyl starch)

BOX 1: Daily maintenance fluid requirement.

Normal daily fluid and electrolyte requirements:

- 25–30 mL/kg/day of water
- 1 mmol/kg/day of Na, K, and Cl
- 50–100 g of glucose

Conditions with increased requirement:

- Vomiting and nasogastric tube loss
- Biliary drainage loss
- High/low volume ileal stoma loss
- Diarrhea/excess colostomy loss
- Fever
- Pancreatic/jejunal fistula/stoma loss
- Urinary loss, e.g., post-AKI polyuria

(AKI: acute kidney injury)

SUMMARY

To conclude, fluids are administered to virtually all acutely ill patients. Choice of fluid should be individualized based on ongoing disease process, acid-base status, and electrolyte requirement. Thorough knowledge about IV fluids and their judicious use in the ED can improve patient outcomes.

TABLE 4: Examples of daily maintenance fluid prescription in an adult (70 kg).

Maintenance fluid	*Water*	*Sodium*	*Potassium*
2,000 mL D 5% + 500 mL NS + 50 mEq KCl	2,500 mL	76 mmol	50 mmol
2,500 mL (4%/0.18%) dextrose-saline + 50 mEq KCl	2,500 mL	76 mmol	50 mmol
2,500 mL isolyte M	2,500 mL	76 mmol	75 mmol

TABLE 5: Drops per minute reference guide.

IV tubing drop factor	20	25	30	50	60	70	75	80	100	110	120	125	130	150	175	200
	Drops per minute															
10 drop/mL	3	4	5	8	10	11	12	13	16	18	20	21	22	25	30	34
15 drop/mL	5	6	7	12	15	17	18	20	25	27	30	31	32	38	44	50
20 drop/mL	6	8	10	16	20	22	24	26	32	36	40	42	44	50	60	68
60 drop/mL	20	25	30	50	60	70	75	80	100	110	120	125	130	150	175	200

Information necessary to calculate IV flow rate:

$$\frac{\text{Volume to be Infused (milliliters)}}{\text{Total infusion time (hours)}} = \text{Hourly IV rate}$$

- Volume of fluid to be infused
- Total infusion time
- Drop factor = Calibration of the administration set used (number of drops per milliliter the tubing delivers; this information is found on the tubing package)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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Assessment of Volume Status and Hemodynamic Monitoring

44 CHAPTER

Sangeeta Chakraborty, Debashish Dhar, Devendra Richhariya

INTRODUCTION

Shock, by definition, is a condition of inadequate tissue perfusion; during resuscitation, the clinician's goal is to restore the patient's perfusion of organs and tissues. The importance of early goal-directed therapy and early intervention by emergency physicians for hypotensive patients has been shown in multiple studies, most classically by Rivers and colleagues for patients presenting in septic shock. One of the most important principles of Rivers' study was the use of targeted and aggressive fluid resuscitation to improve tissue perfusion increase cardiac filling and stroke volume (i.e., cardiac output). Fluid resuscitation is always an important part of the acute resuscitation. It is often less clear and also very difficult to determine before administering a fluid bolus, that patient who is currently hypotensive will actually respond to a fluid bolus. It is estimated in most of the studied studies, >40% of intensive care unit (ICU) patients receiving a fluid bolus did not show the desired increase in cardiac output and unnecessary and excessive fluid administration causes deleterious effects of fluid overload not only pulmonary edema but beyond that. Because of uncertainties of fluid therapy, outcome goals of fluid resuscitation are difficult to achieve. This chapter describes the various tools available for the emergency physician to answer various questions whether hemodynamically unstable patient responds to intravenous fluids, assessment of volume status, and hemodynamic monitoring. Methods for assessing the volume status are broadly categorized into static (traditional) and dynamic measurements (**Table 1**).

STATIC METHODS OF VOLUME ASSESSMENT AND ITS LIMITATIONS

Classic medical school teaching tells us to rely on the physical examination and vital signs to guide our resuscitation strategy, and this instruction extends into our clinical practice. However, when the objective findings are evaluated for their correlation with actual changes in perfusion and cardiac output, few of them perform well. One example is estimation of jugular venous pressure during the physical examination, which is used to evaluate abnormalities of the left-sided circulation. Not only is jugular venous pressure difficult to measure under some circumstances (e.g., when assessing an obese patient), but its true value can be confounded by numerous coexisting pathologies (e.g., valvular disease and pulmonary hypertension). Another commonly used marker, urine output, can fail to accurately indicate the success of resuscitative efforts because it can be difficult to distinguish oliguria secondary to circulatory dysfunction (prerenal azotemia) from intrinsic kidney injury (e.g., acute tubular necrosis) in the acute care setting. Even our most common and fundamental goal in resuscitation—improvement in the arterial pressure—does not necessarily correlate with improved cardiac output and, therefore, does not necessarily reflect improved perfusion.

Once the limitations of the physical examination were realized, advanced resuscitation techniques for patients in shock shifted to using cardiac filling pressures. When the left ventricle is underfilled, an increase in preload brings on a large increase in stroke volume, and the patient is said to be volume responsive. When the left ventricle is closer to maximum end-diastolic volume, the increase in stroke volume is minimal for the same increase in preload guide to fluid therapy. The use of filling pressures makes theoretic sense because, as indicated by physiology and the Frank-Starling curve (**Fig. 1**), ventricular pressures are directly proportional to ventricular volume until they reach a certain point at which this relationship is lost. Therefore, the goal during resuscitation is to administer intravenous fluids to optimally fill the left ventricle, which will increase the stroke volume, but not overfill it, which could result in deleterious side effects such as pulmonary edema. When these filling pressures are interpreted randomly, they are known as static measurements and are thought to be a direct reflection of the ventricular pressure and hence the volume of the cardiac chambers.

Central Venous Pressure

Central venous pressure (CVP) is the most popular of the static pressures and continues to be recommended in resuscitative

TABLE 1: Assessing of the volume status (static and dynamic measurement).

Static measurement	***Dynamic measurement***
• Mean arterial pressure	• Pulse pressure variation (PPV) or stroke volume variation (SVV)
• Central venous pressure	• IVC distensibility index (IVC DI)
• Pulmonary artery occlusion pressure	• End-expiratory occlusion test
• Mixed venous oxygen saturation	• Passive leg raise
• Mixed venous PCO_2	• *Limitations of dynamic indices*: *To predict accurate volume responsiveness by IVC DI, PPV, or SVV, methods the patient must be: Mechanical ventilated tidal volume of at least 8 mL/kg of ideal body weight, no spontaneous breaths of the patient, no cardiac arrhythmias*
• Arterial pH base excess and HCO_3	• *The passive leg raise (PLR) is the only dynamic index to date that has the ability to predict the response to fluids in a spontaneously breathing patient (no need to mechanically ventilate the patient*)
• Echocardiographic parameters: IVC size, LVEDP	
Hemodynamic monitors	
• Invasive monitors	Pulmonary artery catheters (PAC)
• Minimally (less) invasive monitors	• LiDCO, PiCCO (calibrated transpulmonary thermodilution) • Flotrac, LiDCO rapid (noncalibrated)
• Noninvasive monitors	• USCOM (ultrasonic cardiac output monitors) • NICOM (noninvasive cardiac output monitor) • Bioreactance • Bioimpedance

(IVC: inferior vena cava; LVEDP: left ventricular end-diastolic pressure)

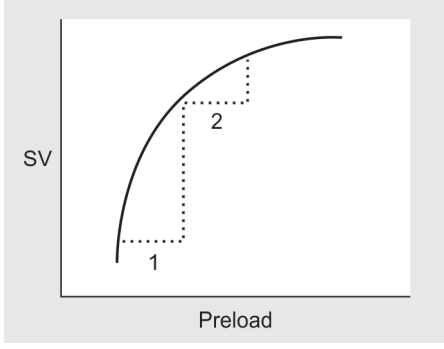


FIG. 1: Frank-Starling relationship of the heart. When the left ventricle is underfilled (1), an increase in preload brings on a large increase in stroke volume, and the patient is said to be volume responsive. When the left ventricle is closer to maximum end-diastolic volume (2), the increase in stroke volume is minimal for the same increase in preload.

protocols and guidelines. Despite these recommendations, the reliability of CVP for guiding fluid resuscitation is controversial because of variations in patients' physiologies (e.g., valvular pathology and right ventricular dysfunction) as well as persistent inaccuracy when it is used as a predictor of response to a volume bolus. An additional limitation to use of the CVP is that it requires insertion of a central venous catheter, which is invasive, and its placement is not readily possible in all emergency departments. Another example of a static measurement of volume status is the estimation of right atrial pressure, based on an ultrasound image of the absolute size of the inferior vena cava (IVC) and its measured respiratory variation. The IVC can be used to estimate right atrial pressures and, by indirect correlation, the CVP, which is the specified target in early goal-directed therapy. Ultrasound scan is an attractive hemodynamic monitor because it is noninvasive, rapid, and reproducible. Although there is debate as to its accuracy when predicting fluid responsiveness, it can be a useful measure when used as part of a comprehensive resuscitative protocol.

Mixed Central Venous Oxygen Saturation

The oxygen content (CaO_2) of the arterial blood coming out from left ventricle to aorta is determined by following formula:

$$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0003 \times PaO_2)$$

Where SaO_2 is the arterial oxygen saturation and PaO_2 is the partial pressure of oxygen in arterial blood. In optimum condition, the CaO_2 is about 20 mL/100 mL of arterial blood which is distributed to the different part of body. In steady state, about 25% of delivered oxygen is utilized by the different body tissues and deoxygenated blood is returned to right atrium and pulmonary artery. The saturation of this deoxygenated blood in pulmonary artery is termed mixed venous oxygen saturation (SvO_2). Nowadays, as pulmonary artery catheter (PAC) is not used commonly in ICU or ER, sampling of central venous catheter is done as surrogate of SvO_2 and is termed central venous oxygen saturation ($ScvO_2$). $ScvO_2/SvO_2$ represents the balance between the tissue demand and the tissue utilization of oxygen. The acceptable value of SvO_2 in resting state is 75–80%.

The $ScvO_2$ measures the saturation of blood in SvC unlike in SvO_2 which measures the mixed blood from both IVC and SVC In pulmonary artery. As the splanchnic oxygen extraction is normally lower than the brain; the oxygen saturation of $ScvO_2$ is 2–3% <SvO_2. Steady state $ScvO_2$ is 65–70%. $ScvO_2$ can be continuously measured and monitored during resuscitation by infrared oximetry based on mass spectrophotometry

using special proprietary central venous catheters available in market. There are various factors which alter $SvO_2/ScvO_2$ value (**Table 2**). Achieving $ScvO_2 > 70\%$ during septic shock resuscitation has been recommended as a part of early goal-directed therapy and has been associated with 16% increased survival when compared to control group. Later studies and evidences have, however, questioned this rationale and failed to find any significant improvement in the outcome.

Arterial Blood Pressure

Arterial blood pressure (ABP) is the pressure generated by the interaction of cardiac output with the arterial wall resistance. As the cardiac output is ejected from left ventricle, it travels downstream from aorta to different arterial branches, arterioles, and metarterioles perfusing different organs. Hence, ABP has been used traditionally as a marker of global tissue perfusion. During resuscitation in emergency room, usually we target mean ABP of > 65–70 mm Hg. In certain condition due to altered physiology and hemodynamic, different mean arterial pressure (MAP) is targeted (**Table 3**). Routinely, noninvasive blood pressure is measured in patients but in shock state they are unreliable; hence direct blood pressure measurement by placing indwelling arterial catheter in a peripheral artery is preferable during shock resuscitation. It provides beat-to-beat display of characteristic arterial pressure waveforms and values. The arterial catheter is commonly placed in radial or femoral artery. Femoral artery catheter is recommended when noninvasive cardiac output measurement is planned. The indwelling catheter is connected to monitor through tubing and transducer assembly. Transducer is the mainstay of the system and should be calibrated ("zeroing") to the ambient pressure at the ipsilateral midaxillary line fourth intercostal space. Transducer converts mechanical energy of the pulse wave into electrical waves which are transmitted to and displayed on the monitor. The waves must be interpreted with corresponding electrocardiogram (ECG) display.

Interpretations: *The arterial wave may be displayed underdamped (causes may be long tubing or high doses of vasopressors) or overdamped (causes may be bubbles, clot, or kinking of the tubing) or errors in system. This will display incorrect systolic/diastolic pressure value but mean pressure will be correct. The beat-to-beat variation in ABP plethysmography with breathing phases happens due to heart lung interaction. In a spontaneously breathing patient at end inspiration, there is decrease in left ventricular stroke volume which is displayed as decreased systolic blood pressure (SBP) while during positive pressure ventilation there is increased SBP value in plethysmograph at end inspiration. Any exacerbation of these variations in display usually indicates hypovolemic state and fluid challenge must be given.*

In monitors displaying dynamic parameters, it is possible to measure these variations and these are termed *systolic pressure variation (SPV) and pulse pressure variation (PPV). SPV variation of 15% and PPV variation of >12% again signify hypovolemia.*

TABLE 2: Common conditions altering mixed venous oxygen saturation.

Factors increasing $SvO_2/ScvO_2$	*Factors decreasing $SvO_2/ScvO_2$*
Increase tissue oxygen supply: • Vasodilatory shock • Hyperbaric oxygen therapy	*Decrease tissue oxygen supply*: • Cardiogenic shock • Hemorrhagic shock • Severe anemia
Decrease tissue oxygen utilization: • Anesthesia • Hypothermia • Cytopathic hypoxia	*Increase tissue oxygen utilization:* • Hyperthermia • Shivering • Exercise • Septic shock

($ScvO_2$: central venous oxygen saturation; SvO_2: venous oxygen saturation)

TABLE 3: Mean blood pressure (MAP) targets during resuscitation in special clinical conditions

Higher MAP target (85–90 mm Hg)	*Lower MAP target (55–60 mm Hg)*
Traumatic brain injury	Polytrauma (damage controlled resuscitation)
Cerebrovascular accident	Hemorrhagic shock
Chronic hypertension	
Hypertensive nephropathy	
Eclampsia	

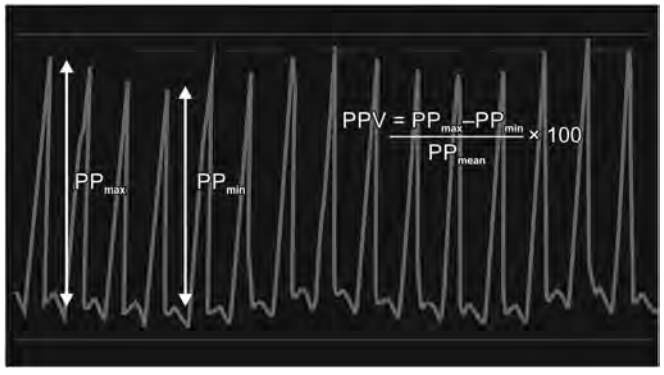
DYNAMIC METHODS OF VOLUME ASSESSMENT AND ITS LIMITATIONS

The counterpart to static measurement of volume status is dynamic measurement. Dynamic measurements differ from static measurements because they involve the monitoring of hemodynamic followed by an intervention (e.g., fluid bolus). Although dynamic measurements are better than static markers in predicting volume responsiveness, their routine use in the emergency department has two major limitations. First, dynamic measurements require the concurrent use of monitoring devices that can detect increases in stroke volume (e.g., ultrasound scan) during the assessment. Second, most dynamic assessments require that patients be intubated and mechanically ventilated. This method is chosen because mechanical ventilation increases intrathoracic pressure, producing a significant respirophasic variation in preload, which mimics a fluid bolus, with venous return being at a minimum at end-inspiration (highest intrathoracic pressure) and a maximum at end-expiration (lowest intrathoracic pressure). *Limitations of dynamic indices—to predict accurate volume responsiveness by IVC DI, PPV, or SVV, methods the patient must be mechanical-ventilated tidal volume of at least 8 mL/kg of ideal body weight, no spontaneous breaths of the patient, and there should be no cardiac arrhythmias. The passive leg raise (PLR) is the only dynamic index to date that has the ability to predict the response to fluids in a spontaneously breathing patient (no need to mechanically ventilate the patient).*

Pulse Pressure Variation and Stroke Volume Variation

Pulse pressure variation, a well-studied dynamic marker of cardiac output, measures the change in pulse pressure (PP) throughout a respiratory cycle on a mechanical ventilator

(**Fig. 2**). An arterial line is required to measure PPV, because systolic and diastolic measurements must be taken at specific points in the respiratory cycle. Once these measurements are recorded, the PPV can be calculated. Specialized monitors automatically perform both the measurements and the calculations in real time. SPV uses the same principal as PPV, except only the systolic pressures are measured at specific times in the respiratory cycle; therefore, it is not as reliable as PPV. PPV is a well-validated predictor of fluid responsiveness and can be applied in variety of clinical settings (emergency department, ICU, and operating room). A PPV > 12.5% suggests that a patient's cardiac output would increase when given a fluid bolus. Conversely, a PPV < 12.5% suggests that giving a fluid bolus would neither increase cardiac output nor improve hemodynamic status. The use of PPV for volume responsiveness in the emergency department has several limitations. One limitation is that this measurement reflects a patient's hemodynamic status at only one point in time, so PPV must be calculated several times during resuscitation, especially before administering a fluid bolus.



[PP_{max}: maximum pulse pressure; PP_{mean}: mean pulse pressure; PP_{min}: minimum pulse pressure (calculated by device)]

FIG. 2: Calculation of PPV using the tracing from an arterial catheter monitor.

Inferior Vena Cava Distensibility Index

The IVC distensibility index (IVC DI) is another commonly used dynamic assessment to determine fluid responsiveness. Ultrasound scan is used to assess the change in size of the IVC during a respiratory cycle in a mechanically ventilated patient. As was the case for PPV, positive intrathoracic pressure is essential to use this technique accurately. The benefit of IVC DI is that it is noninvasive (no arterial line is required) and is reproducible multiple times at the bedside. During the delivery of a mechanical breath, a patient's intrathoracic pressure increases, and venous return decreases, resulting in IVC dilation (an increase in the diameter of the vessel). When the mechanical breath is released, the intrathoracic pressure decreases, and the IVC returns to its normal diameter. The degree of IVC diameter change is measured with ultrasound scan and then the IVC DI is calculated (**Fig. 3**). Many findings suggest that IVC DI is a useful bedside tool for assessing the status of the intravascular volume for patients undergoing fluid resuscitation. There has been, however, variation in the agreed cut off values of the IVC DI across studies. Some studies found a cut off of 12%, but others proposed values as high as 36%. Limitations of measuring the IVC DI are similar to those described for PPV. There is also debate in the literature on what level of the IVC is the best site for measurement. The location of measurement (e.g., at the level of the hepatic or renal vein) can affect the recorded value of the IVC diameter.

End-expiratory Occlusion Test

The end-expiratory occlusion (EEO) test is a relatively new technique for dynamic assessment of fluid responsiveness in mechanically ventilated patients. The EEO test is executed by placing a 15-second expiratory hold on the ventilator (at the end of expiration). A prolonged state of increased preload is created by holding the positive pressure ventilation at it its lowest pressure, mimicking a fluid challenge. This test has the advantage of being able to assess fluid responsiveness even in the presence of arrhythmias, a notable difference from the techniques previously discussed. This technique requires concurrent measurement of stroke volume or cardiac output.

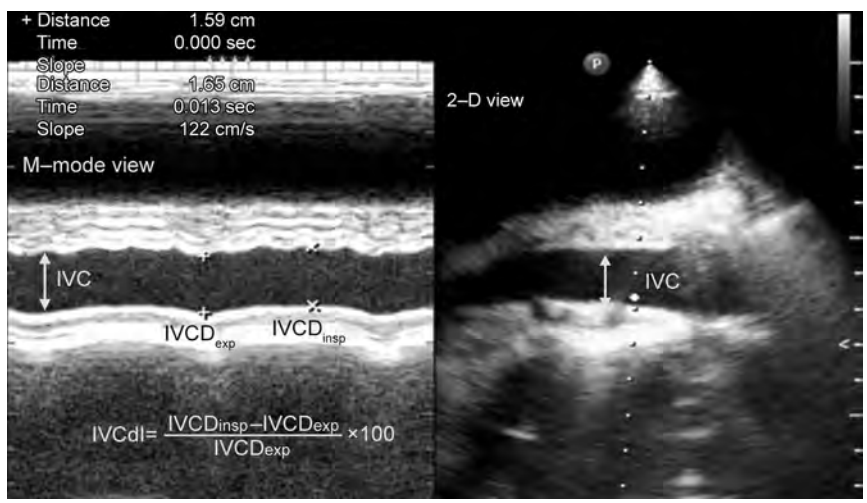


FIG. 3: Inferior vena cava (IVC) distensibility index. Calculation of IVC DI using M-mode ultrasound scan. $IVCD_{exp}$-IVC diameter at end-expiration; $IVCD_{insp}$-IVC diameter at end-inspiration.

FIG. 4: Passive leg raising maneuver. The process begins with the head of the bed and the patient's trunk elevated to approximately 45, at which time baseline parameters are recorded. The patient is then quickly laid back, with head and trunk flat and legs raised to 45, allowing the venous blood pooled in the legs to return to the heart quickly, creating an autologous transfusion. Parameters should be rerecorded 30–90 seconds after raising the legs to evaluate for volume responsiveness.

Although this is a notable limitation, several monitoring approaches have been reported, such as measuring cardiac output by thermodilution or waveform analysis. When such monitoring is available, if the stroke volume or cardiac output during the final 5 seconds of the expiratory hold is 5% higher than the premaneuver value, the patient will likely respond to the administration of a fluid bolus.

Passive Leg Raise

The dynamic techniques described above have one thing in common—the patient must be mechanically ventilated. Although these dynamic indices are fairly well validated, it is shown in **Figure 3** are IVC distensibility index. Calculation of IVC DI using M-mode ultrasound scan. IVC Dexp, (IVC diameter at end-expiration); IVC Dinsp, (IVC diameter at end-inspiration). Assessing volume status would be helpful to have a test that is valid for spontaneously breathing patients. *The passive leg raise (PLR) is the only dynamic index to date that has the ability to predict the response to fluids in a spontaneously breathing patient* (**Fig. 4**). The PLR technique mobilizes pooled venous blood in the lower extremities (~150–300 mL) to the central circulation as an autologous and reversible fluid bolus. In this way, extrinsic fluids are not necessary, and patients do not receive an unnecessary fluid bolus if they are not volume responsive. The PLR is performed by first measuring the baseline stroke volume or cardiac output, followed by remeasuring it 30–90 seconds after lifting the patient's lower extremities. A 10–15% change in stroke volume or cardiac output is an indicator that the patient will respond to exogenous fluid administration. Another benefit to this test is that it has been validated for patients with cardiac arrhythmias (e.g., atrial fibrillation). Similar to the EEO test, studies have used several monitoring systems, including bedside echocardiography, arterial waveform analysis, and bioreactance, to determine change in cardiac output or stroke volume.

DEVICES FOR HEMODYNAMIC MONITORING

The methods described in this chapter permit the clinician to deliver fluid boluses in a goal-directed manner. Unfortunately, many of these methods require the clinician to return to the bedside repeatedly to assess the patient's volume status. This requirement can be challenging and impractical in a busy emergency department. Devices that automatically monitor and display a patient's hemodynamic information are desirable because they allow the use of nurse-directed resuscitation protocols while the clinician leaves the bedside temporarily. Another benefit of such monitors is as an early warning system that alerts clinicians to changes in a patient's hemodynamic status. These devices display hemodynamic information such as stroke volume, cardiac output, and stroke volume variation (SVV). SVV is the amount of variation that occurs over a respiratory cycle in mechanically ventilated patients. It is similar in concept to PPV, except that a device is used to estimate the actual stroke volume rather than using the pulse pressure as a surrogate. Similar to PPV, SVV has been validated across multiple situations as a predictor of fluid responsiveness. An SVV measurement >11.5% suggests that giving a fluid bolus would be beneficial. Conversely, an SVV <11.5% suggests that a fluid bolus would not improve the patient's hemodynamic and might cause harm (e.g., pulmonary edema). Although PPV and SVV are very similar, PPV seems to slightly outperform SVV and requires the same conditions for validity as do PPV and IVC DI. *Two main categories of devices provide hemodynamic data—(1) invasive; and (2) noninvasive monitors* (**Table 1**). Each type has benefits and disadvantages, and neither is perfect. The choice of device depends on several factors.

INVASIVE HEMODYNAMIC MONITORS

Pulmonary Artery Catheter (PAC)

The PAC measures stroke volume and cardiac output by measuring the amount of time, it takes for a known quantity of fluid to traverse the right side of the heart. The longer it takes, the worse the stroke volume. One of the major criticisms of the PAC is its invasive nature, given that it must be inserted through the superior vena cava, into the right side of the heart, across the tricuspid and pulmonary valves, and into the pulmonary artery. Major complications associated with the PAC include pneumothorax, arterial puncture, and hematoma—complications associated with the placement of any central line. Complications specific to PAC include ventricular arrhythmias, ventricular rupture, and pulmonary artery rupture.

PiCCO and LiDCO systems

Two commercially available devices have monitoring principles similar to the PAC but are less (minimally) invasive—the PiCCO and LiDCO systems**.** These devices use an arterial catheter to perform pulse-contour analysis, which is a technique to determine hemodynamic parameters from an arterial waveform. Both devices are periodically calibrated to improve accuracy. Calibration is performed by injecting a fluid into a venous line (ice-cold saline for the PiCCO and lithium for LiDCO) and measuring the fluid in the arterial circulation after it traverses the heart.

The PiCCO system measures the degree of temperature elevation of the saline injected, and the LiDCO system measures the dilution of the lithium that was injected; these measurements are made via a sensor in an arterial line. Monitoring stroke volume and cardiac output with these monitors helps the clinician determine whether a hemodynamically unstable patient would benefit from a fluid bolus, because the response to fluid bolus can be measured. For example, an increase in either parameter by 10–15% after a fluid bolus suggests the patient was volume responsive as part of the hemodynamic resuscitation.

However, failure to increase the stroke volume or cardiac output by 10–15% after a fluid bolus suggests that the hemodynamically unstable patient would not improve with fluid administration and should perhaps receive vasopressors or an inotrope. The PiCCO device is considered a minimally invasive device because it requires the placement of a central venous catheter (the tip of which resides at the junction of the superior vena cava and the right atrium) and a femoral arterial line that will detect changes in saline temperature distally.

The limitations of the PiCCO device include decreased accuracy in patients with low-flow states (e.g., severe heart failure), valvular regurgitation, intracardiac shunts, and aortic aneurysms. The LiDCO device is somewhat less invasive than the PiCCO in that it requires placement of only a peripheral intravenous line and a radial arterial line (a central venous catheter can be used if it is already available). The major limitations to the accuracy of the LiDCO device are similar to those associated with the PiCCO device, including low flow states, valvular regurgitation, and intracardiac shunts.

A limitation specific to the LiDCO device is its use of lithium dye. Although this dye is safe for most patients, it should be avoided in certain situations, including patients who weigh <40 kg, pregnant patients, and those taking lithium as a medication. A third minimally invasive system is the FloTrac/Vigileo system. This system differs from the monitors discussed above in that it requires placement of only an arterial catheter.

The monitor displays hemodynamic data such as stroke volume, cardiac assessing volume status output, and SVV by analyzing arterial waveforms and pressures and integrating this information into a complex algorithm based on the patient's demographics (height, sex, and weight). This device does not require external calibration, and its manufacturer claims that the system is continuously fine tuning and autocalibrating each minute. Autocalibration is based on cadaveric studies, and its accuracy has been questioned. The device has also been found to be inaccurate in certain clinical conditions (e.g., in patients with rapidly changing cardiac output or high cardiac output states).

Several studies found these minimally invasive monitors to be accurate. No single device, however, has gained widespread acceptance in emergency medicine; one of the major reasons for this is their invasiveness, requiring at least an arterial line (and a central line in the case of the PiCCO). Despite their limitations, these devices provide clinicians with hemodynamic monitoring that is otherwise difficult to achieve with traditional methods.

NONINVASIVE HEMODYNAMIC MONITORS

Invasive catheters have the potential to create complications, such as discomfort during placement, infection, and bleeding, so a noninvasive hemodynamic monitor is an appealing concept in the emergency department. *Two examples of completely noninvasive monitors are the ultrasonic cardiac output monitor (USCOM) and the noninvasive cardiac output monitor (NICOM).*

USCOM

The USCOM is a small probe that can be applied intermittently to a patient's chest or suprasternal notch whenever hemodynamic information is needed. The device works by providing a continuous Doppler signal, which measures the velocity of blood flow in the aorta (parasternal view) or the pulmonary blood flow (suprasternal notch). This information is used in conjunction with the patient's height to calculate several hemodynamic parameters, including stroke volume and cardiac output. Beyond the noninvasive nature of this device, another advantage is that bedside nurses can obtain the information for use in resuscitative algorithms.

The USCOM seems to be a promising addition to the emergency department armamentarium, although there are *several limitations* to its general use. The device can easily be applied to a patient, but obtaining an adequate and accurate Doppler signal can be a challenge for novice users and altogether impossible in a percentage of certain populations (e.g., the elderly). Another limitation is that hemodynamic information is not obtained continuously but rather only when the device is applied; this means that crucial information might be missed in patients with a rapidly changing hemodynamic state. Another criticism of the USCOM is the assumption that two patients with the same height will have the same hemodynamic changes when faced with a similar stressor, which might not actually be true. A detailed discussion of this concept is beyond the scope of this chapter, but it is a valid limitation that should be considered.

NICOM: Bioreactance

The NICOM requires the placement of four adhesive electrodes on the patient's anterior thorax. These electrodes measure changes in the frequency of electrical currents as they cross the thorax, converting this information into relevant hemodynamic information, including stroke volume, cardiac output, and SVV. Newer versions of this device incorporate the use of a passive leg raise maneuver to determine volume responsiveness. This device has been found to correlate well with more invasive means of hemodynamic monitoring, such as the PAC. The greatest clinical benefit of this device is that it provides continuous hemodynamic monitoring noninvasively for critically ill patients. Rapidly changing hemodynamic is more likely to be detected with this monitor compared with monitors that use intermittent measurements. Additionally, little training is required to set up and use the device because the sensors are applied to the thorax and do not require constant manipulation, minimizing sampling errors between readings. More clinical trials are needed to determine whether this device improves patient outcomes, but it is a promising technology for continuous hemodynamic monitoring in the emergency department.

SUMMARY

Shock is a physiologic state associated with high morbidity and mortality rates. Emergency physicians have a major impact on patient survival. The clinician has several tools available to evaluate volume status. Each modality has its benefits and limitations but, to date, no one test can indicate with 100% accuracy which patients will be truly volume responsive. Although the search for the Holy Grail of a perfect intravascular monitor continues, we must remember the importance of early, aggressive, and goal-directed interventions for patients in shock. We, therefore, must be astute clinicians and integrate the multitude of variables available at the bedside to assist in our decision making; this is truly the art of medicine. Finally, there is no substitute for the most important intervention—the frequent presence of the physician at the patient's bedside.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Arterial Blood Gas Analysis

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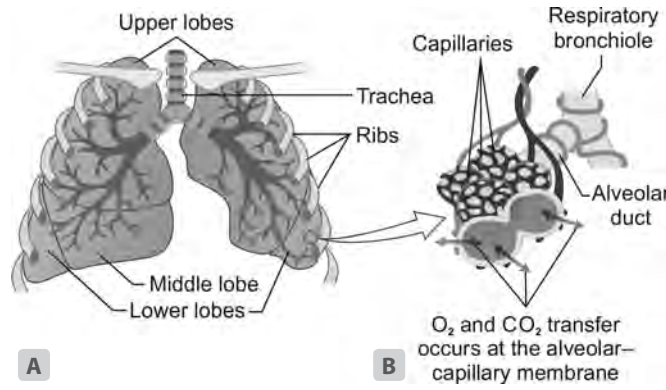
INTRODUCTION

Arterial blood gas (ABG) analysis is a common and useful tool in critically ill patient of emergency department. It gives information on oxygenation status and acid-base disorders. ABG measures the oxygen tension (PaO_2), oxyhemoglobin saturation (SaO_2), acidity (pH), carbon dioxide tension ($PaCO_2$), and bicarbonate (HCO_3) concentration in arterial blood. Some blood gas analyzers also measure the methemoglobin, carboxyhemoglobin, and hemoglobin levels. The newer available machines measure lactate and electrolytes too. ABG analysis provides immense information which helps in management of the critically ill patients. Correct interpretation is the key for usefulness of this diagnostic tool. A thorough understanding of acid–base balance is mandatory. There are three basic approach used to quantify acid-base status are, HCO_3 in relation to CO_2, standard base excess (SBE), and standard ion difference (SID). Important for the emergency physician to know the basics of pulmonary gas exchange and acid-base balance along with normal values of blood gases, indication contraindication and precaution while taking the arterial blood for evaluation.

BASICS OF PULMONARY GAS EXCHANGE

Pulmonary gas exchange is transfer of oxygen from atmosphere to blood and tissue (oxygenation) and carbon dioxide from blood to atmosphere. The gas exchange takes place between alveoli and capillaries as they are in close contact (alveolar-capillary membrane) and thus O_2 and CO_2 able to diffuse. ABG measures the effective gas exchange in form of partial pressure of gas (PaO_2/$PaCO_2$). Partial pressure is contribution of any gas within the gas mixture (air). When gas dissolves in blood, the amount dissolved depends on partial pressure (PaO_2-partial pressure of oxygen in arterial blood). Gas moves from higher partial pressure area to low partial pressure (so at alveolar-capillary membrane oxygen moves from alveoli to blood and carbon dioxide moves from capillary to alveoli until partial pressure is equal) (**Figs. 1A** and **B**). At sea level total pressure of gases in atmosphere is 760 mm of Hg and oxygen is 21% of all gases so partial pressure of oxygen (21% of total pressure) is 160 mm Hg. Carbon dioxide is very small fraction of air so partial pressure of carbon dioxide is negligible.



FIGS. 1A AND B: (A) Normal lung; (B) pulmonary gas exchange.

Carbon Dioxide Elimination

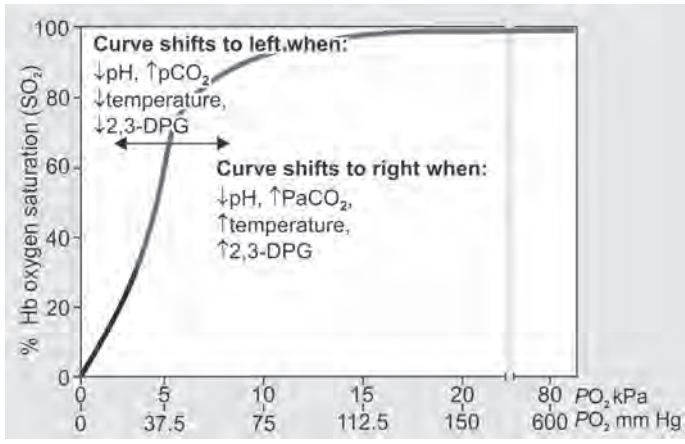
Carbon dioxide elimination (from blood stream to alveoli) is very efficient and uncomplicated and depends on *alveolar ventilation* (total air transported from alveoli to atmosphere). Ventilation is regulated by respiratory center situated in brain stem. Normally, lung is able to maintain normal $PaCO_2$ in high carbon dioxide producing situation such as sepsis. High $PaCO_2$ (hypercapnia) signifies reduced alveolar ventilation.

Hemoglobin Oxygen Saturation

Oxygenation is more complex than carbon dioxide elimination. Almost all oxygen molecules are attached to hemoglobin, so amount of oxygen in blood depends on hemoglobin concentration in blood and saturation of hemoglobin with oxygen (sO_2). PO_2 only measures unbound and free oxygen molecule. PO_2 is not a measure of the amount of O_2 in blood—ultimately, the SaO_2 and the Hb concentration determine the O_2 content of arterial blood.

Oxyhemoglobin Dissociation Curve

Oxygen in blood depends on hemoglobin concentration and sO_2. PO_2 is driving force for oxygen molecule to bind with hemoglobin. So, oxyhemoglobin dissociation curve shows sO_2 at any given PO_2 (generally we can say higher the PO_2—higher the sO_2). But curve is not linear, *flat part*



(2,3-DPG: 2,3-diphosphoglycerate)

FIG. 2: *Oxyhemoglobin dissociation curve*. The curve defines the relationship between PO_2 and the percentage saturation of hemoglobin with oxygen (sO_2). Note the sigmoid shape: It is relatively flat when PO_2 is >80 mm Hg (10.6 kPa) but steep when PO_2 falls below 60 mm Hg (8 kPa).

of the curve shows that PO_2 has little effect on sO_2 over this range. While the *steep part of curve* shows that even small change in PO_2 make significant change in sO_2 over this range (**Fig. 2**).

Alveolar Ventilation and PaO_2

With above discussion, we know PaO_2 regulates SaO_2. But SaO_2 is determined by three factors alveolar ventilation, ventilation perfusion V/Q match, and concentration of oxygen in inspired air (FiO_2).

- *Alveolar ventilation:* With oxygen moves rapidly from alveoli (PO_2) to blood, higher the PaO_2. Increase in alveolar ventilation causes more carbon dioxide elimination (high PO_2 presence) while decrease in alveolar ventilation signifies accumulation of CO_2 at expense of oxygen and fall of Po_2.
- *Ventilation perfusion V/Q mismatch:* In the presence of any lung disease, not all alveoli are well perfused by blood and not all blood flowing through lung gets well-ventilated alveoli. This issue is known as *ventilation perfusion V/Q mismatch.* So, if any amount of blood passing through the poorly ventilated part of lung due to collapse or consolidation, will get less oxygen and more CO_2 than normal and this is called *shunting.* In ventilation perfusion mismatch condition, low PaO_2 and low SaO_2 occur but $PaCO_2$ will not rise till overall alveolar ventilation is maintained.
- *FiO_2 and oxygenation:* Fraction of oxygen in inspired air (% of oxygen in room air is 21%). In any disease process, exact FiO_2 requirement can be fulfilled by supplemental oxygen by using appropriate delivery system.

DISORDERS OF GAS EXCHANGE

Hypoxia is a state in which tissue receives the inadequate oxygenation (cell is not getting enough oxygen). *Hypoxemia* is a state in which O_2 content of arterial blood is reduced (not enough oxygen in blood).

- *Type 1 respiratory impairment*: It is characterized by low PaO_2 and normal or low $PaCO_2$ (due to compensatory hyperventilation). V/Q mismatch is usual mechanism behind this. Pneumonia, acute asthma pulmonary embolism, acute respiratory distress syndrome, pneumothorax, fibrosing alveolitis pulmonary edema, and chronic obstructive pulmonary disease are common causes. High FiO_2 requirements, lactic acidosis and signs of organ dysfunctions (confusion drowsiness hypotension coma) are the markers of severity.
- *Type 2 respiratory impairment*: It is characterized by high $PaCO_2$ (hypercapnia) due to alveolar hypoventilations. Acute rise of $PaCO_2$ gives rise to accumulation of acid in blood. Chronic obstructive pulmonary disease, opiate/benzodiazepine toxicity, exhaustion, inhaled foreign body, flail chest injury, neuromuscular disorders, kyphoscoliosis, and obstructive sleep apnea are the common causes.
- *Hyperventilation*: It leads to $PaCO_2$ (hypocapnia) and resulting raised blood pH. Perioral/extremities tingling, light headedness, and syncope are the common symptoms. Anxiety (psychogenic), pain, hypoxemia, fever, salicylate alicylateecentral entralatee the common sy, and hepatic cirrhosis are the common causes.

BASICS OF ACID-BASE BALANCE

Concentration of free hydrogen ion H^+ in a solution (nmol/L) refers to acidity or alkalinity. H^+ concentration can be expressed as nmol/L or as pH (power of hydrogen). Solution with high hydrogen ion (low pH) acidic and low hydrogen ion (high pH) is alkaline. A negative logarithmic scale expresses the correlation of pH and H^+ concentration (**Table 1**). Normal pH of the human blood is 7.35–7.45 (<7.35 is acidemia and >7.45 is alkalemia). Any process which lowers of pH is acidosis and any process which increases the pH is alkalosis.

Maintaining the Acid-base Balance

- *How H^+ generates in our body*: Generation of energy, fats, and sugars after breakdown generates CO_2 and forms carbonic acid when CO_2 dissolved in blood. Protein

TABLE 1: Correlation of pH and H^+ concentration.

pH	*H^+ nEq/L*
7.70	20
7.60	25
7.50	32
7.40	40
7.30	50
7.20	63
7.10	79
7.00	100
6.90	126

- For H^+ concentration sequentially multiply 40 nEq/L with between pH of 7.4–7.8
- For H^+ concentration sequentially multiply 40 nEq/L with between pH of 6.8–7.4

metabolism produces hydrochloric acid sulfuric acid and other metabolic acids. H^+ must be removed from our body to maintain normal pH. Failure to maintain normal pH leads to inefficient cellular reaction and untimely death.

- *How H^+ removal from our body*: *By respiratory mechanism,* lungs are responsible for excretion CO_2. Our breathing is altered as the CO_2 production is altered. *By renal mechanism,* our kidneys are responsible for the excretion of metabolic acids. Kidneys excrete H^+ and absorb HCO^3. Respiratory and renal system work simultaneously to maintain the pH. If one system overburdened, another system automatically adjusts. If kidneys fail to excrete the H, ventilation increased to exhale more CO_2. *This is known as compensation.* Important to know that respiratory compensation happens in minute to hours while renal compensation takes days to develop.

DISTURBANCE OF ACID-BASE BALANCE

Normal values of gases in arterial blood (**Table 2**) and nomenclature related to acid-base disorder (**Table 3**) such as acidemia, alkalemia, acidosis, alkalosis, respiratory/metabolic, and simple/mixed disorder are important to know before analysis of ABGs. Common acid-base disorders and their cause are shown in **Tables 4** and **5**. Nomogram is the alternative way to know the disturbance in acid-base balance simple or mixed acid-base disorder (**Fig. 3**) (pH, H^+, and $PaCO_2$ is plotted, if values fall outside designated areas, indicate mixed acid-base disorder).

CONCEPTS IN ACID BASE DISORDERS AND FORMULAS

Concepts in acid-base disorders and formulas used in interpretation of arterial blood gas are given in **Boxes 1** to **4**.

STEPS IN THE INTERPRETATION OF ARTERIAL BLOOD GAS

After understanding the concepts and formulas used in interpretation of arterial blood gas, stepwise approach is used for evaluation of any arterial blood gas disorder **Box 5**.

TABLE 2: Normal values of gases in arterial blood.

	Normal range	*For calculation*
pH	7.34–7.45	7.4
pCO_2	35–45	40
HCO_3	22–26	24
PO_2	≥80	≥95

STRONG ION DIFFERENCE APPROACH VERSUS TRADITIONAL APPROACH

The Stewart or strong ion approach to acid-base disturbances has gained acceptance among many intensivists because of perceived weaknesses of the traditional approach in the evaluation of patients with critical illnesses. As per Stewart approach, dissociation (pH) is governed by laws of physical chemistry.

- *Law of conservation of mass*: Amount of substance in a solution remains constant unless added or removed or generated or destroyed by chemical reaction.
- *Law of conservation of electric charge*: Sum of all cations always equal sum of all anions.

TABLE 3: Nomenclature for acid-base disorders.

Acidemia	Fall in arterial pH
Alkalemia	Rise in arterial pH
Acidosis	A process that acidifies body fluids (increased H^+ concentration) and if unopposed leads to fall in pH. This can be caused by a fall in the serum bicarbonate (HCO_3) concentration and/or an elevation in pCO_2
Alkalosis	A process that alkalinizes body fluids (decreased H^+ concentration) and if unopposed leads to rise in pH. This can be caused by an elevation in the serum HCO_3 concentration and/or a fall in pCO_2
Metabolic disorder	*Primary change in HCO_3 (increased in alkalosis and reduced in acidosis)*
Respiratory disorder	*Primary change in H_2CO_3, i.e., CO_2 (increased in acidosis and reduced in alkalosis)*
Simple acid-base disorder	The presence of a single primary disorder with the appropriate respiratory or renal compensation
Mixed acid-base disorder	It means simultaneous presence of more than one acid-base disorder. Mixed acid-base disorders can be suspected from the patient's history, from a lesser- or greater-than-expected compensatory respiratory or renal response, and from analysis of the serum electrolytes and anion gap. *Always correlate with history*
Primary disorders not only change acid-base equilibrium directly, but also set in motion secondary compensatory changes in the other member of the pCO_2-HCO_3^- pair. It requires normal lungs and kidneys. Remember that compensation never returns the pH fully back to normal	

TABLE 4: Primary changes in acid-base disorder and compensatory response.

Disorder	*Primary disturbance*	*Compensatory Response*	*Mechanism involved in compensatory response*
Metabolic acidosis	Decrease in HCO_3	Decrease in pCO_2	Hyperventilation
Metabolic alkalosis	Increase in HCO_3	Increase in pCO_2	Hypoventilation
Respiratory acidosis	Increase in pCO_2	Increase in HCO_3	Increased H^+ secretion
Respiratory alkalosis	Decrease in pCO_2	Decrease in HCO_3	Decreased H^+ secretion

TABLE 5: Important causes of various acid-base disorders.

(AG) Metabolic acidosis	*(NAG) Metabolic acidosis*	*Respiratory acidosis*	*Metabolic alkalosis*	*Respiratory alkalosis*
MUDPILERS:	***HARDUPS:***	CNS depression (drugs/CVA)	***CLEVER PD:***	***CHAMPS:***
M = Methanol	H = Hyperalimentation	Nerve damage beyond CNS	C = Contraction	C = CNS disease meningitis, encephalitis, hemorrhage
U = Uremia	A = Acetazolamide	(High spinal cord injury phrenic palsy)	L = Licorice*	H = Hypoxia, hepatic failure and heart failure
D = DKA/Alcoholic ketosis	R = Renal tubular acidosis	Guillain–Barré syndrome	E = Endo: Conn's/ Cushing's/Bartter's*	A = Anxiety
P = Paraldehyde	D = Diarrhea	Airway obstruction	V = Vomiting, NG aspirate	M = Mech ventilators
I = Isoniazid	U = Ureteropelvic shunt	Pulmonary edema	E = Excess alkali*, electrolyte disturbance—hypokalemia*, hypomagnesemia	P = Progesterone, pneumonia, pulmonary embolism, and pregnancy
L = Lactic acidosis	P = Posthypocapnia	Hemothorax/pneumothorax	R =Refeeding alkalosis*	S = Salicylates/sepsis
E = Ethanol/Ethylene glycol	S = Spironolactone	Myopathy, electrolyte disturbances—hypokalemia and hypophosphatemia	P = Posthypercapnia	
R = Rhabdomyolysis/ Renal failure		Neuromuscular disorders—myasthenia gravis, Lambert–Eaton syndrome, aminoglycosides, and colistin	D = Diuretics	
S = Salicylates		Chest wall deformity—kyphoscoliosis, flail chest	* = Associated with high urine Cl levels	

(AG: anion gap; NAG: nonanion gap; DKA: diabetic ketoacidosis; CNS: central nervous system; CVA: cerebrovascular accident; NG: nasogastric)

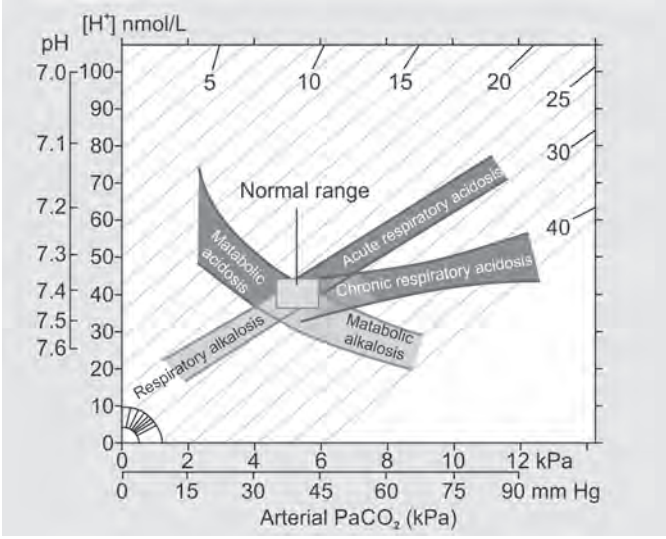


FIG. 3: Nomogram for assessment of acid-base disorder.

BOX 1: The Henderson–Hasselbalch equation.

It shows that the pH is determined by the ratio of the serum bicarbonate (HCO_3) concentration and the pCO_2.

pH = pK + log $(HCO_3)/(H_2CO_3)$
= Kidney/Lung
= [Metabolic/Respiratory]

- **$H^+ = 24 \times pCO_2/HCO_3$ (validity check)** ***Formula 1***

pH and pCO_2 Relationship in Respiratory Disorders:

- $\frac{\Delta H^+}{\Delta PaCO_2}$ **<0.3 – Chronic** ***Formula 2***

>0.8— acute and 0.3–0.8—acute on chronic

- *Law of mass action*: Dissociation equilibrium of all incompletely dissociated substance must be satisfied at all times. According to this approach, HCO_3^- is a dependent variable (**Fig. 4**).

Three mathematically *independent* determinant of blood pH is:

- Strong ion difference (SID)
  SID = $([Na^-] + [K^-] + [Ca^{2+}] + [Mg^{+2}]) - ([Cl^-]) = [HCO_3^-] + [A^-]$
  $SID_a = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-])$
  $SID_e = [HCO_3^-] + [A^-]$
  Total charges contributed by all nonbicarbonate buffers, primarily albumin, phosphate, and, in whole blood, hemoglobin. *Normal SID is 40–42.*
- Total weak acid buffers (A TOT) = Total A^- and its weak acid $([A^-] + [HA])$
- PCO_2
  SIG = SIDa – SIDe. It Is due to unmeasured anions. It represents SBE.
  - *Metabolic acidosis*: Decrease in SID by addition of strong anions
  - *Metabolic alkalosis*: Increase in SID by additions of strong cations (with weak anions)

Stewart approach is much more cumbersome and may be more prone to error, given its dependence upon multiple measurements of different variables. When measurements obtained from automated blood chemistry devices are used to calculate the *strong ion gap (SIG),* the results can also vary substantially depending upon which device is used. Therefore, the traditional approach in the analysis of all acid-base disturbances is preferred. Moreover, if serum albumin concentration is considered in the traditional analysis of acid-base disturbances, Stewart approach is nonsuperior over the traditional Schwartz-Bartter approach to acid-base disturbances.

BOX 2: Analysis of compensation in acid-base disorders.

- **Metabolic compensation of respiratory disorder:**
  - *Respiratory acidosis:* ***Formula 3***

    ΔHCO_3 = change from 24; ΔpCO_2 = change from 40

    Acute: $\Delta HCO_3^- = 1/10\ (\Delta pCO_2)$ Chronic: $\Delta HCO_3^- = 4/10\ (\Delta pCO_2)$

    Add ΔHCO_3 to 24 (normal HCO_3). Match with HCO_3 on ABG. If two match it is simple respiratory disorder. If calculated HCO_3 is more or less than on ABG, there is primary metabolic alkalosis and metabolic acidosis respectively also
  - *Respiratory alkalosis:* ***Formula 4***

    Acute: $\Delta HCO_3^- = 2/10\ (\Delta pCO_2)$ Chronic: $\Delta HCO_3^- = 5/10\ (\Delta pCO_2)$

    Subtract ΔHCO_3 from 24 (normal HCO_3). Match with HCO_3 on ABG. Similar interpretation as above
- **Respiratory compensations for metabolic disorders:**
  - *Metabolic acidosis:* ***Formula 5***

    Expected $pCO_2 = [(1.5\ HCO_3) + 8] \pm 2$. (Match with ABG pCO_2)
  - *Metabolic alkalosis:* ***Formula 6***

    Expected $pCO_2 = [(0.7\ HCO_3) + 21] \pm 2$ (If ABG pCO_2 is more or less than calculated pCO_2, there is primary respiratory acidosis or alkalosis respectively also)

BOX 3: Anion gap concept.

Normal anion gap is 10 ± 2 mmol/L

- Anion gap = $Na^+ - (Cl^- + HCO_3^-)$ ***Formula 7***

The "normal" anion gap in patients with hypoalbuminemia is about 2.5 mEq/L lower for each 1 g/dL decrease in the plasma albumin concentration from normal

- Corrected AG = Calculated AG + 2.5 (albumin normal i.e., 4 – albumin measured) ***Formula 8***

Raised anion gap acidosis:

Anion gap raised in lactic acidosis (e.g., hypoxemia, ischemia, shock, and sepsis), ketoacidosis (diabetes, starvation, and alcohol excess), renal failure (accumulation of sulfate, phosphate, and urate), poisoning (aspirin, methanol, and ethylene glycol), and massive rhabdomyolysis

If the anion gap is raised, *calculate the osmolal gap* in case of compatible situations

- Osmolal gap = Measured osmolality − Calculated osmolality ***Formula 9***
- S Osm = 2(Na) + BUN/2.8 + Glucose/18 ***Formula 10***

Normal osmolal gap <15 mOsm/L Osmolar gap may be increased in methanol poisoning ethanol poisoning hyperlipidemia chronic renal failure and myeloma

Normal anion gap (hyperchloremic) acidosis:

Predominantly due to loss of HCO_3^-

Non anion gap (NAG) acidosis seen in renal tubular acidosis (types 1, 2, and 4), diarrhea (HCO_3^- loss), adrenal insufficiency, ammonium chloride ingestion, urinary diversion (e.g., ureterosigmoidostomy), and drugs (e.g., acetazolamide)

Check urine anion gap (UAG)—To get clue for site of loss; *renal versus gastrointestinal*

- UAG = (Urine Na^+ + Urine K^+) − Urine Cl^- ***Formula 11***

Negative UAG = (Urine Cl^- >> Urine Na^+ + Urine K^+) = suggestive of GI loss of HCO_3

Positive UAG = (Urine Cl^- < Urine Na^+ + Urine K^+) = suggestive of renal tubular acidosis

If metabolic alkalosis—check spot urinary chloride, urine Cl^- > 20 mEq/L or > 20 mEq/L

Assessment of oxygenation:

It is equally or even more important to assess oxygenation while interpreting the ABG. PaO_2 < 45 mm Hg: Severe, 45–59 mm Hg: Moderate, 60–79 mm Hg: Mild

Always check *PAO_2–PaO_2 gradient* (Where PAO_2 is pressure of alveolar oxygen and PaO_2 is pressure of arterial oxygenation)

Equation for the calculation of alveolar PO_2: (PAO_2)

- $PAO_2 = (760-47) \times FiO_2 - (pCO_2/0.8)$ ***Formula 12***

  $= 150—(pCO_2/0.8)$ or room air. Check on room air if possible

Where 760—barometric pressure at sea level, 47—water vapor pressure, 0.8—respiratory quotient

(A–a) O_2 gradient = PAO_2–PaO_2 (normal: 5–25 mm Hg)

BOX 4: Delta ratio.

Delta ratio (used to assess raised AG acidosis and also assess whether mixed acid-base disorder is present):
Delta ratio = Δ AG/Δ HCO_3 (Δ AG = measured anion gap-normal anion gap Δ HCO_3 = normal HCO_3—measured HCO_3)
Consider normal AG = 12 and normal HCO_3 = 24
Delta ratio = Measured anion gap—12/24—measured HCO_3
Delta ratio value and interpretation:
<0.4—normal anion gap metabolic acidosis
0.4–0.8—mixed-normal anion gap + high anion gap metabolic acidosis
0.8–2—pure high anion gap acidosis
>2—Mixed-high anion gap acidosis + metabolic alkalosis

BOX 5: Steps in interpretation of arterial blood gas.

- ***Perform validity check to assess the consistency of the ABG*:**
  $H^+ = 24 \times pCO_2/HCO_3$
  Calculate x H^+ from pH
  Match the two. If both correlate then ABG is valid
- ***Look at pH—< 7.40—acidosis; >7.40—alkalosis***
- ***If pH indicates acidosis, then look at $PaCO_2$ and HCO_3^-***
- ***If $PaCO_2$ is ↑, then it is primary respiratory acidosis*:**
  - To determine whether it is acute or chronic: $\Delta H+/\Delta PaCO_2$ <0.3—chronic >0.8—acute and 0.3–0.8—acute on chronic
  - Calculate compensation by the respective methods:
    - Acute: $[HCO_3^-]$ ↑ by 1 mEq/L for every 10 mm Hg ↑ in $PaCO_2$ above 40
    - Chronic: $[HCO_3^-]$ ↑ by 3.5 mEq/L for every 10 mm Hg ↑ in $PaCO_2$ above 4
- ***If $PaCO_2$ ↓ and HCO_3^- is also ↓→ primary metabolic acidosis*:**
  Calculate expected $PaCO_2$ as follows: $PaCO_2 = [1.5 \times HCO_3 + 8] \pm 2$ metabolic acidosis only
  If $PaCO_2$ < expected $PaCO_2$ → concomitant respiratory alkalosis
  If $PaCO_2$ > expected $PaCO_2$ → concomitant respiratory acidosis
- ***If HCO_3^- is ↓, then AG should be examined. Anion gap = Na^+ - (Cl^- + HCO_3^-) normal anion gap 12*:**
  - If AG is unchanged → then it is hyperchloremic metabolic acidosis
  - If AG is ↑→ then it is wide AG acidosis
  - If the anion gap is raised, calculate the osmolal gap also
    Osmolal gap = Measured osmolality − Calculated osmolality
    S Osm = 2 (Na) + BUN/2.8 + Glucose/18 (normal osmolal gap < 15 mOsm/L)
- ***Check Delta ratio Δ AG/Δ HCO_3^- Delta Ratio = Measured anion gap—12/24—Measured HCO_3***
  Delta ratio Value and interpretation <0.4, normal anion gap metabolic acidosis,
  0.4–0.8 mixed-normal anion gap + high anion gap metabolic acidosis
  0.8–2 pure high anion gap acidosis, >2—mixed-high anion gap acidosis + metabolic alkalosis
- ***If pH indicates alkalosis, then look at HCO_3^- and $PaCO_2$***
- ***If $PaCO_2$ is ↓→ then it is primary respiratory alkalosis*:**
  - Whether it is acute or chronic (with the same formula as above)
  - Calculate compensation by the respective methods:
    Acute: $[HCO_3^-]$ ↓ by 2 mEq/L for every 10 mm Hg ↓ in $PaCO_2$ below 40
    Chronic: $[HCO_3^-]$ ↓ by 5 mEq/L for every 10 mm Hg ↓ in $PaCO_2$ below 40
- ***If $PaCO_2$ ↑ and HCO_3^- also ↑→ then it is primary metabolic alkalosis***
  Calculate the expected $PaCO_2$
  $PaCO_2 = [0.7 \times HCO_3^- + 21] \pm 2$ Or 40 + (0.7 ΔHCO_3) → metabolic alkalosis only $PaCO_2$ < expected $PaCO_2$ → concomitant respiratory alkalosis. $PaCO_2$ > expected $PaCO_2$ → concomitant respiratory acidosis
- ***Check urinary chloride*:**
  - If urinary chloride < 20 → chloride responsive or ECV depletion
  - If urinary chloride > 20 → chloride resistant

Continued

Continued

- ***If pH is normal ABG may be normal or mixed disorder*:**
  - ↑$PaCO_2$ and ↓HCO_3^- → respiratory and metabolic acidosis
  - ↓$PaCO_2$ and ↑HCO_3^- → respiratory and metabolic alkalosis

Calculate % difference ($\Delta HCO_3^-/HCO_3^-$ and $\Delta PaCO_2/PaCO_2$) to see which is dominant disorder

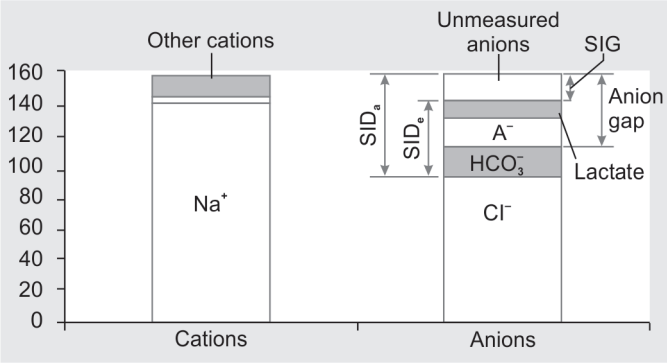


FIG. 4: Strong ion difference (SID) approach for assessment of acid-base disorder.

ARTERIAL BLOOD GAS SAMPLING TECHNIQUE

Before Sampling

The first thing the need (indications) for arterial sampling should be ascertained along with contraindications if any (**Table 6**). Oxygen saturation, oxygen therapy should be noted and discussed with the patient about the procedure and related complications such as bleeding, bruising, arterial thrombosis, infection, and pain. Then obtain consent to proceed. Prepare the heparinized syringe with cap, universal precautions. Look for the suitable artery for sampling by palpating the radial, brachial or femoral artery (**Fig. 5**). Radial artery of the nondominant arm should be preferred for routine sampling.

Sampling from Radial Artery

Allen test is performed to ascertain the adequate collateral circulation from ulnar artery (**Figs. 6A** to **C**). Position the patient's hand and insertion of needle is important for adequate sampling as shown in **Figure 7**. Clean the sampling site with an alcohol swab and obtain at least 3 mL of blood.

After Sampling

Sample site should be pressed for at least 5 minutes until bleeding has stopped. Presence of air bubbles may compromise the results so remove all the bubbles from the samples. Sample should be analyzed immediately else it should be stored in crushed ice (**Fig. 8**).

SUMMARY

Thus, analysis of ABG is an essential tool in management of critically ill patients. Always remember to assess oxygenation problem first. Next follow stepwise approach and correlate to clinical history while interpreting the ABG. ABG is a useful bedside tool in management of intensive care unit (ICU) patients.

TABLE 6: Indication and contraindications of arterial blood sampling.

Indications	• To assess derangement of oxygenation, its severity and cause • Assessment of acid-base disorder to identify primary disorder/disorders and plan its management • To check response to the interventions • Aids in adjustment of ventilator settings • For detection of abnormal hemoglobin (carboxy- and methemoglobin) and its severity
Contraindications	• An abnormal modified Allen test • Local infection or distorted anatomy at the puncture site • Severe peripheral vascular disease of the artery selected for sampling • Active Raynaud's syndrome

Selection of artery: Radial artery (preferred), femoral artery in case of shock if radial artery is not palpable (beware of coagulopathy). Avoid brachial artery sampling due to poor collateral circulation and risk of limb ischemia.

Precautions while taking sample: Avoid air bubbles. (Air contamination: spurious increase in PaO_2). Analyze within 30 min (Blood cells consume O_2, produce CO_2, and lower pH). If delay cool to 5°C immediately. Avoid excessive use of heparin (drop in $pCO_2 > PO_2$. pH usually remains unchanged).

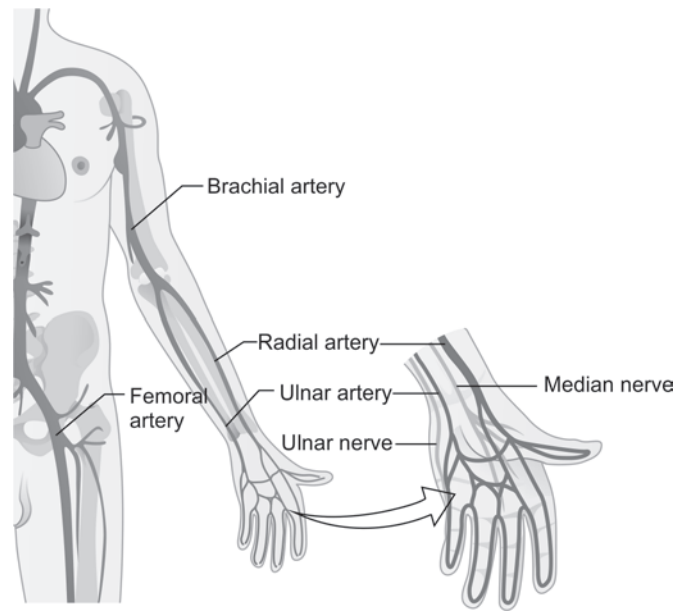
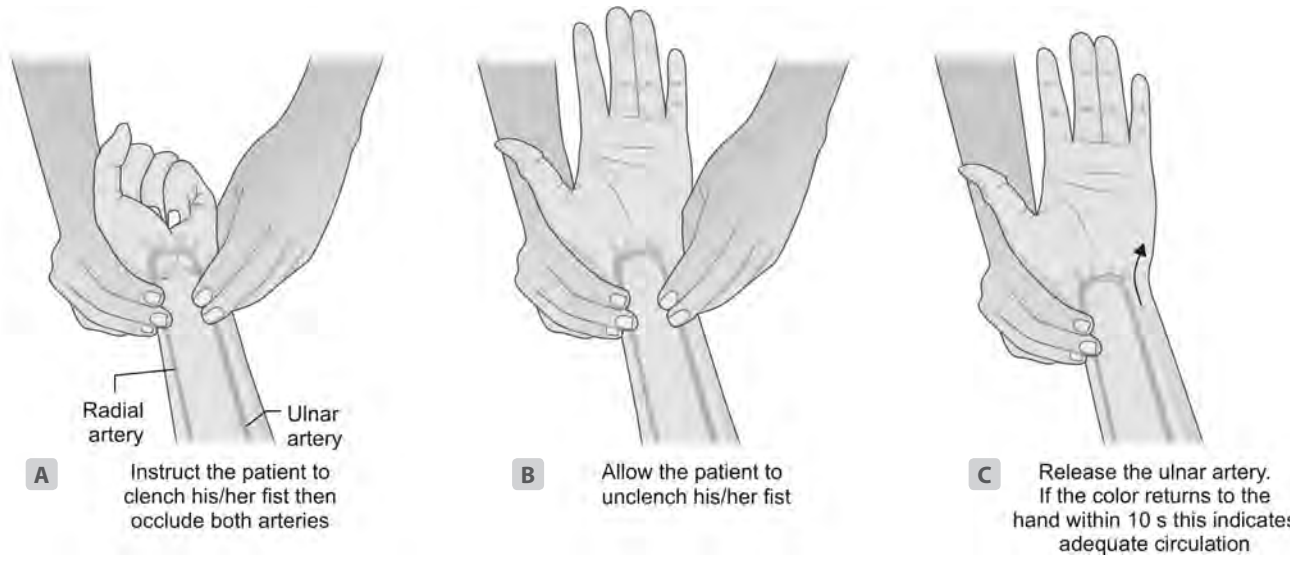


FIG. 5: Various arterial puncture sites.


Radial artery
Ulnar artery
A
Instruct the patient to clench his/her fist then occlude both arteries
B
Allow the patient to unclench his/her fist
C
Release the ulnar artery. If the color returns to the hand within 10 s this indicates adequate circulation

FIGS. 6A TO C: Allen test.

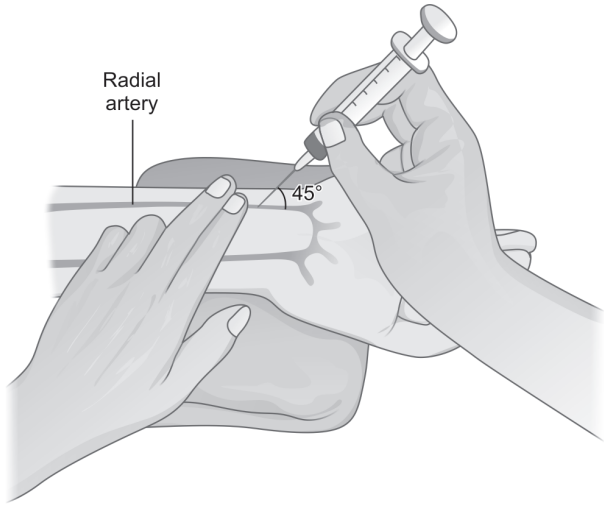


FIG. 7: Wrist position for arterial blood sampling.

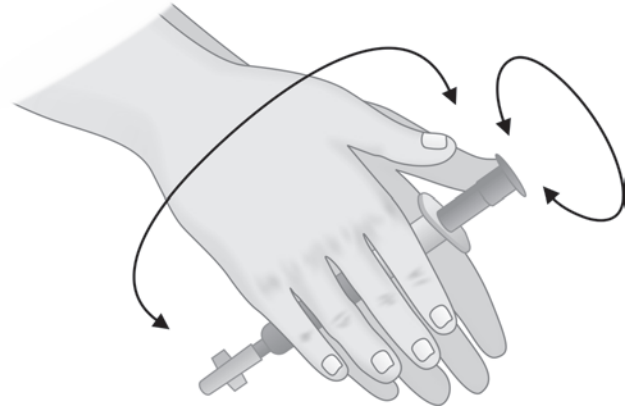


FIG. 8: Correct method of mixing sample.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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46 CHAPTER

Electrolyte Imbalances

Ayşegül Bayır

INTRODUCTION

Electrolyte imbalances are common clinical problems that may occur in emergency departments, which may cause fatal rhythm problems and central nervous system complications and may result in cardiac arrest, if their differential diagnosis and proper treatment are not performed. Therefore, in life-threatening electrolyte disorders, treatment should be initiated before the results of the biochemistry laboratory are obtained. In this section, problems related to four electrolytes (sodium, potassium, calcium, and magnesium) that play an important role in the human body will be explained.

HYPERNATREMIA

It occurs when serum sodium level is measured over 145 mmol/L and a clinical picture related to this. Tonicity shows the activity of solutes that cannot easily penetrate the cell membrane and provides the transcellular distribution of water. It is the most effective anion that provides osmolality of extracellular fluid. Hypernatremia is accompanied by hypertonicity, decreased cell volume, and usually dehydration. If hypernatremia develops within 48 hours, it is called acute hypernatremia and if it develops over 48 hours, it is called chronic hypernatremia.

Pathophysiology

Extracellular and intracellular fluid osmolality is equal to each other. Water passes through the cell membrane comfortably. There is mainly sodium outside the cell and potassium ion inside the cell. Serum sodium concentration, as seen in the equation below, is closely related to the amount of potassium and water in the body.

Plasma osmolality: It is formulated as plasma osmolality: 2 (Na) mEq/L + serum glucose (mg/dL)/18 + BUN (mg/dL)/2.8 and its normal limit is 275–290 mOsm/kg. Plasma sodium and plasma osmolality are kept in balance by water intake and excretion.

$$\text{Na} = \text{total body (Na + K)/total body water}$$

Hypernatremia occurs either due to increased salt consumption, using hypertonic salt solutions, or loss of water from the body without electrolyte. When osmolality increases, arginine vasopressin (AVP) hormone and thirst are increased and balance is achieved. Intracellular fluid is drawn into the intravascular area due to increased osmolality. Dehydration develops in the cells that work as an osmoreceptor or tonicity receptor in the brain. These cells work like a mechanoreceptor and provide AVP release and thirst. This regulator system activates even when a large amount of salt is taken or fluid is lost and keeps serum sodium within normal limits. However, this physiological regulatory system may be insufficient for oral intake in people with impaired-mental status, advanced elderly or care patients, critical care intensive care patients who are hospitalized, children, and infants.

Etiology

Not replacing serious water losses without solutes. These losses can be caused by sweating, burns, losses through the gastrointestinal system (GIS) (vomiting, osmotic diarrhea, and loss of small intestine fluids), urinary losses, central diabetes insipidus (DI), nephrogenic DI, osmotic diuresis, and diseases (adipsic DI) that affect osmoreceptors in hypothalamus or the feeling of thirst. Intracellular water loss, excessive salt intake (or intentional or unintentional increased intake of oral salt), iatrogenic (hypertonic saline infusion, sodium bicarbonate therapy, intrauterine hypertonic saline administration for abortion induction), and some medications (lithium, phenytoin, and corticosteroids) can cause hypernatremia.

Clinical Findings

Advanced age, oral intake and/or impairment of consciousness, debility, physical disability, diuretic therapy, uncontrolled DI, hospitalization, and insufficient parent or nurse care at home are risk factors for hypernatremia.

In physical examination, hemodynamic status should be evaluated first and vital parameters should be monitored. Clinical findings are based on volume deficiency, hypertonicity, and dehydration in the cells in central nervous system. Neurological evaluation should be done very well. In patients with severe hypernatremia, brain hemorrhage due to tear may occur in the cerebral vessels. Hypotension, orthostatic hypotension, tachycardia, oliguria, dryness of the skin and mucous membranes, and turgor-tonus decrease occur due

to hypovolemia. In addition, lethargy, irritability, cloudiness, confusion, widespread weakness, myoclonic jerks, seizures, and coma are neurological signs and symptoms.

Diagnostic Tests and Differential Diagnosis

The diagnosis is made when the serum sodium level is above normal. Urine osmolality is an important test to differentiate the cause of hypernatremia. Plasma osmolality is determined. Serum and urine sodium, potassium, calcium, and magnesium levels are required. Kidney functions and blood glucose level are the other required tests. AVP level is also checked if necessary. The amount of 24-hour urine is important for diagnosis.

If urine sodium level is below 10 mEq/L, it supports volume deficiency. In hypovolemic patients, if urinary sodium is low but urine osmolality is high (usually above 600 mOsm/kg), it indicates extrarenal (GIS or skin) fluid loss. If urine osmolality is low (below 300 mOsm/kg) and urinary sodium is above 10 mEq/L, renal loss is considered. Basal AVP level and urine osmolality response to single dose AVP are examined for central and nephrogenic DI differential diagnosis.

Brain computed tomography (CT) and magnetic resonance imaging (MRI) may be requested to investigate central causes.

Treatment of Hypernatremia

The most important determinants in treatment are the acute or chronic distinction of hypernatremia, the severity of clinical findings, the level of volume deficiency, and the underlying causes. Treatment should be started immediately in patients with acute hypernatremia, severe central nervous system signs, or severe dehydration. In acute hypernatremia, serum sodium should be reduced to 2–3 mEq/L/h and not >12 mEq/L/day. In patients with asymptomatic or slightly symptomatic chronic hypernatremia, serum sodium is reduced to 0.5 mEq/h and 8–10 mEq/24 h. In patients with volume deficiency, volume replacement should first be done with isotonic sodium chloride. During the treatment, the patient is followed up with hourly neurological examination, serum and urine electrolyte measurements. The total amount of water in the body must first be known in order to calculate the amount of fluid to be given during treatment.

Total body water (TBW); is calculated with TBW = weight (kg) × correction factor formula. Correction factor is used as 0.6 for children, 0.5 for women, and 0.6 for men.

The amount of water to be given is determined by the formula below.

$$\text{Water deficit} = \text{Current TBW} \times (\text{Serum Na}/140) - 1$$

Generally, hypotonic (5% dextrose) fluids are used to lower serum sodium. Change in serum Na = (infusate Na – serum Na)/(TBW + 1) formula is used to find the amount of decrease in serum sodium each 1-liter intravenous (IV) fluid will provide. The sodium content of some solutions used in IV fluid treatment is shown in **Table 1**.

In patients with hypervolemic hypernatremia, hemodialysis treatment is planned for patients with loop diuretics and, if necessary, severe loading findings (congestive heart failure and acute pulmonary edema). As soon as life-threatening hypernatremia is treated, the underlying cause should also be treated. Attention should be paid when using glucose-containing fluids in diabetic patients.

Specific Precaution in the Treatment of Hypernatremia

- If hypernatremia has acute or life-threatening symptoms, treatment with hypotonic fluids should be initiated immediately.
- Treatment priority in patients with volume deficiency and with hypotensive, tachycardic, and shock is to support circulation with isotonic fluids.
- Chronic or asymptomatic hypernatremia should not be improved quickly; treatment should be given for the underlying cause.
- In acute hypernatremia, serum sodium should be reduced to 2–3 mEq/L/h and not >12 mEq/L/day.
- In patients with asymptomatic or mildly symptomatic chronic hypernatremia, serum sodium should be reduced by 0.5 mEq/h and no >8–10 mEq/24 h.

HYPONATREMIA

It is the condition that the serum sodium level is below 135 mEq/L. It is the most common electrolyte disorder. Hyponatremic patients are generally patients treated at home or in hospital due to their comorbidity (heart failure and renal failure). Hyponatremia is the most common electrolyte problem that occurred during the hospital follow-up and treatment of any disease. The incidence in hospitalized patients is 15–30%. Hyponatremia is divided into three according to serum sodium level.

1. *Mild hyponatremia*: Serum sodium level is 130–134 mEq/L.
2. *Moderate hyponatremia*: Serum sodium level is 129–125 mEq/L.
3. *Severe hyponatremia*: Serum sodium level is below 125 mEq/L.

It is also classified as hypovolemic, euvolemic, and hypervolemic hyponatremia according to its volume reserve. Once again, it is divided into hypotonic hyponatremia, isotonic hyponatremia, and hypertonic hyponatremia according to osmolality. According to the duration of hyponatremia

TABLE 1: Common fluids for fluid and electrolyte treatment.

Crystalloid fluid	*Osmolality mOsm*	*pH*	*Na^+ mEq/L*	*K^+ mEq/L*	*Cl^- mEq/L*	*Ca^{++} mEq/L*	*Glucose gr/L*	*Lactate mEq/L*
%0.9 NaCl	308	5	154	0	154	0	0	0
%0.45 NaCl	155	5	77	0	77	0	0	0
%5 dextrose	252	4	0	0	0	0	50	0
%0.45 NaCl + %5 dextrose	406	4.5	77	0	77	0	50	0
Lactated ringers	275	6.5	130	4	109	3	0	28

occurrence, it is called acute if it occurs in <48 hours, and chronic hyponatremia if it appears in >48 hours.

Etiology and Pathophysiology

Hyponatremia is caused by the kidney's inability to perform the water extraction function or excessive intake of water. Increased osmolality stimulates the thirst center in the hypothalamus. As a result, AVP, that is, antidiuretic hormone (ADH) is secreted from the posterior hypophysis. ADH reduces thirst increasing water reabsorption from collector tubules. Hyponatremia occurs if ADH secretion persists or if it is released inappropriately. Tissue perfusion decreases due to low cardiac output or arterial vasodilation in diseases such as heart failure and cirrhosis. As a result, ADH secretion is increased by stimulating the baroreceptors in the carotid sinus and arcus aorta, the renin-angiotensin system is activated and natriuretic peptides are secreted. Thus, water retention increases. ADH hormone, which is secreted in high amounts in inappropriate ADH syndrome, causes water retention and hyponatremia.

Clinical Findings

A decrease in serum osmolality leads to osmotic gradient with brain cells and causes water entry into brain cells. Accordingly, clinical signs and symptoms related to brain edema and central nervous system appear. Central nervous system findings appear suddenly especially in acute hyponatremia cases and come to the forefront. If it remain untreated, the mental state changes, seizures, coma and, death may occur. Treatment of hyponatremic patients presenting with central nervous system symptoms should be performed urgently with hypertonic saline.

Chronic hyponatremia is more common than acute hyponatremia. As serum sodium levels decrease over a longer period of time, brain cells produce idiogenic osmoles as their adaptation mechanism. Thus, the brain suffers less and clinical findings are less severe. Sometimes chronic hyponatremic patients may be asymptomatic. Nausea, vomiting, weakness, anorexia, imbalance, dizziness, confusion, forgetfulness, lethargy, and muscle cramps are other findings that may be seen in hyponatremia.

Diagnostic Tests and Differential Diagnosis

Anamnesis and physical examination are important guiding tools for determining the underlying cause. During the physical examination, the findings of hypovolemia are investigated. Hypotension, tachycardia, dryness of mucous membranes, and decreased turgor are evaluated.

Urinary sodium, serum, and urine osmolality together with serum sodium level are important tests for diagnosis. Urine osmolality is <100 mOsm in primary polydips. Urinary osmolality above 100 mOsm shows high ADH level. Serum osmolality is important for the differential diagnosis of real and pseudohyponatremia. Due to hyperlipidemia or hyperproteinemia (such as myeloma) in pseudohyponatremia, the protein or lipid ratio of plasma fluid drops from 97 to 80%. For this reason, serum sodium level is measured high. In this state, the patient's osmolality is normal.

Serum glucose, mannitol, glycine (used in some gynecological and urological processes), sucrose, and maltose levels are high in hypertonic hyponatremia. Renal functions, other serum electrolytes, serum lipid levels, and proteins are also requested for differential diagnosis of hyponatremia. As a further examination, thyroid hormones and suprarenal hormones may be requested. If urine sodium is above 20–40 mEq/L, inappropriate ADH release syndrome is considered. Urine sodium is below 25 mEq/L in hypovolemic hyponatremia. Serum uric acid level is found low in inappropriate ADH syndrome. Brain CT and chest radiography may be requested to investigate the underlying cause of inappropriate ADH syndrome.

Treatment of Hyponatremia

Immediately 100 mL 3% (513 mEq sodium) NaCl is administrated IV in 10 minutes in patients with acute severe central nervous system findings as there is high risk of herniation. If the clinical findings have not changed, infuse 2 more 100 mL. 3% NaCl intravenously. A total of three doses can be applied. Since the risk of herniation is low in moderate or mild symptomatic patients, 3% NaCl is infused at a rate of 0.5–2 mL/kg/h. Patients with chronic hyponatremia are at risk of osmotic demyelination syndrome (ODS), which can sometimes be irreversible. Patients who are in high-risk group especially for ODS are patients accompanied by alcoholism, chronic hepatic disease, cirrhosis, hypokalemia, and malnutrition.

In patients with low ODS risk, a maximum of 10–12 mEq/L increase should be achieved in 24 hours. In patients with a high risk of ODS, a maximum of 4–6 mEq/L improvement is achieved in 24 hours.

If chronic hyponatremia is severe, i.e., serum sodium is below 125 mEq/L or symptomatic (lethargy, confusion, and seizure), 3% NaCl is recommended for treatment as in acute hyponatremia. Initially, 3% NaCl is given to these patients to raise the basal sodium level to 4–6 mEq. If the urine/serum electrolyte ratio is below 0.5, water is restricted or vasopressin antagonists are given. If this ratio is above 1, salt tablets are added to the diet and loop diuretics are also given.

Serum sodium level should be closely monitored during treatment. To find the amount of fluid required to close the sodium deficit, and how much the liquid given in the treatment raises serum sodium: Na deficit = TBW × (desired Na – actual Na) can be used.

Each 1 mL/kg of 3% NaCl administered increases serum sodium by approximately 1 mEq/L. It is this calculation rather than others recommended to be followed by international guides.

Specific Precaution in Hyponatremia Treatment

- If patients with acute hyponatremia and severe central nervous system findings and herniation risk, their serum sodium level should be improved rapidly by giving 3% 100 mL NaCl IV three times.
- In moderate or mild symptomatic patients, serum sodium is corrected by infusing 3% NaCl at 0.5–2 mL/kg/h.
- The underlying cause should be treated in patients with chronic hyponatremia. Serum sodium should be corrected slowly due to the risk of ODS.
- In patients with hypotonic hyponatremia, sodium should be corrected up to 10 mEq in 24 hours and 18 mEq in 48 hours.

HYPERKALEMIA

Potassium is the major intracellular cation, predominantly in the cell. 98% of the potassium in the body is contained in the cell. While serum potassium level is 3.5–5 mEq/L, it is found in the cell at 140 mEq/L level. Na-K-ATPase pump provides sodium and potassium passage through the cell membrane. Potassium regulates excitability in all muscles including myocardium and nerves. Changes in serum potassium levels above or below normal levels can cause fatal rhythm problems, cardiac arrest, paralysis of the muscles, and respiratory arrest. Serum potassium level is determined by exogenous potassium intake, absorption, potassium exchange between extracellular fluid and cells, and the balance between and potassium excretion through urine.

Hyperkalemia is that serum potassium level is above 5 mEq/L. If serum potassium level is between 5 and 6 mEq/L, it is considered as mild, if it is between 6.1 and 7 mEq/L, moderate, and if it is above 7 mEq/L, it is considered as severe hyperkalemia.

Etiopathology of Hyperkalemia

Hyperkalemia occurs when potassium intake (diet containing high potassium low sodium) increases, supportive tablets containing potassium, IV fluids containing high potassium, or nutritional solutions are taken, and in cases such as saved (2–3-week-old) bank blood transfusion, cardioplegic solutions, metabolic acidosis, hypoaldosteronism, pseudohypoaldosteronism rhabdomyolysis, electrical trauma, hemolysis, hyperkalemic periodic paralysis, and decreased potassium excretion; kidney failure (GFR—if the glomerular filtration rate falls below 15–20 mL/kg, even if a high amount of potassium is not taken, potassium level may increase), renal tubular acidosis, drugs (potassium-sparing diuretics, ACE inhibitors, NSAI, penicillin G potassium, heparin, beta-blockers antifungals, and succinylcholine), and pseudohyperkalemia.

Clinical Symptoms Findings

Central nervous system and neuromuscular system findings are seen together. Muscle weakness, depression, muscle cramps, ascending paralysis in muscles, respiratory arrest, cardiac rhythm problems (extrasystoles, bradycardia, AV block, and ventricular tachycardia), and cardiac arrest can be seen. Changes in electrocardiography (ECG) support hyperkalemia.

Diagnostic Tests

Kidney functions (urea and creatinine), other electrolytes, pH, bicarbonate level (blood gases), whole blood test, urine potassium, and creatinine are the tests that can be requested. ECG should be drawn to all patients to assess cardiac exposure. ECG findings are generally correlated with serum potassium levels. However, the potassium level is not required to increase too high to see fatal rhythm problems. While serum potassium level in the early period is 5.5–6.5 mEq/L, prominent narrow-bottomed T wave spikes, short QT, and ST segment depression especially in precordial derivations are considered as ECG findings.

If the serum potassium level increases above 6.5 mEq/L (between 6.5 and 8 mEq/L), the P wave disappears, the PR interval is extended, and the QRS complex expands. If the serum potassium level increases above 8 mEq/L, the QRS complex expands completely and branch blocks, ventricular tachycardia, ventricular fibrillation, and asystole are observed.

Treatment of Hyperkalemia

The basis of the treatment is to ensure membrane stabilization especially in cardiac myocytes, to excrete potassium into the cell, to limit potassium intake and increase excretion (**Table 2**). Patients with severe hyperkalemia, potassium levels above 7 mEq/L, patients with cardiac rhythm problems in ECG are monitored by immediately opening the airway and vascular access. IV 10% calcium chloride 10 mL is infused with slow push (at 5–10 min). Thus, the effect of potassium on the myocardial cell membrane is eliminated. If the patient still has ECG findings and clinical findings have not improved, the same dose of calcium chloride can be given again. IV 50 mEq sodium bicarbonate is given in 5–10 minutes. This treatment allows potassium to be excreted into the cell. Insulin + glucose mixture (25 g glucose + 10 units of insulin) is infused in 15–20 min. Also 10–20 mg. Potassium is transferred into the cell by giving nebulized albuterol. Diuretics and potassium-sparing oxalate treatment are other treatment methods that can be applied. Hemodialysis should be done for the treatment of resistant hyperkalemia.

Insulin + glucose, sodium bicarbonate, and albuterol treatments are given to patients with moderate hyperkalemia, and hyperkalemic (6.1–7 mEq/L) but without cardiac findings.

In patients with mild hyperkalemia (5–6 mEq/L), furosemide IV 40–80 mg and potassium-sparing resins can be given in the form of oral or enema in 15–30 g of oxalate 50–100 mL with 20% sorbitol.

TABLE 2: Treatment of hyperkalemia and complications.

Drugs/ treatment	*Mechanism of action*	*Management of treatment*
Calcium	Membrane stabilization	As a cardiac antidote, only if ECG changes/ dysrhythmia and/or blood potassium level >7 mEq/L
Insulin + glucose	Moves potassium to intracellular space	Blood glucose level should be monitored closely
Sodium bicarbonate	Moves potassium to intracellular space	If hyperkalemia is accompanied with acidosis
B2 Agonist	Moves potassium to intracellular space	As a rescue treatment with insulin + glucose
Diuretics	Excretion of potassium by urine	If hyperkalemia is accompanied with hypervolemia
Ion exchange resins	Potassium ion exchange	Effects is seen 4 hours
Dialysis (hemodialysis or hemofiltration)	Remove excess potassium from blood	In renal failure and/or refractory hyperkalemia

Specific Precaution in the Treatment of Hyperkalemia

- Pseudohyperkalemia (excessive tightening of the tourniquet during blood collection, leukocytosis, or thrombocytosis) should be excluded.
- 10 mL of calcium chloride, which provides membrane stabilization immediately, should be given IV to the patients with severe hyperkalemia and rhythm problems in ECG.
- Other methods of lowering potassium are 25 g glucose + 10 units of insulin mixture, sodium bicarbonate, and nebulized albuterol treatments.
- Mild hyperkalemic patients are given loop diuretics and oxalate.
- Hemodialysis treatment should be carried out for resistant hyperkalemia.

HYPOKALEMIA

It is the clinical picture related to the serum potassium level below 3.5 mEq/dL. It is classified as mild hypokalemia if serum potassium level is 3–3.5 mEq/L, and life-threatening hypokalemia if below 2.5 mEq/L. Life-threatening hypokalemia causes fatal rhythm problems and is mortal.

Etiology of Hypokalemia

Redistribution from extracellular fluid into the cell, diarrhea, vomiting, diuretics, primary or secondary hyperaldosteronism, laxative use, renal tubular acidosis, hypomagnesemia, replacement with potassium-free fluids, hypercortisolism, and tube drainage are the main causes of hypokalemia.

Clinical Signs and Findings

Clinical findings occur due to the underlying cause rather than the hypokalemia itself. The symptoms are mainly related to the neuromuscular system and the cardiovascular system. Muscle weakness (usually seen if potassium is below 2.5 mEq/L), rhabdomyolysis, cramps, polyuria, and palpitations are observed. Respiratory failure and death may occur as a result of paralysis in the respiratory muscles. Nausea, vomiting, and anorexia occur as a result of being affected by GIS muscles. Some patients develop concomitant diarrhea, and some patients develop ileus.

Different rhythm problems occur in hypokalemic patients. Sinus bradycardia, paroxysmal atrial tachycardia, sinus bradycardia, premature ventricular or atrial beats, AV block, ventricular tachycardia, and ventricular fibrillation are findings that can be seen in ECG. In addition, ST segment depression, decrease in the amplitude of the T wave, and U wave at the end of the T wave are among other ECG findings.

Diagnostic Tests

Potassium in spot urine is the diagnostic test most commonly used. If urinary potassium is below 20 mEq/L, oral intake deficiency, loss through GIS, or potassium shift from the extracellular fluid into the cell is considered. If urine potassium is above 40 mEq/L, the loss of potassium with urine is considered to be high. Low sodium and high potassium levels in spot urine support the diagnosis of secondary hyperaldosteronism. Osmolality test must be requested. In addition, urine osmolality should be checked. Urine chlorine level and serum bicarbonate level, kidney functions are also among the tests to be requested. ECG should be done in all hypokalemic patients.

Treatment of Hypokalemia

The aim of the treatment is to prevent potassium loss, replacement of lost potassium, and prevention of recurrence of hypokalemia by treating the problem causing hypokalemia. Drugs (laxatives, diuretics, and ACE inhibitors) that cause potassium loss should be discontinued at the start of treatment. If diuretic therapy is required, potassium-sparing diuretics should be preferred.

Each 1 mEq/L decrease in serum potassium indicates an approximate deficiency of 200–400 mEq. Mild-to-moderate hypokalemia (2.5–3.5 mEq/L) is usually minimally symptomatic or asymptomatic. Replacing these patients with oral potassium tablets is sufficient. IV and more aggressive treatments are required in patients with cardiac rhythm problems or severe hypokalemic. Potassium can cause phlebitis during IV infusion. Maximum 20 mEq IV potassium replacement can be performed per hour. Both ECG and serum potassium levels monitoring should be done during replacement. Maximum IV 120 mEq replacement can be done daily.

Hypercalcemia

Calcium is an electrolyte which has an important role in the functioning of many processes such as enzymatic reaction in the cell, contraction in all muscles including the heart muscle, receptor activation, and coagulation. It is used as a cardiac antidote in hyperkalemia and hypermagnesemia, as it antagonizes potassium and magnesium in the cell membrane. Half of the calcium is bound to albumin in the extracellular fluid. The rest is the ionized active form. Calcium balance in the body is provided by parathormone and vitamin D. There is a close relationship between the total amount of calcium in the body and the serum albumin level. Every 1 g/dL increase in serum albumin increases the total calcium in the body by 0.8 mg/dL. In the case of hypoalbuminemia, ionized calcium levels may be normal, but in reality, the total amount of calcium is low. Hypercalcemia occurs when total serum calcium level is above 10.5 mEq/L or ionized calcium level is above 4.8 mg/dL.

Etiology of Hypercalcemia

Hyperparathyroidism (primary, secondary, and tertiary), malignancy (solid tumors or leukemia), thyrotoxicosis, immobilization, drugs (lithium, theophylline, thiazide group diuretics, estrogens, and antiestrogens), hypervitaminosis A, hypervitaminosis D, chronic renal failure milk-alkaline syndrome, pheochromocytoma, adrenal insufficiency, rhabdomyolysis, acute renal failure, familial hypocalciuric hypercalcemia, metaphyseal chondroplasia, and Paget's disease are the causes of hypercalcemia.

Clinical Findings

Symptoms begin to appear when the total calcium level in the body exceeds 12–15 mEq/L. The symptoms are; difficulty swallowing, constipation, peptic ulcer, and symptoms related to pancreatitis GIS. Generally, hypercalcemia has serious negative effects on the neuromuscular system, central nervous

system, and cardiovascular system. Fatigue, muscle weakness, exhaustion, depression, hallucination at higher blood levels, disorientation, loss of tonus, seizures, and coma may be seen. In severe hypercalcemia, signs of dehydration can be seen, as the kidneys' ability to concentrate urine is affected. Myocardial depression, decreased automaticity, refractory period shortening, and arrhythmias occur in the cardiovascular system. The QT interval is shortened, the PR interval and the QRS complex expand. Sodium, potassium, magnesium, and phosphate loss together with liquid and calcium in the urine are also seen.

Diagnostic Tests

First of all, remeasurement should be done to confirm hypercalcemia and corrected calcium level should be calculated to find whether there is an increase in total calcium level. Corrected calcium = serum calcium + 0.8 × (4 - serum albumin).

The degree of hypercalcemia is a key to identifying the underlying cause. Mild or borderline high calcium levels or long-term slightly high calcium levels support primary hyperparathyroidism. If the serum calcium level exceeds 13 mEq/L, the symptoms become evident. One of the main purposes in diagnosis is to determine whether hypercalcemia is caused by a parathyroid hormone (PTH) related problem.

Renal functions, blood levels of other electrolytes, PTH, and vitamin D levels should be requested. Serum phosphate level, serum chlorine level, and calcium levels in urine may be requested.

Treatment of Hypercalcemia

Patients with mild chronic hypercalcemia are asymptomatic or clinical findings are very few. Urgent treatment is not required in these patients (serum calcium level below 12 mEq/L). Drugs that increase the level of calcium (lithium treatment, thiazide group diuretics) and calcium-rich diet are prohibited to these patients. Abundant hydration is provided. Long-term inactivity is prevented.

Patients with moderate hypercalcemia (serum calcium 12–14 mEq/L), if not symptomatic, undergo the same treatment applied for mild hypercalcemia patients. Treatment of patient who are symptomatic, high serum calcium with neurologic symptoms are treated with intravenous saline, aggressive hydration and bisphosphonates.

Intravenous hydration is started immediately in patients with severe hypercalcemia (if corrected serum calcium level is 14 mEq/L or serum ionized calcium level above 10 mEq/L), whose serum calcium level is acutely elevated and with serious central nervous system findings (lethargy, stupor, and coma). Generally, IV isotonic sodium chloride is given at a rate of 200–300 mL/h, with 100–150 mL of urine output per hour. However, more aggressive fluid replacement can be performed in patients without cardiovascular and renal failure. These patients should be targeted to have an isotonic saline infusion at a rate of 500 mL/h and an hourly urine output of 300 mL. Loop diuretics can be given to patients with renal or heart failure together. Salmon calcitonin 4 U/kg IV, bisphosphonates (zoledronic acid 4 mg IV in 15 minutes, pamidronate 60–90 mg in 2 hours) can also be used to lower serum calcium. Bisphosphonates cannot be used in patients with severe renal impairment. Alternatively, denosumab can be given in these patients. In very extreme cases, 10–50 mg/kg ethylenediaminetetraacetic acid (EDTA) can be given as a chelator in 4 hours or PO4 50 mEq in 8 hours. Hemodialysis is the most effective form of treatment for all patients with resistant hypercalcemia, renal, and heart failure. Causal treatment should also be done simultaneously.

HYPOCALCEMIA

A serum calcium level below 8.5 mg/dL or serum ionized calcium level below 4.2 mg/dL is called hypocalcemia.

Etiology of Hypocalcemia

Hypoparathyroidism, pseudohypoparathyroidism, vitamin D metabolism disorder, thyroid surgery, magnesium metabolism disorders, renal failure, tumor lysis syndrome, burns, sepsis, pancreatitis, fluorine poisoning, phosphate infusion, some drugs (anticonvulsants, antifungals, loop diuretics, bisphosphonates, and isoniazid), citrated blood transfusion, and toxic shock syndrome can be considered as the cause.

Symptoms and Clinical Findings

Generally, symptoms begin when the serum ionized calcium level drops below 2.5 mg/dL. The main symptoms and signs include extremity and facial paresthesia, Chvostek and Trousseau sign, muscle cramps, hyperreflexia, stridor, bronchospasm, carpopedal spasm, tetany, personality disorder, memory and concentration difficulties, seizure, cloudiness, extrapyramidal findings, and congestive heart failure.

Electrocardiography findings include prolonged QT interval, QRS and ST changes mimicking ischemia, and ventricular arrhythmias.

Diagnostic Tests in Hypocalcemia

Serum albumin level, kidney functions, serum levels of other electrolytes, serum vitamin D level, PTH level, and serum phosphate level should be requested. All patients should have ECG. High serum alkaline phosphatase level is important for secondary hypoparathyroidism or severe vitamin D deficiency. High amylase level supports the diagnosis of pancreatitis as the underlying cause. Calcium level in urine should be checked. Low urinary calcium level indicates hypoparathyroidism and vitamin D deficiency.

Treatment of Hypocalcemia

Treatment of severe acute symptomatic hypocalcemia is urgent. If the patient has carpopedal spasm, tetany, convulsion, and QG prolongation in ECG or if it is not symptomatic and if the patient's corrected calcium level is below 7.5 mg/dL, IV calcium gluconate is given. The patient is given IV 10–20 mL of 10% calcium gluconate in 100 mL of 5% dextrose or isotonic sodium chloride in 10 minutes. Afterwards, IV infusion starts with 100 mL of 10% calcium gluconate in 1,000 mL of 5% dextrose or isotonic sodium chloride at a rate of 50 mL/h. The cardiac rhythm of the patient must be monitored during IV calcium infusion.

It is preferable to treat orally calcium in patients with moderately acute (corrected calcium level 7.5–8 mg/dL or ionized calcium level 1.9–2.1 mEq/L) or chronic hypocalcemia

patients. These patients are either asymptomatic or have mild symptoms, such as oral paresthesia. These patients are given oral elemental 1,500–2,000 mg calcium citrate or calcium carbonate in two doses daily. Meanwhile, if the patient's vitamin D level is low, treatment is started and hypomagnesemia is treated.

Specific Precaution in the Treatment of Hypercalcemia and Hypocalcemia

- In patients with severe hypercalcemia, IV isotonic sodium chloride is given at a rate of 200–300 mL/h, with 100–150 mL of urine output per hour.
- Loop diuretics are not recommended for patients without renal or heart failure.
- Salmon calcitonin and bisphosphonates can also be used to lower serum calcium.
- Hemodialysis is the most important form of treatment for all patients with resistant hypercalcemia, kidney, and heart failure.
- In severe acute symptomatic hypocalcemia, 10–20 mL of 10% calcium gluconate in 100 mL of 5% dextrose or isotonic sodium chloride is given IV immediately in 10 minutes.
- Patients with moderate acute hypercalcemia are given two doses of oral elemental 1,500–2,000 mg of calcium citrate or calcium carbonate daily.

HYPERMAGNESEMIA

The level of serum magnesia is above 2.2 mEq/L. Hypermagnesemia is not a common problem, if renal failure or high dose magnesium infusion is not performed. Generally, serum magnesium concentration rises slightly and is asymptomatic or minimally symptomatic. Significant clinical symptoms occur when serum magnesium level exceeds 4 mEq/L.

Etiology of Hypermagnesemia

The most common cause is renal failure. In addition, taking high doses of magnesium orally, long-term constipation and the use of enemas containing magnesium are the main reasons.

Clinical Signs and Findings

As a result of hypermagnesemia, symptoms and symptoms related to the neuromuscular system and cardiovascular system occur. Headache, dizziness, lethargy, somnolence, nausea, weakness or loss of deep tendon reflexes, hypotension, and bradycardia are symptoms that can be seen in mild and moderate hypermagnesemia. It can be fatal if the serum magnesium level rises above 10 mEq/L. Flask muscle paralysis, respiratory muscle paralysis, respiratory arrest, cardiac arrhythmia, and cardiac arrest are observed.

Treatment of Hypermagnesemia

Drugs containing magnesium should be discontinued. In severe hypermagnesemia, cardiovascular support may be required until the serum magnesium level is reduced to an optimal level. 5–10 mL 10% calcium chloride is given IV to patients with fatal cardiac rhythm problems. If necessary, the same dose can be repeated. The excretion of magnesium can be increased by giving loop diuretics together with isotonic sodium chloride IV to those with normal renal function. Dialysis therapy can be applied to patients with severe hypermagnesemia and/or those with kidney failure.

HYPOMAGNESEMIA

Serum magnesium level is below 1.3 mEq/L. It is an electrolyte imbalance that can be seen in 12% of hospitalized patients and 60–65% of intensive care patients. Symptomatic hypomagnesemia can often accompany some metabolic problems, such as hypokalemia and hypocalcemia.

Etiology of Hypomagnesemia

The most important reason is increased excretion from kidneys or GIS due to diarrhea. Diseases that impair absorption from GIS or reduced oral magnesium intake also lower serum magnesium levels. Thyroid dysfunction and drug interaction can also lower serum magnesium levels.

Clinical Symptoms and Findings of Hypomagnesemia

Signs and symptoms related to the neuromuscular system and cardiovascular system are at the forefront. Tremor, weakness, apathy, irritability, convulsion, tetany, and coma can be seen. In addition, atrial and ventricular arrhythmias related to the cardiovascular system can be observed.

Among the ECG findings, PR interval and enlargement of the QRS complex and T wave spikes can be seen.

Treatment of Hypomagnesemia

If there are signs of central nervous system (such as seizures) or cardiac findings in severe or symptomatic hypomagnesemia, IV 1–2 g magnesium sulfate is given in 5–60 minutes. If the patient comes with convulsions and there is concomitant hypocalcemia, calcium replacement should also be performed. If there are cardiac arrest and Torsades de pointes, 1–2 g magnesium sulfate should be given IV in 5–20 minutes during resuscitation.

Specific Precaution in the Treatment of Hypermagnesemia and Hypomagnesemia

- 5–10 mL 10% calcium chloride is given IV to patients with hypermagnesemia with fatal rhythm problems.
- Patients with severe hypermagnesemia undergo dialysis therapy.
- In severe or symptomatic hypomagnesaemia, 1–2 g magnesium sulfate should be given IV in 5–20 minutes in case of convulsions and cardiac arrest.

SUMMARY

Electrolytes play an important role in maintaining the homeostatic environment within the body. They help to regulate neurological and cardiac function, fluid balance, oxygen delivery, acid-base balance, and much more. Electrolyte abnormalities can develop due to increased intake or decreased removal of an electrolyte. The most common cause of electrolyte disturbances is kidney failure. Most

common electrolyte disorders involve sodium, potassium, and calcium. Others such as magnesium and phosphorus although important are relatively less common. Electrolytes basically help in maintaining voltages across cell membranes and also help in carrying nerve impulses to heart, nerves, and muscles. It is the function of kidneys to maintain the electrolyte concentration in blood constant. During illnesses such as diarrhea and vomiting, kidneys try to maintain electrolytes. Electrolyte imbalance is one of the common presentations in emergency department and emergency physician should have sound knowledge to manage.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Sepsis

Ravi Jain, Yash Javeri

INTRODUCTION

The terminology of sepsis evolved from ancient Greek language, from the term "*sepo*" that literally means "*I rot*". Documentation related to this can be traced to ancient Greek texts dating back to 400 BC. Hippocrates, a physician and philosopher, viewed sepsis as dangerous biological decay that could potentially occur in the body. With evolving knowledge of modern medicine and understanding of sepsis, definition of sepsis has also evolved.

DEFINITION

First practical definition of sepsis came in 1992, when consensus conference considered basic pathophysiological facts and defined sepsis as "the systemic response to infection," as presented in this particular definition, it was clear that majority of harm is caused by body's own response and not the inciting event itself.

The definition further evolved and presently sepsis-3 in 2016, defines sepsis as a "*life-threatening organ dysfunction caused by dysregulated host response to infection.*" Whereas septic shock is recognized as, "*A subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.*"

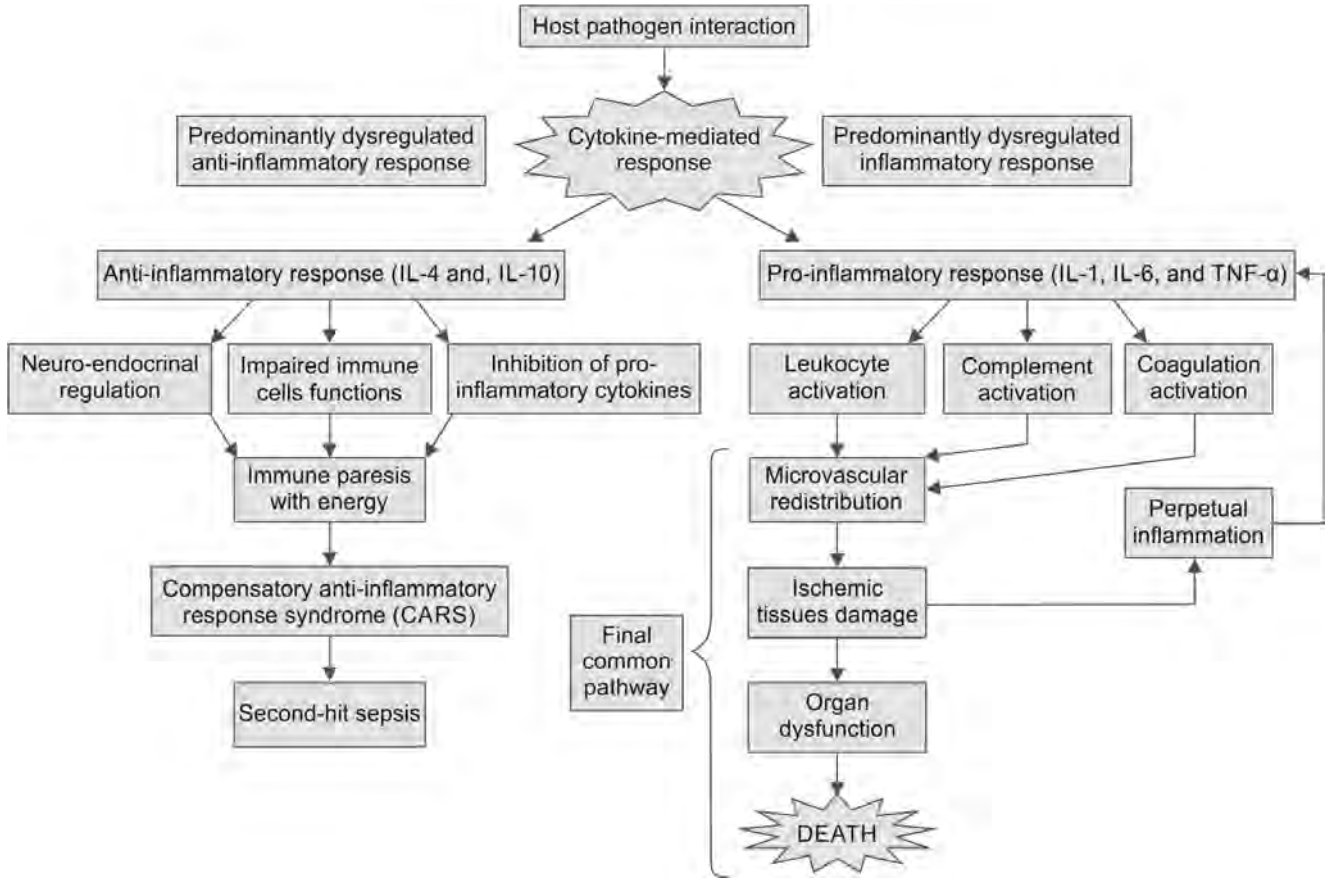
In present definition of sepsis, authors emphasized that previous distinction of sepsis, severe sepsis, and septic shock are no longer relevant. An infection without organ dysfunction or hypotension or evidence of hypoperfusion does not warrant similar aggressive response, and can simply be categorized as having an infection only and not "sepsis". Whereas previous "severe sepsis" is now termed as "sepsis". For standardization of organ dysfunction purpose, task force promotes use of quick sequential organ failure assessment (qSOFA) score in out of ICU settings and sequential organ failure assessment (SOFA) score for intensive care unit (ICU) settings. Further details of scoring system and comparison are provided ahead in chapter. By these definitions, it is clear that only infection is not the actual problem. But it is just a starting process and rest damaging work is done by the overwhelming response to infection by body's defense mechanism. Practically sepsis can be initiated from variety of organ system infections and by variety of organisms. Effective early treatment and control hold the key for successful management of sepsis and various aspects of general emergency room interventions have been proven to be very crucial for ultimate outcome.

EPIDEMIOLOGY

Sepsis is one of the leading top five causes of mortality globally, and is the most common cause of mortality in hospitals. Majority of sepsis cases come from community and about one-fifth of cases got readmitted in 30 days of discharge after sepsis. Cost of hospital stay with sepsis is almost double than any other illness. It is one of the leading cause of hospital readmissions and the costliest disease by cost burden and Disability-adjusted Life Year (DALY*) on society. This makes early identification of sepsis syndromes very important for reducing the disease mortality and morbidity burden and that in term reflect in DALYs.

PATHOPHYSIOLOGY

Sepsis pathogenesis is characterized by an inflammatory cascade. The cascade has humoral, cellular, complement, and cytokine components. **Flowchart 1** is a simple depiction of a complex host and pathogen interaction model that if remains unchecked, and dysregulated, ultimately leads to final common pathway of cell injury and death. The endothelial cell is the focal point of interactions between the inflammatory events and disordered hemostasis. Vascular bed-specific factors and endothelial cell injury can shift the balance between antithrombotic or prothrombotic state. The mediators ultimately lead to microvascular plugging and vasoconstriction. The resultant hypoperfusion/ischemia leads to acute organ dysfunction. Uninterrupted, a vicious cycle ensues that can end in death. Disease course is a result of several innate, immunological, and external factors. Disease progression in sepsis is highly heterogeneous and unpredictable. Sepsis is a dynamic disease with progress to sepsis or a septic shock. Organ failure is linked to mortality in sepsis.



FLOWCHART 1: Pathogenesis of sepsis—inflammatory cascade.

Infection Site and Microbiologic Considerations

Site of infection and type of microorganism are equally important factors for pathophysiology of sepsis. Pulmonary infections are the most common type of infection, followed by the abdomen and urinary tract infections. Site determination is not done in approximately 20–30% cases, and even when the site is strongly suspected a similar proportion has a sterile culture or microbiological isolates that are questionable. Occult sites such as pleural, peritoneal, and paranasal-sinus infections can easily be missed, even with the use of appropriate imaging. In fact, no imaging study can definitively rule out infection.

DIFFERENTIALS

There can be many other noninfectious conditions that can present with vasodilatory of distributive shock, some of them have been enlisted here, they have been discussed in different chapter elsewhere, and hence a detailed description is out of the scope of this text.

- Drug and transfusion-related reactions
- Anaphylactic shock
- Neurogenic shock
- Adrenal/thyroid insufficiency
- Toxicity (e.g., drugs)
- As a component of multiorgan dysfunction syndrome

SCREENING AND DIAGNOSIS OF SEPSIS

Step-1: Suspicion of Sepsis

Sepsis is a clinical syndrome, and first step toward establishing diagnosis of sepsis is to establish/suspect a source of infection that may be overt or occult. Various system infections present with some common general symptoms and then systemic manifestations of those infections. Most of the times systemic infections have typical case definition type presentation, but real challenge is when infections present with atypical or occult presentation. There may be many reasons for atypical/occult presentations such as uncontrolled diabetes, immune compromised status, etc. Simple screening tool for rule in/out sepsis in emergency department (**Table 1**).

Step-2: Categorization of Sepsis/Septic Shock

Sepsis-3 definition suggests clinical criteria to operationalize and rapidly categorize patients according to new definition. A *qSOFA score* (**Table 2**) of ≥2 points or a worsening **SOFA score** (**Table 3**) of ≥2 points is taken as marker of organ dysfunction and in event of suspected infection qualifies for sepsis. Among these two scores, qSOFA is of utility while triaging patients in emergency room as many data in SOFA score will not be available at first point of contact.

TABLE 1: Screening tool for rule in/out sepsis in emergency department.

This is a simplified tool that can be used to screen patients for sepsis in the ED or in critical care unit		
• Obtain proper history for any potential source of infection	Lung infections, kidney infections such as urinary tract infection, infection lingering in the abdomen, meningitis and endocarditis, skin and soft tissue infection, wound infection, catheter-related infections, and blood stream infections	YES/ NO
• Search for signs and symptoms that would indicate	Fever > 38.3°C or temperature < 36°C, altered mental status with a GCS < 15, Heart rate > 90 bpm (tachycardia), respiratory rate > 20 bpm (tachypnea) , leukocytosis or leukopenia (WBC count > 12,000 µ/L or <4,000 µ/L, respectively)	YES/ NO
• *If both the above are yes, suspicion of infection is present* • *Laboratory investigations that should be ordered are complete blood count with differential, blood lactate and cultures, and basic metabolic panel. Ultrasound abdomen, CT scan, chest X-ray, amylase, lipase, ABG, and procalcitonin should be obtained according to the signs and symptoms and according to physician discretion*		
• Whether organ dysfunction criteria present?	If suspicion of infection and organ dysfunction are present, the patient's condition is labeled as septic shock and should be entered into the protocol	YES/ NO

(ABG: arterial blood gas; CT: computed tomography; ED: emergency department; GCS: Glasgow Coma Scale)

TABLE 2: qSOFA score.

H	*H*ypotension: SBP ≤ 100 mm Hg
A	*A*ltered mental status (any GCS < 15)
T	*T*achypnea: Respiratory rate ≥ 22/min

Step-3: Approach to Diagnose Source and Establish Basic Physiology Status

Routine complete blood count, other organ functions testing should be done to find a baseline organ function or to establish a recent organ dysfunction. Early appropriate cultures and microbiological examinations should be sent as soon as possible as they are the cornerstone in sepsis management and result may alter even after first dose of antimicrobial therapy. These microbiological examinations help in tailor-made antimicrobial therapy later in the course of hospitalization. Imaging modalities such as ultrasonography, roentgenography, and advance imaging should be done as and when required to establish or rule out any specific systemic infection under question. There is apparently minimal role of biomarkers in sepsis diagnosis and emergency room management with one exception of lower respiratory tract infections. *A recent Cochrane review suggests using procalcitonin in suspected lower respiratory tract infection to establish role of antibiotics and bacterial infection.* Procalcitonin use is proven to reduce antibiotics use in such situation without having any significant harm.

MANAGEMENT

Sepsis management is essentially based on managing all three aspects of sepsis pathophysiology, i.e., (1) infection, (2) host response, (3) hemodynamic instability leading to organ dysfunction. For simple understanding of this concept a management scheme is described in **Flowchart 2** and divided in three subheadings.

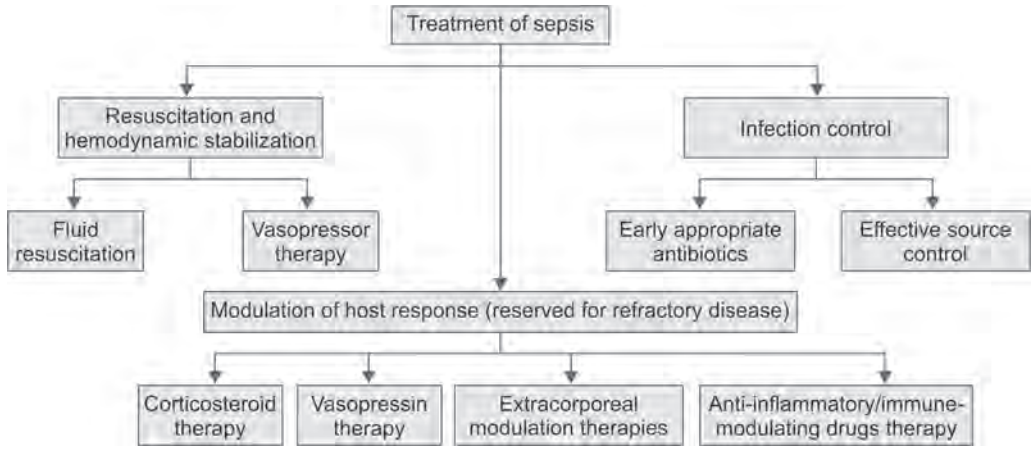
1. Resuscitation and hemodynamic stabilization
2. Infection control
3. Modulation of host response

Sepsis management starts right in the emergency room with triaging. *Surviving sepsis campaign (SSC) suggests 1-hour bundle* (**Table 4**) *for early sepsis management.* Following the care bundle protocol is vital in maintaining uniformity of care at emergency rooms. This care bundle has five key elements to be completed within first hour of "time zero" or "time of presentation."

TABLE 3: SOFA score.

Organ failure	***Variables***	***Score 0***	***Score 1***	***Score 2***	***Score 3***	***Score 4***
Respiratory	PaO_2/FiO_2	>400	<400	<300	<200 MV	<100 MV
Renal	Creatinine mg/dL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
	UOP mL/day	>500 mL			<500 mL	
Cardiovascular All doses in µg/kg/min	Mean arterial pressure (mm Hg)	>70	<70			
	• Dopamine • Dobutamine			<5 Any dose	>5	>15
	Epinephrine				<0.1	>0.1
	Norepinephrine				<0.1	>0.1
Hepatic	Bilirubin (Mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Hematological	Platelets (10^9/L)	>150	<150	<100	<50	<20
CNS	GCS	15	13–14	10–12	6–9	<6

(CNS: central nervous system; GCS: Glasgow coma scale; MV: mechanical ventilation)



FLOWCHART 2: Sepsis management scheme.

TABLE 4: HOUR-1 bundle of surviving sepsis campaign.	
Bundle elements to be completed within first hour	Measure lactate level. Remeasure if initial lactate is >2 mmol/L
	Obtain blood cultures prior to administration of antibiotics best practice statement
	Administer broad-spectrum antibiotics strong recommendation
	Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
	Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg
"Time zero" or "time of presentation"	Time of triage at the first point of contact or, if patient is referred from another care location, represent the time when sepsis is first identified through chart review.

Resuscitation and Hemodynamic Stabilization

After identification of sepsis immediate commencement of resuscitation is the key priority. SSC guidelines suggest 30 mL/kg crystalloids should be given immediately. During resuscitation, additional fluids can be given by frequent assessment of hemodynamic status. Hemodynamic status assessment should be based on clinical examination and physiological variables such as heart rate, blood pressure, arterial oxygen saturation, respiratory rate, capillary refill time, urine output, etc., these can be supplemented by various invasive and noninvasive hemodynamic monitoring tools to improve accuracy. If any amount of uncertainty exists for differentials of shock, then cardiac function assessment can add to hemodynamic assessment.

Dynamic variables, such as inferior vena cava (IVC) collapsibility, echocardiographic evaluation, passive leg raising (PLR) with continuous monitoring for changes in cardiac output (CO) or stroke volume (SV) [assessed by arterial pulse contour analysis (PCA), transpulmonary thermodilution (TPTD) technology, aortic flow velocity, or echocardiography methods], "mini bolus" of intravenous fluid, trend evaluation of central venous pressure (CVP) with fluid resuscitation, pulse pressure, and SV variation (PPV or SVV) evaluation in mechanically ventilated patients with normal heart rhythm, are always better to predict fluid tolerance and responsiveness than *static variables* such as single CVP, SV, CO, systolic blood pressure, and cardiac ejection fraction measurements. During resuscitation a mean arterial pressure (MAP) of 65 mm Hg can be targeted in patients requiring vasopressors support. If hyperlactatemia is present and there is no plausible explanations for it (liver disease, drug-induced like metformin, thiamine deficiency, etc.), then resuscitation can be targeted to normalize lactate levels.

Infection Control

Infection control is the cornerstone therapy for sepsis. *Important contents have been included in HOUR-1 bundle itself, like obtain blood cultures and administer early and appropriate empirical broad-spectrum antibiotics.* There is now good amount of evidence and literature supporting that delaying antimicrobial therapy by each hour leads to substantially increased chances of failure. *Choice of initial antibiotics* depends on the various historical aspects, case definition, imaging-based focus of infection, and information of local antibiogram. This initial therapy needs modification once the source and culprit organism is identified, and more targeted antibiotics should be continued (**Table 5**).

Apart from antibiotics therapy whenever medically and logistically feasible an identified and controllable source of infection should be removed. These include minor imaging-guided drainage procedures to surgeries for source control and removal of suspected vascular or other catheters.

Modulation of Host Response

These therapies include, inclusion if intravenous cortico-steroid therapy (injection hydrocortisone 200 mg/day in continuous infusion or divided doses) for septic shock refractory to fluid resuscitation and vasopressor support, immunoglobulin therapies, extracorporeal blood purification therapies (cytokine or endotoxin adsorption therapy), addition of immune supplementary feeding (Ω3 fatty acid/glutamine supplementation), addition of trace elements (e.g., selenium, etc.), investigational anti-inflammatory agents (e.g., ulinastatin), antioxidant vitamins (vitamin C and thiamin), etc. This list can be exhaustive, however, apart from steroid therapy, evidences in favor of any other are lacking and should always be started under expert supervision. Due to the

TABLE 5: Common infections and empirical treatment regimen.

Condition	*Suspected organisms*	*Empiric regimen*	*Remarks*
Cholera	*V. cholerae*	• Doxycycline 300 mg oral stat • Azithromycin oral in children (20 mg/kg) and pregnant women (1 g)	• Rehydration (oral/IV) is essential • Antibiotics are adjunctive therapy
Enteric fever	*S. typhi, S. paratyphi A*	Inpatients: Ceftriaxone 2 g IV BD for 2 weeks +/-Azithromycin 500 mg BD for 7 days	• Majority of strains are fluoroquinolones resistant • IV therapy can be changed to oral cefixime when patient is afebrile to finish total duration of 14 days
Biliary tract infections (cholangitis, cholecystitis)	Enterobacteriaceae *(E. coli, Klebsiella* species)	• Ceftriaxone 2 g IV OD or • Piperacillin-tazobactam 4.5 g IV 8 hourly or • Cefoperazone-sulbactam 3 g IV 12 hourly • For 7–10 days	• Surgical or endoscopic intervention to be considered if there is biliary obstruction • High prevalence of ESBL producing • *E. coli*, *Klebsiella* species strains. De-escalate therapy once antibiotic susceptibility is known
Spontaneous bacterial peritonitis	Enterobacteriaceae (*E. coli, Klebsiella* species*)*	• Cefotaxime 1–2 g IV TDS or • Piperacillin-tazobactam 4.5 g IV 8 hourly or • Cefoperazone-sulbactam 3 g IV 12 h	De-escalate to ertapenem 1 g IV OD for 5–7 days once the patient improves
Secondary peritonitis, Intra-abdominal abscess/GI perforation	Enterobacteriaceae (*E. coli, Klebsiella* species), *Bacteroides* (colonic perforation), Anaerobes	• Piperacillin-tazobactam 4.5 g IV 8 hourly or • Cefoperazone-sulbactam 3 g IV 12 hourly in severe infections • In very sick patients, if required, addition of cover for yeast (fluconazole IV 800 mg loading dose day 1, followed by 400 mg)	• *Source control is important to reduce bacterial load* • If excellent source control for 5–7 days; otherwise 2–3 weeks suggested
Pancreatitis Mild-moderate	Sterile	No antibiotics	
Post-necrotizing pancreatitis: infected pseudocyst; pancreatic abscess	*Enterobacteriaceae, Enterococci, S. aureus, S. epidermidis, anaerobes, Candida* species	• Piperacillin-tazobactam 4.5 g IV 8 hourly empirically or • Cefoperazone-sulbactam 3 g IV 8 hourly in severe infections • In very sick patients, if required, addition of cover for yeast (fluconazole IV 800 mg loading dose day 1, followed by 400 mg 2nd day onward) and for *Enterococcus* (vancomycin/teicoplanin) may be contemplated • For 7–10 days	Duration of treatment is based on source control and clinical improvement
Liver abscess	Polymicobial	Amoxicillin-clavulanate/third-generation cephalosporin + Metronidazole 500 mg IVTID/800 mg oral TID for 2 weeks	Ultrasound-guided drainage indicated in large abscesses, signs of imminent rupture and no response to medical treatment
Acute bacterial meningitis	*S. pneumoniae, H. influenzae, Neisseria meningitidis*	• Ceftriaxone • 2 g IV 12 hourly/cefotaxime • 2 g IV 4–6 hourly • 10–14 days treatment	• Antibiotics should be started as soon as the possibility of bacterial meningitis becomes evident, ideally within 30 minutes. Do not wait for CT scan or LP results • No need to add vancomycin as primary agent, as ceftriaxone-resistant *Pneumococcus* is not common in India • *Listeria* is also rare in India and so ampicillin is also not indicated • Adjust therapy once pathogen and susceptibilities are known

Continued

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Condition	Suspected organisms	Empiric regimen	Remarks
Meningitis—Postneurosurgery or Penetrating head trauma	*Staphylococcus epidermidis, Staphylococcus aureus, Propionibacterium acnes, Pseudomonas aeruginosa, Acinetobacter baumannii*	• Meropenem 2 g IV 8 hourly and • Vancomycin 15 mg/kg IV 8 hourly for 14 days	May need intraventricular therapy in severe cases
Brain abscess, Subdural empyema	Streptococci, Bacteroides, Enterobacteriaceae, *S. aureus*	• Ceftriaxone 2 g IV 12 hourly or • Cefotaxime 2 g IV 4–6 hourly and • Metronidazole 1 g IV 12 hourly • Duration of treatment to be decided by clinical and radiological response, minimum 2 months required	• Exclude TB, *Nocardia*, *Aspergillus*, and *Mucor* • If abscess <2.5 cm and patient neurologically stable, await response to antibiotics. Otherwise, consider aspiration/surgical drainage and modify antibiotics as per sensitivity of aspirated/drained secretions
Cellulitis	*Streptococcus pyogenes* (common), *S. aureus*	• Amoxicillin-clavulanate 1.2 g IV TDS/625 mg oral TDS or • Ceftriaxone 2 g IV OD +/– Clindamycin 600–900 mg IV TDS	Treat for 5–7 days
Necrotizing fasciitis	*Streptococcus pyogenes, S. aureus*, anaerobes, Enterobacteriaceae (polymicrobial)	• Piperacillin-tazobactam 4.5 g IV 6 hourly or cefoperazone-sulbactam 3 g IV 12 hourly and • Clindamycin 600–900 mg IV 8 hourly • Duration depends on the progress	Early surgical intervention crucial
Community-acquired Pneumonia	*S. pneumoniae*, *H. influenzae*, *Legionella*, *E.coli*, *Klebsiella* species, *S. aureus*	Mild-to-moderate cases: • Amoxycillin—500 mg–1 g TDS oral • If IV indicated, amoxycillin-clavulanate 1.2 g IV TDS or ceftriaxone 2 g IV OD For severe cases: • Amoxycillin-clavulanate 1.2 g IV TDS or Ceftriaxone 2 g IV OD • Duration 5–8 days	• If MRSA is a concern, add linezolid 600 mg IV/oral BD • If atypical pneumonia suspected, doxycycline 100 mg BD or • Azithromycin 500 mg oral/IV OD
Lung abscess, Empyema	*S. pneumoniae*, *E. coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *S. aureus*, anaerobes	• Piperacillin-tazobactam 4.5 g IV 6 hourly or • Cefoperazone-sulbactam 3 g IV 12 hourly	3–4 weeks treatment required
Acute uncomplicated cystitis	*E. coli*, *Staphylococcus saprophyticus* (in sexually active young women), *Klebsiella pneumoniae*	• Nitrofurantoin 100 mg BD for 7 days or • Cotrimoxazole 960 mg BD for 3 *Legionella* 5 days or • Ciprofloxacin 500 mg BD for 3 *Legionella* 5 days	Get urine cultures before antibiotics and modify therapy based on sensitivities
Acute uncomplicated pyelonephritis	*E.coli*, *Staphylococcus saprophyticus* (in sexually active young women), *Klebsiella pneumoniae, Proteus mirabilis*	• Amikacin 1 g OD IM/IV or • Gentamicin 7 mg/kg/day OD (Monitor renal function closely and rationalize according to culture report) • Complete total duration of 14 days	Urine culture and susceptibilities need to be collected before starting antimicrobial treatment to guide treatment

Continued

Continued

Condition	Suspected organisms	Empiric regimen	Remarks
Septic abortion	Bacteroides, *Prevotella bivius,* Group B, Group A *Streptococcus*, *Enterobacteriaceae*, *C. trachomatis, Clostridium perfringens*	• Ampicillin 500 mg QID + metronidazole 500 mg IV TDS if patient has not taken any prior antibiotic (start antibiotic after sending cultures) • If patient has been partially treated with antibiotics, send blood cultures and start piperacillin-tazobactam or cefoperazone-sulbactam till the sensitivity report is available	
Acute osteomyelitis OR Septic arthritis	• *S. aureus, Streptococcus pyogenes* • *Enterobacteriaceae*	• Ceftriaxone 2 g IV OD Followed by oral therapy by: • Cloxacillin 500 mg q 8 hourly or • Cephalexin 500 mg q 6 hourly	• Treat based on culture of blood/synovial fluid/bone biopsy • Orthopedic consultation is essential for surgical debridement • Duration: 4–6 weeks (From initiation or last major debridement)
For burns wound that is clinically or microbiologically not infected			• *Prophylactic parenteral antibiotics in burns are NOT indicated* • Topical antibiotics to be given after debridement
For burns wound that are clinically or microbiologically infected	*Strep pyogenes, Enterobacter* species, *S. aureus, S. epidermidis*, *Pseudomonas*, fungi (rare)	*Burn wound sepsis*: • Piperacillin-tazobactam or cefoperazone-sulbactam or with or without: Vancomycin/teicoplanin (if there is suspicion for MRSA) • Antifungal therapy: When extensive burns and patient not responding to antibiotics ○ If hemodynamically stable: Fluconazole ○ If hemodynamically unstable: Echinocandin *Burn wound cellulitis*: • Cefazolin or • Clindamycin or • Vancomycin if there is suspicion for MRSA • With and without (for burns involving the lower extremity or feet or burns in patients with diabetes) • Piperacillin-tazobactam or • Cefoperazone-sulbactam	• Antibiotic choices are dependent on the antibiogram of the individual institution • Surgical debridement as necessary • Amphotericin B is toxic to all burn patient as renal system compromised, hence Caspofungin may be used
Febrile neutropenia	*Suspected gram negative infections*	Hemodynamically stable patient: • Start IV ceftazidime Hemodynamically unstable: • Start BL-BLI agent (cefoperazone-sulbactam/piperacillin-tazobactam) OR • Carbapenem (meropenem/imipenem/doripenem) +/– • Glycopeptides antibiotics	• No need to add glycopeptide in the initial regimen, except in specific situations where MRSA infection is suspected • Re-assess after 48 hours for effectiveness of therapy • Modify therapy based on c/s results
The choices of antibiotics are not to be followed strictly as they depend on local epidemiology and antibiogram			

focused nature of this text, detailed discussion of modulation of host response becomes out of the scope for discussion in this text. One can find detailed evidence-based discussion in SSC guidelines for management of sepsis and septic shock.

OTHER SUPPORTIVE THERAPIES

Ventilation

Principles of ventilation initiation remain same as for any other condition in emergency or critical care unit. It is strongly recommended to maintain lung protective ventilation in cases of sepsis-induced acute respiratory distress syndrome (ARDS) using a target tidal volume of 6 mL/kg predicted body weight (PBW) and using an upper limit goal for plateau pressures of 30 cmH_2O over higher plateau pressures. When in ICU and patient diagnosed with ARDS early proning, should also be considered to improve survival chances.

Sedation and Analgesia

After ICU admission and stabilization of initial hemodynamics, suitability for weaning from ventilation should be assessed at regular interval for this daily spontaneous awakening and breathing trials (SAT and SBT) are highly recommended.

Glycemic Control

Critical care experts follow a standardized approach for management of glycemic control and variability with protocols. Usually for this strategy, short-acting insulin infusions are given targeting a blood sugar level of <180 mg%. Intravenous insulin administration, in comparison to subcutaneous injection has significant advantages of reliable response and absorption in cases of septic shock and low perfusion states. This is later converted to usually followed sliding scales and subcutaneous administration after stabilization.

Venous Thromboembolism Prophylaxis

Surviving sepsis campaign guidelines recommend adding pharmacological venous thromboembolism (VTE) prophylaxis [with low molecular weight heparin (LMWH) preferably than unfractionated heparin (UFH)] in absence of contraindication. They further also suggest to add mechanical VTE prophylaxis, if any contraindication to LMWH exists.

Stress Ulcer Prophylaxis

Surviving sepsis campaign guideline recommends, adding stress ulcer prophylaxis for risk of upper gastrointestinal bleeding in sepsis and septic shock with proton pump inhibitor (PPI) drugs preferably. However, nowadays studies proved that any hemodynamically stable patient on enteral feeds has low risk of GI bleeding as feeding has protective role and hence PPIs are not given to these patient subgroups.

Nutrition

Early enteral feeding is encouraged in patients with sepsis and septic shock. Even in hemodynamically unstable patients, with high vasopressor requirements at least trophic/hypocaloric feeding (targeting <70% of target nutrition goal in first 48 h) is recommended. This aggressive enteral feeding approach has several protective effects such as reduced inflammatory response, maintenance of gut integrity, prevention of gut permeability to microbiota, modulation of metabolic responses, and improving insulin resistance. Prepared standard formula feeding is usually sufficient in satisfying needs of almost all the patients. Any specific additives such as microelements, immune supplementary feeding (Ω3 fatty acid/glutamine supplementation), antioxidant vitamins (vitamin C and thiamine) are not supported yet by SSC guidelines and have investigational role only.

DISPOSITION

After gauzing the response to emergency room, therapies decision should be made about the location of care. The patients should be admitted after the goals of care and prognosis is discussed with family and patient. These discussions should always be documented and incorporated in medical records for future references. Goals of care should be communicated and handed over to the critical care team so that it can be met and addressed as early as possible as and no later than 72 hours. To improve family satisfaction, a comprehensive management plan has been outlined in **Flowchart 3** for emergency department management of sepsis.

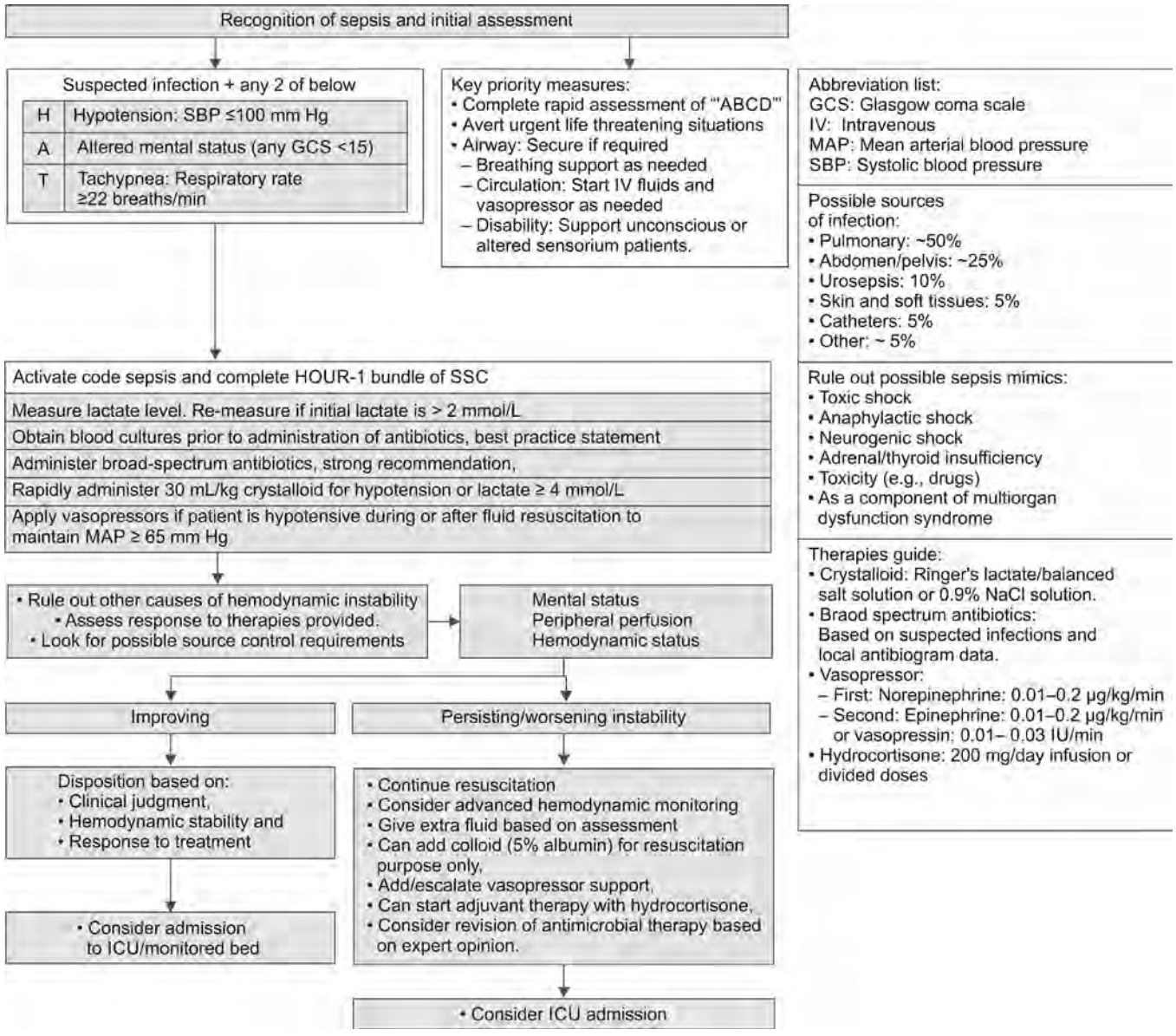
CODE SEPSIS

Sepsis has been identified as a major health problem and one of the leading causes of morbidity and mortality worldwide. There has been limited adherence to the sepsis care bundles. Hence now an emerging concept of *"Code Sepsis"* is adopted in many emergency rooms, to streamline the response and rapid deployment of specialized medical service. Code concept revolves around earliest completion of HOUR-1 bundle and meeting the targets of resuscitation. This exercise improves compliance to SSC care bundle and has been proven to reduce mortality related to sepsis.

SUMMARY

Sepsis is a life-threatening condition, which arises from host response to infection. Early identification and intervention is the key for successful management of sepsis. Emergency room management and promptness makes a lot of difference in overall out comes. Using "code sepsis" to assess and follow-up adherence to HOUR-1 bundle can become vital in comprehensive implementation of quality care, which may ultimately lead to improved outcomes.

Unprecedented scenario of COVID-19 pandemic has led to a very dynamic and fluid condition for safe and effective management of suspected or confirmed COVID-19 patients. Up to date information of progression of epidemic and communications with local governing authorities is the key to make institutional strategies for management. Presented flow and management protocol will need dynamic changes as future progression of epidemic and evidences evolve and emerge.


Recognition of sepsis and initial assessment
Suspected infection + any 2 of below
H Hypotension: SBP ≤100 mm Hg
A Altered mental status (any GCS <15)
T Tachypnea: Respiratory rate ≥22 breaths/min
Key priority measures:
• Complete rapid assessment of "'ABCD"'
• Avert urgent life threatening situations
• Airway: Secure if required
– Breathing support as needed
– Circulation: Start IV fluids and vasopressor as needed
– Disability: Support unconscious or altered sensorium patients.
Abbreviation list:
GCS: Glasgow coma scale
IV: Intravenous
MAP: Mean arterial blood pressure
SBP: Systolic blood pressure
Possible sources of infection:
• Pulmonary: ~50%
• Abdomen/pelvis: ~25%
• Urosepsis: 10%
• Skin and soft tissues: 5%
• Catheters: 5%
• Other: ~ 5%
Activate code sepsis and complete HOUR-1 bundle of SSC
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L
Obtain blood cultures prior to administration of antibiotics, best practice statement
Administer broad-spectrum antibiotics, strong recommendation,
Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg
Rule out possible sepsis mimics:
• Toxic shock
• Anaphylactic shock
• Neurogenic shock
• Adrenal/thyroid insufficiency
• Toxicity (e.g., drugs)
• As a component of multiorgan dysfunction syndrome
• Rule out other causes of hemodynamic instability
• Assess response to therapies provided.
• Look for possible source control requirements
Mental status
Peripheral perfusion
Hemodynamic status
Therapies guide:
• Crystalloid: Ringer's lactate/balanced salt solution or 0.9% NaCl solution.
• Braod spectrum antibiotics: Based on suspected infections and local antibiogram data.
• Vasopressor:
– First: Norepinephrine: 0.01–0.2 µg/kg/min
– Second: Epinephrine: 0.01–0.2 µg/kg/min or vasopressin: 0.01– 0.03 IU/min
• Hydrocortisone: 200 mg/day infusion or divided doses
Improving
Persisting/worsening instability
Disposition based on:
• Clinical judgment,
• Hemodynamic stability and
• Response to treatment
• Continue resuscitation
• Consider advanced hemodynamic monitoring
• Give extra fluid based on assessment
• Can add colloid (5% albumin) for resuscitation purpose only,
• Add/escalate vasopressor support,
• Can start adjuvant therapy with hydrocortisone,
• Consider revision of antimicrobial therapy based on expert opinion.
• Consider admission to ICU/monitored bed
• Consider ICU admission

FLOWCHART 3: Summary of managing sepsis in emergency department.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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ONLINE REFERENCES

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48
CHAPTER

Overview of Shock

Khusrav Bajan, Devendra Richhariya

INTRODUCTION

The word "shock" is derived from French word "choc" coined by French surgeon Henri LeDran. In 1827, an English surgeon, George Guthrie, first used the word "shock" in association with a physiological response to injury. Shock is best defined as a physiologic state of circulatory failure, resulting in insufficient tissue perfusion and oxygenation.

The diagnosis of shock is based on *hemodynamic parameters, clinical findings, and abnormal laboratory values.* Typically, hemodynamic parameters include systolic blood pressure < 90 mm Hg, mean blood pressure < 60 mm Hg; clinical findings include altered mentation, decreased urine output, etc., and abnormal laboratory values include elevated serum lactate and metabolic acidosis. *The skin, the kidneys, and the brain* provide us with three types of ***"windows"*** through which we can visualize the effects of impaired tissue perfusion (**Fig. 1**).

Etiopathophysiology of Shock

Shock state can result from four potential pathophysiological mechanisms (**Figs. 2A** to **D**)

1. *Hypovolemia*: Due to internal or external body fluid losses.
2. *Cardiogenic factors*: Myocardial infarction, myocarditis, etc.
3. *Obstruction*: Pulmonary embolism, cardiac tamponade, and tension pneumothorax
4. *Distributive*: Septic shock and anaphylactic shock

To understand these mechanisms, we need to revise basic physiologic equation of cardiac output. The blood pressure is product of cardiac output and systemic vascular resistance and CO is product of stroke volume and heart rate, thus:

$$BP = CO \times SVR \text{ and } BP = (SV \times HR) \times SVR$$

In this equation, BP represents contractility, SV represents preload, and SVR represents afterload. Hence, the forces which determine cardiac output are preload, contractility, and afterload and pathophysiological mechanisms of shock affect one of these factors, for example, in hypovolemic shock, there is reduced preload; in cardiogenic, shock there is decrease in cardiac contractility; in obstructive shock, there is increase in afterload; and in distributive shock (**Flowchart 1**), there is decrease in SVR and CO is high, although CO may be low due to myocardial depression.

We need to discuss the concept of oxygen delivery to tissues to better understand the concept of shock. Oxygen delivery to the tissues depends on cardiac output, hemoglobin concentration of blood, and the saturation of hemoglobin with oxygen,

$$DO_2 = CO \times CaO_2 = CO \times (1.34 \times Hb \times SaO_2) \times 10$$
$$VO_2 = CO \times 13.4 \times Hb \times (SaO_2 - SvO_2)$$

Where, DO_2—oxygen delivery, CO—cardiac output, CaO_2—oxygen content of blood, VO_2—oxygen consumption, Hb—hemoglobin concentration, SaO_2—% saturation of hemoglobin, SvO_2—% saturation of mixed venous blood.

Oxygen delivery to tissues is reduced in hypovolemic, obstructive, and cardiogenic shock, as a result of anemia, hypoxemia, and low cardiac output (**Table 1**). In hypovolemic shock, reduction in CO is due to decrease in preload. In obstructive shock, venous return to left ventricle is

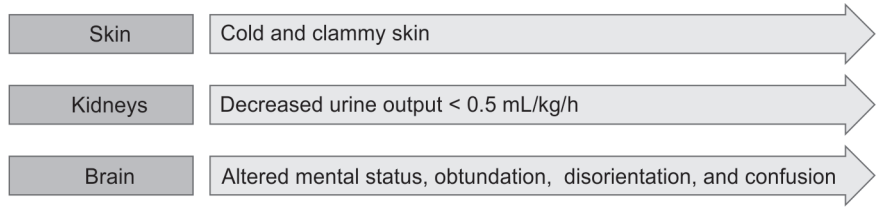
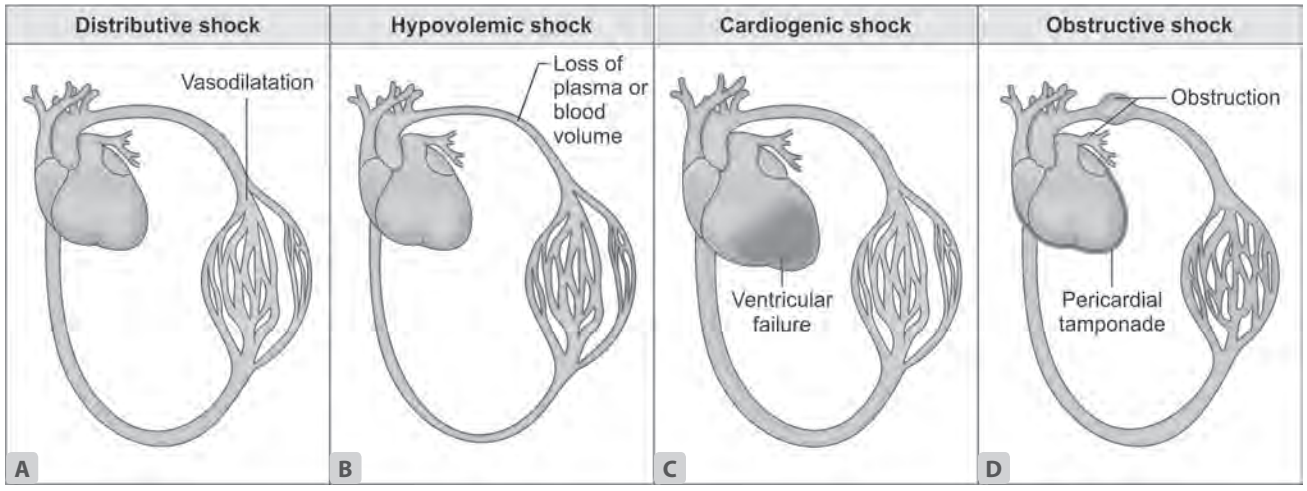
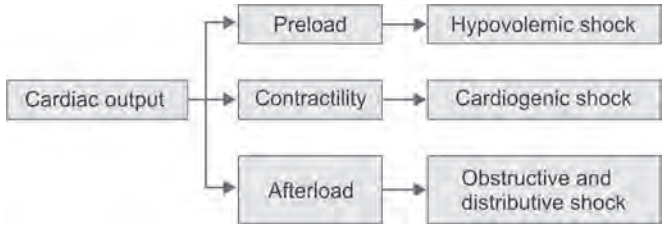


FIG. 1: Signs of hypoperfusion.



FIGS. 2A TO D: Pathophysiologic mechanism of shock.



FLOWCHART 1: Basic pathophysiological mechanisms.

TABLE 1: Pathophysiologic type of shock and their causes.

Types of shock	*Causes*
Hypovolemic	Hemorrhagic, trauma, and dehydration
Cardiogenic	Myocardial infarction, cardiomyopathy, valvular disease, and arrhythmias
Obstructive	Pulmonary embolism, tamponade, and tension pneumothorax
Distributive	Sepsis and anaphylaxis

reduced, whilst, in cardiogenic shock, impaired contractility predominates. In septic shock, there is profound inflammatory response, which leads to vasodilation, increased cardiac output despite impaired myocardial contractility and relative hypovolemia. There are abnormalities in perfusion at microcirculatory level resulting in locally reduced DO_2 despite global supranormal values. In addition, sepsis-induced myocardial dysfunction prevents oxygen utilization at cellular level.

CLINICAL PRESENTATION

Early signs include orthostatic hypotension, mild tachycardia, diaphoresis, and late signs are hypotension, significant tachycardia, tachypnea, and altered mental status. There may be signs of vasoconstriction (narrow pulse pressure and cool extremities) or vasodilation (wide pulse pressure and warm extremities) depending on type of shock. The following **Table 2** is showing clinical features of various type of shock. If Swan–Ganz catheter placement for invasive hemodynamic monitoring is used, then hemodynamic variables of type of shock can be identified (**Table 3**). Initial assessment of patient with features of shock is summarized in **Flowchart 2**.

TABLE 2: Clinical presentation of shock.

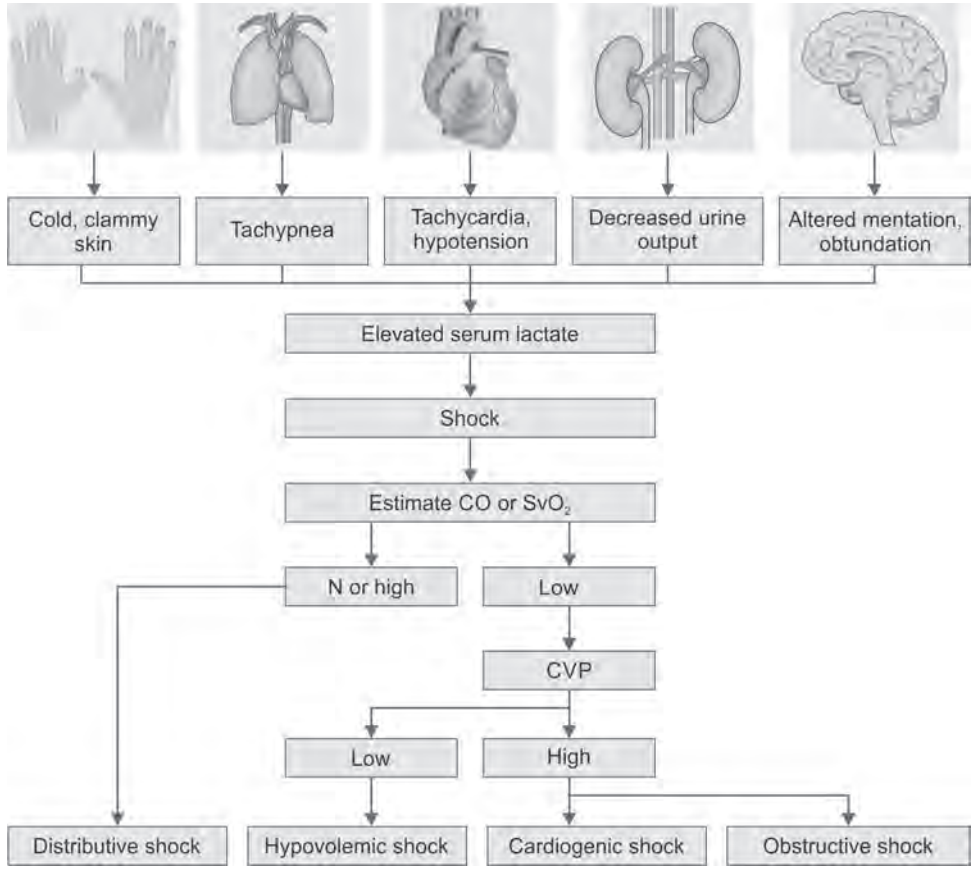
	Cardiogenic	*Hypovolemic*	*Distributive*
Pulse pressure	Decreased	Decreased	Increased
Diastolic pressure	Decreased	Decreased	Markedly decreased
Extremities	Cool	Cool	Warm
Nail bed blood return	Slow	Slow	Rapid
JVP	Raised	Low	Low
Respiratory crepts	+++	–	–
S3, S4 gallop	+++	–	–
Chest X-ray	Cardiomegaly, pulmonary edema	Diminished cardiac size	Normal or with pneumonia
Site of infection	–	–	+++
Other significant systemic manifestations are altered mentation, decreased urine output (<0.5 mL/kg/h).			

TABLE 3: Hemodynamic variables for shock.

Type of shock	*Cardiac index*	*SVR*	*PVR*	*SvO_2*	*Wedge Pressure*
Cardiogenic	↓	↑	N	↓	↑
Hypovolemic	↓	↑	N	↓	↓
Distributive	N - ↑	↓	N	N - ↑	N - ↓
Obstructive	↑	N - ↑	↑	N - ↓	N - ↓

USE OF ULTRASOUND IN EVALUATION AND DIAGNOSIS OF SHOCK

Ultrasound (USG) evaluation of shock has revolutionized the care in emergency department/intensive care unit (ED/ICU).



FLOWCHART 2: Algorithm for initial assessment of shock.

TABLE 4: Different probes available commonly for shock evaluation.

Type of USG probe	*Area of examination*
1–5 MHz; phased array	Heart (echocardiography)
2–5 MHz; curvilinear	Abdomen
6–13 MHz; linear	Blood vessels; thorax

It is a noninvasive, convenient, prompt, repeatable bedside evaluation technique of shock resuscitation. Various protocols (e.g., RUSH, E-FAST, FALLS, etc.,) for quick assessment and to provide point-of-care management of shock has been described.

USG in Diagnosis of Shock

Appropriate probes to be selected for optimum bedside USG resolution of different organs (**Table 4**). Prior clinical history and examination are mandatory and the USG examination is planned accordingly. The common USG findings suggestive of different types of shock are given in (**Table 5**). USG is used for immediate screening and stabilization pending specific appropriate management. The findings of USG will vary with preexisting comorbidities and duration of shock. Hence, individualized interpretation and clinical corroboration are essential.

MANAGEMENT OF SHOCK

Management of shock may be considered in terms of general measures that are applicable to all shock patients and specific measures as per the type of shock.

General Measures

Airway, breathing, circulation and O_2, IV, monitor are simple basic rules.

- *Airway/breathing*: Every shock patient should be given supplemental oxygen through face mask with the aim of improving arterial oxygen saturation and oxygen delivery to tissues. In cases of major hemodynamic instability, intubation and mechanical ventilation should be considered so as to reduce oxygen consumption by respiratory muscles and reduce work of breathing. Intubation at an early stage also facilitates insertion of invasive lines for hemodynamic monitoring and vasoactive drug administration, which is otherwise difficult and may be risky in confused and agitated patient.
- *Circulation*: The primary aim is restoration of adequate tissue perfusion and IV fluid administration is the initial treatment in all types of shock and if fluid therapy is not sufficient then vasopressors and inotropes need to be added. The initial fluid resuscitation is done through two large bores (16 or 18 G) IV cannulae. If needed then insertion of invasive lines should be considered for

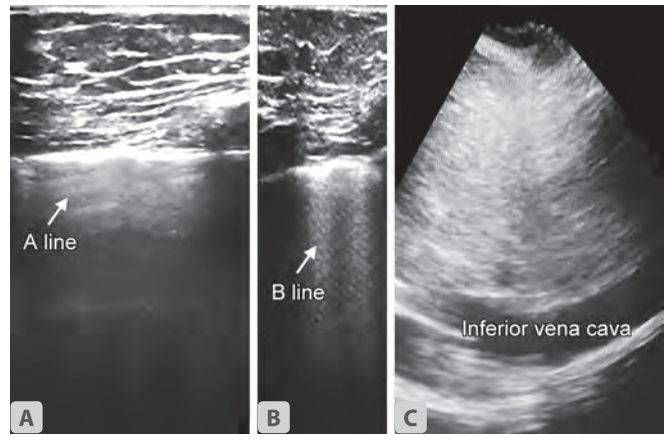
TABLE 5: Common USG findings of different types of shock.

Type of shock	*Common suggestive USG findings*
Hypovolemic Shock (e.g., trauma, aortic dissection, GI loss, etc.)	• Hypercontractile heart with systolic collapse (kissing) of the chambers • Collapsed IVC and IJV • Hyperechoic free fluid in pleural and abdominal cavities • Major abdominal organ/vessel injury
Obstructive shock (e.g., pulmonary embolism, cardiac tamponade, tension pneumothorax, etc.)	• Dilatation of right heart chambers with shifting of intravascular septum with maintained left contractility • Pericardial fluid collection • Dilated IJV and IVC • Absent lung sliding
Cardiogenic shock (e.g., acute MI, stress cardiomyopathy, etc.)	• Hypocontractile dilated heart chambers • Regional wall motion abnormalities • Dilated IJV and IVC • B lines (comet) in lungs
Distributive shock (e.g., septic shock, anaphylactic shock, etc.)	• Unremarkable USG echocardiography may be normal or hyper-/hypocontractile ventricles • IJV/IVC caliber to guide fluid resuscitation • Fluid collection in pleural cavity or abdominal cavity may suggest source of sepsis • Consolidation/abscess/fluid collection as source of sepsis

(GI: gastrointestinal; IVC: inferior vena cava; IJV: internal jugular vein; MI: myocardial infarction)

better hemodynamic monitoring and vasoactive drug administration.

- *Fluid therapy and use of USG in fluid resuscitation*: Optimizing cardiac preload and restoring circulating volume are the basic aspects of correcting tissue hypoxia, increasing cardiac output, and reestablishing perfusion in shock patients. Even patients with cardiogenic shock may benefit from initial fluid resuscitation, since acute edema may result in decrease in effective intravascular volume. The replacement fluid should be chosen so as to replace the type of fluid lost, for example, in hemorrhagic shock, patient clearly requires blood. Crystalloids, colloids, and blood are the usual replacement fluids. The fluid resuscitation should be optimized as per the hemodynamic, urine output, and ongoing losses. Once the type of shock has been known, the USG evaluation may be used to plan fluid resuscitation specific management. Optimized fluid therapy during resuscitation is the best practice. Repeated lung USG, echocardiography and measurement of inferior vena cava/internal jugular vein caliber may optimize resuscitative fluid therapy (**Figs. 3A** to **C**). All such parameters must be measured repeatedly and interpreted in combination with other hemodynamic and clinical features (**Table 6**).



(USG: ultrasound)

FIGS. 3A TO C: USG-guided fluid resuscitation in a shock patient. (A) Lung USG depicting A lines initially. (B and C) Appearance of B line in lung and noncollapsible inferior vena cava after fluid resuscitation.

TABLE 6: USG findings for fluid therapy guidance during resuscitation.

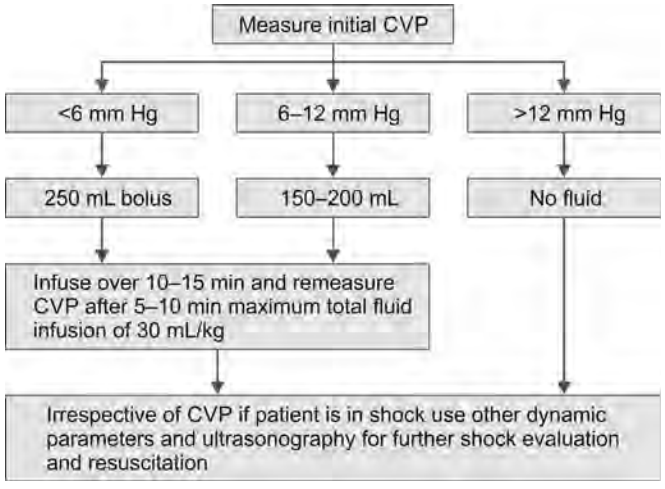
USG parameters	*Findings to continue fluid therapy*	*Findings to restrict fluid therapy*
Lung USG	• A Line present • B line <5	• A line difficult to delineate • Increased B line >5 (**Figs. 3A** and **B**)
IVC caliber	• Size <1.5 cm; collapsibility >50% • IVC collapsibility index >18%	• Size >2.5 cm; no respiratory variation, collapsibility <50% • IVC collapsibility index <12% (**Fig. 3C**)
Echocardiography	• Improved ventricular contractility and ejection fraction • Cardiac output increase	Decreased contractility and ventricular dilatation

(IVC: inferior vena cava; USG: ultrasound)

Resuscitation Guided by CVP, MAP, and $ScvO_2$

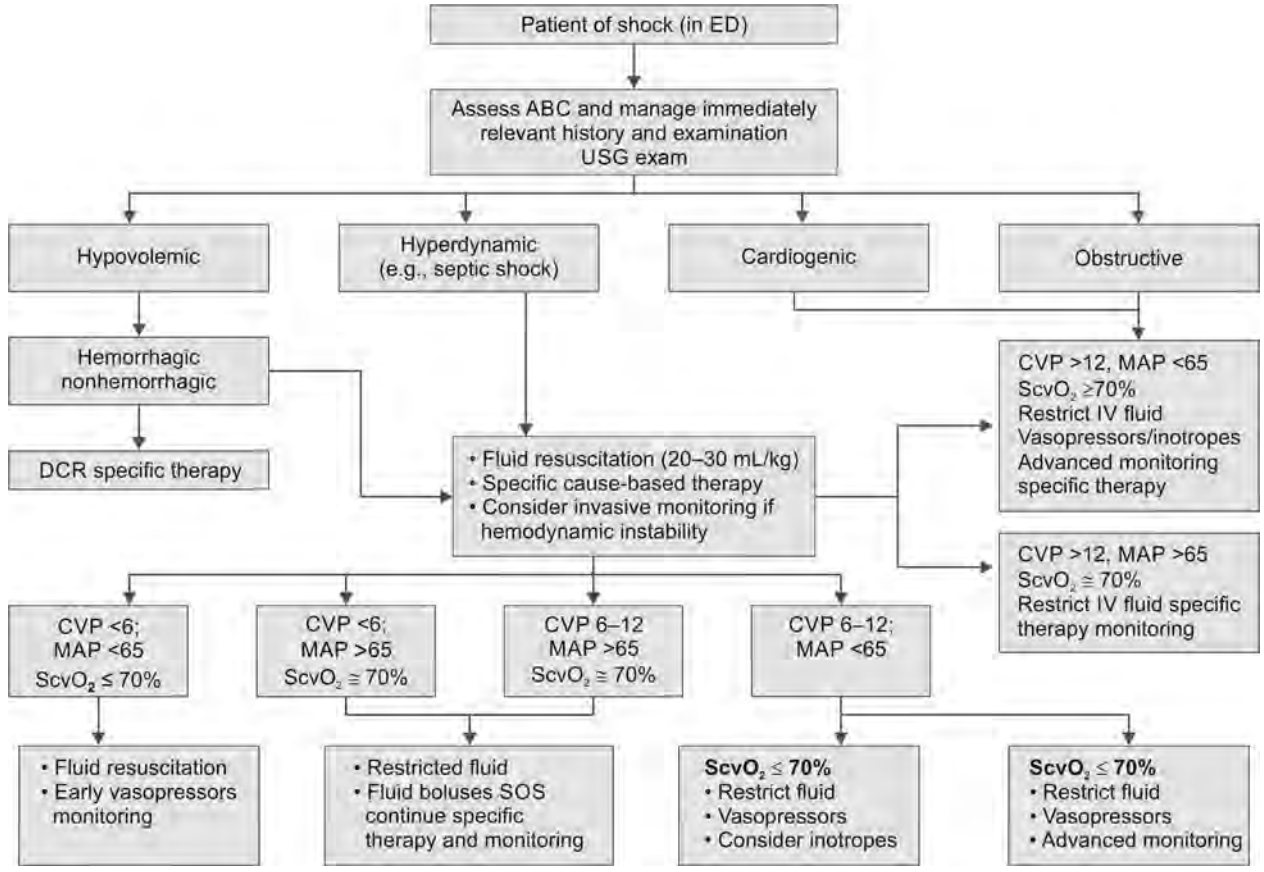
The central venous pressure (CVP) represents "preload" and is used as a surrogate of left ventricular end diastolic volume which determines cardiac output. Thus, venous return to the right atrium ("preload") is maintained if CVP is maintained within normal range. The target CVP during shock resuscitation is 6–12 mm Hg. No single CVP value is adequate and trend during fluid resuscitation is important. Low CVP usually signifies hypovolemia. Higher CVP during resuscitation is ominous and is associated with poor outcome in critically ill. Despite limitations, CVP is a convenient way to assess and monitor initial fluid therapy during resuscitation and has been used widely (**Flowchart 3**). Mini repeated fluid boluses (200–250 mL) of crystalloids may be infused in adults

over 10–15 minutes and CVP measured after 5–10 minutes to guide fluid resuscitation. Mean arterial pressure (MAP) continuous central venous oximetry ($ScvO_2$) parameter should also be taken in to account for resuscitation (**Flowchart 4**). If target CVP is not achieved in shock resuscitation after acute infusion of about 20–30 mL/kg of fluid then other dynamic parameters must be used to plan further fluid therapy and management of shock.



FLOWCHART 3: Fluid resuscitation guided by CVP alone.

Vasoactive drugs: Vasopressors are indicated in cases of persistent hypotension despite fluid resuscitation. It is reasonable to use vasopressor temporarily, while fluid resuscitation is ongoing in cases of major hemodynamic instability. *Noradrenaline is the first choice*; it has predominantly α-adrenergic properties and its modest β-adrenergic effects help to maintain cardiac output. Other vasopressors are adrenaline and dopamine. In randomized controlled trials, dopamine had no advantage over noradrenaline as first-line vasopressor and was found to be more arrhythmogenic. Adrenaline has predominantly β-adrenergic action at low doses, with α-adrenergic effects becoming more prominent in high doses. It is also more arrhythmogenic, decreases splanchnic circulation, and increases lactate levels. Trial has not shown beneficial effects of adrenaline over noradrenaline. Vasopressin deficiency can develop in patients with hyperkinetic forms of distributive shock and administration of low dose vasopressin can lead to substantial increase in blood pressure. *Amongst inotropes, dobutamine is the agent of choice,* it has predominantly β actions. Other agents are phosphodiesterase III inhibitors, such as milrinone and newer agent such as levosimendan, which acts primarily by binding to cardiac troponin C and increasing the calcium sensitivity of cardiac myocytes.



(CVP: central venous pressure; MAP: mean arterial pressure; $ScvO_2$: continuous central venous oximetry)

FLOWCHART 4: Resuscitation of shock guided by CVP, ABP and $ScvO_2$ (USG and other dynamic parameters may also be incorporated simultaneously).

SPECIFIC MEASURES

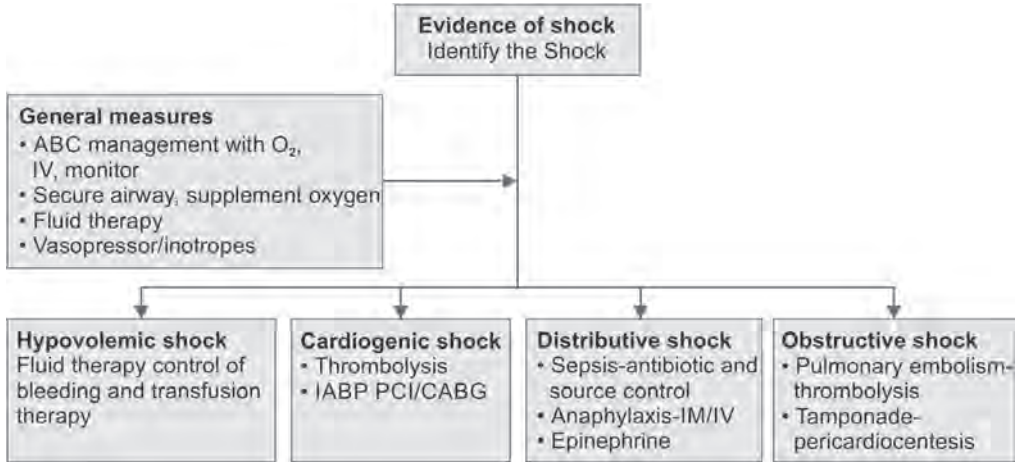
- *Hypovolemic shock*: Fluid administration is the first intervention, but in some trauma patients, it can be delayed until bleeding is controlled. Hemorrhagic shock warrants to identify the source of bleeding and appropriate control by surgical, radiological, or endoscopic intervention. Hypovolemic shock due to intra-abdominal pathologies such as perforation and obstruction also need surgery.
- *Cardiogenic shock*: If evidence of acute myocardial infarction with cardiogenic shock, then along with ventilator and inotropic supports intra-aortic balloon counterpulsation (IABP) is of great help. With IABP support, immediate reperfusion therapy in the form of either thrombolysis (if catheterization laboratory is not available) or immediate cardiac catheterization followed by percutaneous coronary intervention or emergency coronary artery bypass surgery should be done.
- *Distributive shock*: The management of septic shock consists of early goal-directed therapy and administration of antibiotics within 1 hour after sending cultures. Source of sepsis should be sought for with appropriate source control.
- *Obstructive shock*: The main causes are pulmonary embolism and cardiac tamponade. In case of pulmonary embolism, thrombolysis or embolectomy is the options, while in cardiac tamponade, urgent pericardiocentesis will lead to relief of symptoms.
- *Use of USG in specific management of shock*: USG is valuable and may be lifesaving to use for specific management and procedures during shock (**Table 7**). USG can be used for emergency relieve of tamponade, tension pneumothorax, abdominal compartment syndrome, etc. USG will improve the safety of vascular access during emergency.

SUMMARY

Shock is a medical emergency and resuscitation should begin immediately with simultaneous investigations to achieve good outcome. Correction of tissue hypoxia and restoration of adequate perfusion are of prime importance. It is very necessary to determine the type of shock to implement specific measures and correct the cause. The patient should be optimized with prompt resuscitation in emergency room to achieve reasonable hemodynamic stability before shifting to operation room, radiology, or ICU (**Flowchart 5**).

TABLE 7: Specific uses of USG in shock management.

Diagnostic	Tapping of pleural/abdominal fluid collection
Therapeutic	• Pericardiocentesis for tamponade • Thoracentesis for pneumothorax, hemothorax • Abscess drainage
Vascular access	• Central venous catheterization • Arterial line insertion • Dialysis catheter insertion



(CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump; PCI: percutaneous coronary intervention)

FLOWCHART 5: Summary evaluation and management of shock.

MULTIPLE CHOICE QUESTIONS

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49 CHAPTER

Vasopressors and Inotropes in Resuscitation

Manish Mehta

INTRODUCTION

Emergency physician and acute care providers are managing very complex patient population with serious comorbid conditions, and they often require vasopressors inotropes and chronotropes for preservation of vital organ perfusion during acute and severe illness. Although the usage of these drugs is disease specific and therapy is tailored to individual patient. Various physiologic parameters such as fluids status and cardiovascular reserve may also affect patient's response to these drugs. In few patients, the requirement of these drugs is high to achieve the treatment goals. Emergency physicians must be well aware with the use of these drugs as they produce different hemodynamic effect. *Vasopressors* produce peripheral vasoconstrictions increase in systemic vascular resistance (SVR) and mean arterial pressure (MAP). *Inotropes* are used to raise the cardiac contractility, cardiac output, and MAP. *Chronotropes* are used to increase the heart rate.

PHYSIOLOGY: RECEPTORS AND MECHANISMS OF ACTION

The main categories of adrenergic receptors relevant to vasopressor activity are the alpha-1, beta-1 and beta-2 adrenergic receptors, as well as the dopamine receptors. Various receptors and their mechanism of action are described in **Table 1**.

- *Alpha-adrenergic*: Alpha-1 adrenergic receptors, mostly located in vascular walls and also in heart, activation of these receptors induces significant vasoconstriction and also duration of contraction without increasing chronotropy.
- *Beta-adrenergic*: Beta-1 adrenergic receptors are situated in the heart and activation of these receptors causes increases in cardiac contractility, cardiac output, and MAP (inotropic) and chronotropic effect with minimal vasoconstriction. Beta-2 adrenergic receptors activation in blood vessels causes vasodilation.

TABLE 1: Receptor activity and clinical effects.

	Receptor activity				
Drug	***Alpha-1***	***Beta-1***	***Beta-2***	***Dopaminergic***	***Predominant clinical effects***
Phenylephrine	+++	0	0	0	SVR↑↑, CO↔/↑
Norepinephrine	+++	++	0	0	SVR↑↑, CO↔/↑
Epinephrine	+++	+++	++	0	CO↑↑, SVR↓ (low dose) SVR/↑ (higher dose)
Dopamine (μg/kg/min)*					
0.5–2	0	+	0	++	CO
5–10	+	++	0	++	CO↑, SVR↑
10–20	++	++	0	++	SVR↑↑
Dobutamine	0/+	+++	++	0	CO↑, SVR↓
Isoproterenol	0	+++	+++	0	CO↑, SVR↓

+++: Very strong effect; ++: Moderate effect; +: Weak effect; 0: No effect.

*Doses between 2 and 5 μg/kg/min have variable effects.

(CO: cardiac output; SVR: systemic vascular resistance)

- *Dopamine*: Dopamine receptors are situated in the renal, splanchnic (mesenteric), coronary, and cerebral vascular beds; stimulation of these receptors leads to vasodilation. A second subtype of dopamine receptors causes vasoconstriction by inducing norepinephrine release.
- *Calcium sensitizers*: Some agents increase the sensitivity of the myocardial contractile apparatus to calcium, causing an increase in myofilament tension development and myocardial contractility (e.g., pimobendan and levosimendan). These agents have additional pharmacological properties, such as phosphodiesterase inhibition, which increase inotropy and vasodilation.
- *Angiotensin*: Angiotensin receptors (AT1 and AT2) are G-coupled protein receptors with angiotensin II as their ligand. Angiotensin II is a vasoconstrictor that is a part of the renin-aldosterone-angiotensin system (RAAS). When receptors are stimulated, cytosolic calcium concentration increases to mediate vasoconstrictive effects as well as aldosterone and vasopressin secretion.

COMMON PHARMACOLOGICAL AGENTS

Adrenergic Agents

Adrenergic agents such as phenylephrine, norepinephrine, dopamine, and dobutamine are the most commonly used vasopressor and inotropic agents in critically ill patients (**Table 2**).

- *Norepinephrine*: Norepinephrine acts as strong alpha-1 and modest beta-1 adrenergic receptors, thus producing potent vasoconstriction and causes modest increase in cardiac output. So the final effect is increase in systolic and diastolic blood pressure, pulse pressure with modest effect on cardiac output. Minimal chronotropic effect is also noticed. A reflex bradycardia usually occurs in response to the increased MAP, such that the mild chronotropic effect is cancelled out and the heart rate remains unchanged or even decreases slightly. Norepinephrine is the preferred vasopressor for the treatment of septic shock.
- *Phenylephrine*: Phenylephrine exhibits alpha-adrenergic agonist activity and therefore results in vasoconstriction with minimal cardiac inotropy or chronotropy. MAP is augmented by raising SVR. It can be given as bolus to correct sudden and severe hypotension.
  Phenylephrine is reserved for patients in whom norepinephrine is contraindicated due to arrhythmias or who have failed other therapies because it may decrease stroke volume.
- *Epinephrine*: Epinephrine (adrenalin) has potent beta-1 adrenergic receptor activity and moderate beta-2 and alpha-1 adrenergic receptor effects thus vasoconstriction bronchodilation and positive inotropy are final outcome. At high infusion rate, it causes increase in coronary blood flow as myocytes are stimulated to release the local vasodilators. Patient on epinephrine is on high risk for arrhythmia

TABLE 2: Common vasopressors and inotropes.

Agent	*Initial dose*	*Maintenance dose*	*Maximum dose*	*Characteristics and role*
Vasopressors (alpha-1 adrenergic)				
Norepinephrine	• 8–12 µg/min (0.1–0.15 µg/kg/min) • A lower initial dose of 5 µg/min may be used, e.g., in older adults	2–4 µg/min (0.025–0.05 µg/kg/min)	35–100 µg/min (0.5–0.75 µg/kg/min; up to 3.3 µg/kg/min has been needed rarely)	• Initial vasopressor of choice in septic, cardiogenic, and hypovolemic shock • Must be diluted, e.g., a usual concentration is 4 mg in 250 mL of D5W or NS (16 µg/mL)
Epinephrine (adrenaline)	1 µg/min (0.014 µg/kg/min)	1–10 µg/min (0.014–0.14 µg/kg/min)	10–35 µg/min (0.14–0.5 µg/kg/min)	• Initial vasopressor of choice in anaphylactic shock • Typically an add on agent to norepinephrine in septic shock • Increases heart rate; may induce tachyarrhythmias and ischemia • Must be diluted; e.g., a usual concentration is 1 mg in 250 mL D5W (4 µg/mL)
Phenylephrine	100–180 µg/min (0.5–2 µg/kg/min)	20–80 µg/min (0.25–1.1 µg/kg/min)	80–360 µg/min (1.1–6 µg/kg/min)	• Pure alpha-adrenergic vasoconstrictor • Initial vasopressor when tachyarrhythmias preclude use of norepinephrine • May decrease stroke volume and cardiac output in patients with cardiac dysfunction • May be given as bolus dose of 50–100 µg to support blood pressure during rapid sequence intubation • Must be diluted; e.g., a usual concentration is 10 mg in 250 mL D5W OR NS (40 µg/mL)

Continued

Continued

Agent	*Initial dose*	*Maintenance dose*	*Maximum dose*	*Characteristics and role*
Dopamine	2–5 µg/kg/min	5–20 µg/kg/min	20–>50 µg/kg/min	• An alternative to norepinephrine in septic shock in highly selected patients (e.g., with compromised systolic function or absolute or relative bradycardia and low risk of tachyarrhythmias) • More adverse effects (e.g., tachycardia, arrhythmias particularly at doses >20 µg/kg/min) and less effective than norepinephrine for reversing hypotension in septic shock • Lower doses (e.g., 1–3 µg/kg/min) should not be used for renal protective effect and can cause hypotension during weaning • Must be diluted; e.g., a usual concentration is 400 mg in 250 mL D5W (1.6 mg/mL)
Antidiuretic hormone				
Vasopressin	0.01–0.03 units/min	0.03–0.04 units/min	• 0.04–0.07 units/min • Dose >0.04 units/min can cause cardiac ischemia and should be reserved for salvage therapy)	• Add on to norepinephrine to raise blood pressure. Not to be used as first-line vasopressor • Pure vasoconstrictor; may decrease stroke volume and cardiac output in myocardial dysfunction or precipitate ischemia in coronary artery disease • Must be diluted, e.g., a usual concentration is 25 units in 250 mL D5W OR NS (0.1 units/mL)
Inotrope (beta-1 adrenergic)				
Dobutamine	0.5–1 µg/kg/min	2–20 µg/kg/min	20–40 µg/kg/min; doses >20 µg/kg/min are not recommended in heart failure and should be reserved for salvage therapy	• Initial agent of choice in cardiogenic shock with low cardiac output and maintained blood pressure • Add-on to norepinephrine for cardiac output augmentation in septic shock with myocardial dysfunction • Increases cardiac contractility and rate; may cause hypotension and tachyarrhythmias • Must be diluted; a usual concentration is 250 mg in 500 mL D5W OR NS (0.5 mg/mL)
Inotrope (nonadrenergic, PDE3 inhibitor)				
Milrinone		0.125–0.75 µg/kg/min		• Alternative for short-term cardiac output augmentation to maintain organ perfusion in cardiogenic shock refractory to other agents • Increases cardiac contractility and heart rate at high doses; may cause peripheral vasodilation ,hypotension, and/or ventricular arrhythmias • Renally cleared; dose adjustment in renal impairment needed • Must be diluted; e.g., a usual concentration is 40 mg in 200 mL D5W (200 µg/mL)

(D5W: 5% dextrose water; MAP: mean arterial pressure; NS: 0.9% saline)

and splanchnic vasoconstriction in comparison to norepinephrine, dopamine, and vasopressin. Epinephrine is used for treatment of anaphylaxis, as a second-line agent after norepinephrine in septic shock, and for management of hypotension following coronary artery bypass surgery.

- *Dopamine*: Dopamine has a variety of effects depending upon the dose range administered and response is patient specific:
  - At doses of 1–2 μg/kg/min, dopamine acts predominantly on dopamine-1 receptors in the renal, mesenteric, cerebral, and coronary beds, resulting in selective vasodilation.
  - At doses of 5–10 μg/kg/min, dopamine also stimulates beta-1 adrenergic receptors and increases cardiac output, predominantly by increasing stroke volume with variable effects on heart rate.
  - At doses >10 μg/kg/min, the predominant effect of dopamine is to stimulate alpha-adrenergic receptors and produce vasoconstriction with an increased SVR. The usual dose range for dopamine is 2–20 μg/kg/min.
- *Dobutamine*: Dobutamine is an inotrope that causes vasodilation. It increases myocardial oxygen consumption such as isoproterenol. Dobutamine is useful in severe, medically refractory heart failure and cardiogenic shock. Dobutamine is also useful in pharmacological cardiac stress testing.
- *Isoproterenol*: Isoproterenol also is an inotropic and chronotropic agent rather than a vasopressor. The drug high affinity for beta-2 adrenergic receptor causes vasodilation and a decrease in MAP. Therefore, it is useful in hypotension due to bradycardia.

Noradrenergic Agents

A number of agents produce vasoconstriction or inotropy through nonadrenergic mechanisms, including phosphodiesterase (PDA) inhibitors and nitric oxide synthase inhibitors, calcium sensitizers, or angiotensin II.

- *Phosphodiesterase (PDE) inhibitors*: PDE inhibitor such as inamrinone (formerly known as amrinone) which is replaced by the second-generation milrinone improves cardiac output and reduces the SVR (inotrope and vasodilatory actions). Milrinone is used to treat patients with impaired cardiac function and medically refractory heart failure. It cannot be used in hypotensive patients due to its vasodilatory properties. Milrinone can be used in pulmonary vascular hypertension patients as it decreases the pulmonary vascular resistance.
- *Calcium sensitizers*: Levosimendan increases ventricular contractility, improves the cardiac output, arteriolar, and venous dilatation. It also improves the glomerular filtration rate in acute decompensated heart failure (ADHF) and also cardioprotective in ischemic situation.

Vasopressin

In response to hypotension pain nausea hypoxia and increased plasma osmolality, vasopressin [antidiuretic hormone (ADH)] is released from posterior pituitary. Vasopressin is also released from heart if any cardiac muscle stress or from adrenal glands also in response to increase in catecholamine secretion.

Vasopressin causes increase in SVR but minimal effect on cardiac output due to reflexive increase in systemic vagal tone. It is primarily used as a second-line agent in vasodilatory shock, particularly septic shock, or anaphylaxis that is unresponsive to epinephrine.

Vasopressin (ADH) is used in the management of diabetes insipidus and esophageal variceal bleeding. Adverse effects of vasopressin include hyponatremia and pulmonary vasoconstriction.

CLINICAL APPLICATION OF VASOPRESSORS AND INOTROPES IN SHOCK RESUSCITATION

Vasopressors and inotropes are used in various clinical situations described below and summarized in **Table 3**.

Septic shock management starts with source control, volume assessment correction of hypovolemia timely, and appropriate antibiotics, vasopressors are also required to maintain perfusion. Norepinephrine is the drug of choice in shock related to sepsis. Perfusion markers should be assessed regularly such as urine output, mental status, skin perfusion, and serum lactate levels. If resuscitation goals are not met then vasopressin should be started in low dose (0.04 U/min) is safe and effective. If patient has myocardial dysfunction (elevated cardiac filling pressor, low cardiac output, and signs of low perfusion in spite of fluid and vasopressor therapy) then dobutamine can be added. Dopamine can only be added in patient with low risk for arrhythmias.

Cardiogenic shock following the acute coronary syndrome, revascularization is the definitive treatment in this condition with temporary measures such as intra-aortic balloon pump (IABP) and ventricular assist device. Severe hypotension is supported by vasopressors, systolic blood pressor <70 staring the norepinephrine is the best strategies (with low-dose dopamine or/and dobutamine).

Inotropic support is required in ADHF to lower the end-diastolic pressure. Hypotensive patient of ADHF benefited with the dobutamine and milrinone. Inotropes are only recommended if patient has elevated left heart filling pressure or severely impaired cardiac index.

In postcardiac arrest patient in which MAP 70–90 is recommended, norepinephrine is reasonable choice over the dopamine.

Neurogenic shock after spinal trauma is presented by vasodilation, hypotension, and bradycardia. To maintain the MAP 85 or above, dopamine and norepinephrine are the reasonable choice to stimulate $\alpha 1$ and $\beta 1$ receptor activity if cervical injury is present and phenylephrine is the choice if lower thoracic injury is present.

Anaphylaxis is the condition where patient present with acute onset skin and mucosal involvement along with hypotension and respiratory distress after exposure to allergens. Epinephrine is the drug of choice 0.01 mg/kg of: 1,000 solution, maximum 0.5 mg intramuscular can be administered.

FUNDAMENTAL CONCEPTS FOR USE AND PRACTICAL ISSUES

Use of vasopressor and inotropes in resuscitation is based on three fundamental concepts:

1. *One drug many receptor concepts*: Any given vasopressors and inotropes exhibit multiple effects as they act on multiple receptors.

TABLE 3: Clinical applications of vasopressors and inotropes in shock resuscitation.

Type of shock	*First-line therapy*	*Second-line therapy*
Sepsis and shock	• Norepinephrine infusion at 0.1–1 mg/kg/min • Low-dose vasopressin 0.04 U/min	• Dopamine infusion at 5–15 mg/kg/min • Epinephrine infusion at 0.02 mg/kg/min
Cardiogenic shock with LVF	• SBP <70, norepinephrine infusion at 0.1–1 mg/kg/min (0.5–30 mg/min) SBP 70–90, dopamine infusion at 15 mg/kg/min • SBP >90, dobutamine infusion at 2–20 mg/kg/min	Milrinone, 50 mg/kg loading dose, then 5–10 mg/kg/min (not recommended post-MI)
Cardiogenic shock with pulmonary embolism	Dobutamine infusion at 5 mg/kg/min, norepinephrine infusion at 0.1–1 mg/kg/min	Phenylephrine infusion at 10–20 mg/kg/min
Neurogenic shock	Dopamine infusion at 5–15 mg/kg/min	Norepinephrine infusion at 0.1–1 mg/kg/min, phenylephrine infusion at 10–20 mg/kg/min
Anaphylactic shock	Epinephrine, 1 mL of 1:10,000 solution (100 mg), can be given as a slow IV push, then as a 0.02 mg/kg/min infusion (5–15 mg/min)	Norepinephrine infusion at 0.1–1 mg/kg/min (0.5–30 mg/min)
Hemorrhagic shock	Volume resuscitation	Dopamine infusion at 5–15 mg/kg/min as an adjunct
Drug overdose and shock	Norepinephrine infusion 0.1-1 µg/kg/min	• Phenylephrine infusion at 10–20 mg/kg/min • Glucagon given as a 5-mg IV bolus, then 1–5 mg/h infusion • calcium gluconate, 0.6 mL/kg bolus, then a 0.6–1.5 mL/kg/h infusion • Insulin started at 0.1 units/kg/h IV and titrated to a goal of 1 unit/kg/h

(LVF: left ventricular failure; SBP: systolic blood pressure)

2. *Dose responsive curve concept*: Many drugs action is based on "dose responsive curve" and drug like dopamine effect is dose dependent
3. *Direct and reflex action concept*: Norepinephrine-induced beta-1 adrenergic stimulation alone would normally cause tachycardia. However, the elevated MAP from norepinephrine alpha-adrenergic receptor-induced vasoconstriction results in reflex decrease in heart rate.

- *Volume resuscitation*: Coexistent hypovolemia should be corrected before starting the vasopressor in order to maximally effective.
- *Selection of vasopressor*: Choice of drug should be based on underlying etiology of shock. Then need to be titrated on the bases of signs of perfusion and urine output. If one agent is ineffective, the second drug may be added.
- *Rout of administration*: To facilitate the rapid delivery of the drug to the heart for systemic distribution, vasopressors and inotropes should be infused by placing the central venous catheter. Risk of peripheral extravasation of drug will also be eliminated. Vasopressors and inotropes can be given by appropriately placed peripheral cannulas till the time central line is placed.
- *Tachyphylaxis*: Drug must be titrated regularly, to avoid tachyphylaxis phenomenon as responsiveness of the drug reduced over the time.

COMPLICATIONS

Hypoperfusion

Excessive vasoconstriction with inadequate perfusion commonly occurs in setting of inadequate cardiac output or inadequate volume resuscitation. Perfusion of extremities, mesenteric organ and kidneys are also affected due to hypotension and vasopressors.

Initially skin color at the tips of the fingers and/or toes changes, which may progress to black color of digits, frank necrosis which require autoamputation of the digits. Renal insufficiency, oliguria, and acute limb ischemia may develop in patients with underlying peripheral artery disease.

Inadequate mesenteric perfusion increases the risk of gastritis, shock liver, intestinal ischemia, or translocation of gut flora with resultant bacteremia. Despite these concerns, maintenance of MAP with vasopressors appears more effective in maintaining renal and mesenteric blood flow than allowing MAP to drop, and maintenance of MAP with vasopressors may be life-saving despite evidence of localized hypoperfusion.

Dysrhythmias

Stimulation of beta-1 adrenergic receptors exerts powerful chronotropic effects. This causes the risk of sinus tachycardia (most common), atrial fibrillation, reentrant atrioventricular node tachycardia, or ventricular tachyarrhythmias.

Myocardial Ischemia

The chronotropic and inotropic effects of beta-adrenergic receptor stimulation can increase myocardial oxygen consumption. While there is usually coronary vasodilation in response to vasopressors, perfusion may still be inadequate to accommodate the increased myocardial oxygen demand. Daily ECG on patients treated with vasopressors or inotropes may screen for occult ischemia, and excessive tachycardia

should be avoided because of impaired diastolic filling of coronary arteries.

Local Effects

Peripheral extravasation of vasopressors into surrounding connective tissue can lead to excessive local vasoconstriction with subsequent skin necrosis. To avoid this complication, vasopressors should be administered via a central vein catheter whenever possible. If infiltration occurs, local treatment with phentolamine (5–10 mg in 10 mL of normal saline) injected subcutaneously can minimize local vasoconstriction.

Hyperglycemia

Hyperglycemia may occur due to inhibition of insulin secretion. The magnitude of hyperglycemia generally is minor and is more pronounced with norepinephrine and epinephrine than dopamine. Monitoring of blood glucose while on vasopressin can prevent complications of untreated hyperglycemia.

SUMMARY AND RECOMMENDATIONS

- Vasopressors are a powerful class of drugs that induce vasoconstriction and elevate MAP.
- Alpha-1 adrenergic receptors induce vasoconstriction, while beta-1 induces inotropy plus chronotropy, and beta-2 receptors induce vasodilation. One subtype of dopamine receptor induces norepinephrine release with subsequent vasoconstriction, although many dopamine receptors induce vasodilation. Some agents increase the sensitivity of the myocardial contractile apparatus to calcium while others cause direct vasoconstriction via angiotensin II receptor stimulation.
- Vasopressors are indicated for a MAP <60 mm Hg, or a decrease of systolic blood pressure that exceeds 30 mm Hg from baseline, when either condition results in end-organ dysfunction due to hypoperfusion.
- Hypovolemia should be corrected prior to the institution of vasopressor therapy for maximum efficacy. Patients should be reevaluated frequently once vasopressor therapy has been initiated. Common issues that arise include tachyphylaxis, which may require dose titration, and additional hemodynamic insults, which should be recognized and managed.
- Choice of an initial agent should be based upon the suspected underlying etiology of shock (e.g., dobutamine for cardiogenic shock without significant hypotension, norepinephrine for septic and cardiogenic shock with hypotension, and epinephrine for anaphylactic shock).
- Complications of vasopressor therapy include hypoperfusion (particularly affecting the extremities, mesentery or kidneys), dysrhythmias, myocardial ischemia, peripheral extravasation with skin necrosis, and hyperglycemia.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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50 CHAPTER

Perfusion Endpoint in Resuscitation of Shock

Nisreen Hamza Maghraby, Zainab Musa Al Alawi

INTRODUCTION

Shock is a life-threatening condition of circulatory failure, causing inadequate oxygen delivery (DO_2) to meet cellular metabolic needs and oxygen consumption requirements, producing cellular, and tissue hypoxia. This results in metabolic acidosis, inflammation, coagulopathy, and then multiorgan failure (MOF) and death. There are five types of shock, each of them presents differently—(1) distributive, (2) cardiogenic, (3) obstructive, (4) neurogenic, and (5) hypovolemic (**Fig. 1**). Generally, shock has four stages based on physiologic parameters, including (1) heart rate, (2) blood pressure, (3) mental status, and (4) urine output. However, their utility in the initial assessment of shock has been questioned and these parameters alone are insufficient to define adequate management and resuscitation. So, well-defined endpoints in resuscitation are needed. Resuscitations primary goal is to restore adequate tissue DO_2 to match the metabolic demand at the level of the tissue. This is mostly accomplished through restoring volume to improve preload and cardiac output (CO), but sometimes medications and optimization of hemoglobin are required. Macrocirculatory endpoints, such as blood pressure and CO, should be the initial focus of resuscitation. Even though restoration of hemodynamic indices does not guarantee tissue-level DO_2 and significant abnormalities at cellular level may continue to exist. Therefore, microcirculatory and metabolic endpoints should be considered to guide further interventions. This chapter will be reviewing the *macro- and micro circulation endpoints* (**Table 1**) in addition to clinical assessment of perfusion.

MACROCIRCULATORY ENDPOINT

In the emergency department (ED), when starting to resuscitate, target macrocirculatory endpoints first, because they can be measured quickly at the bedside. Aims to address intravascular volume status, mean arterial pressure (MAP) and CO. Early recognition of abnormalities with these endpoints and optimizing resuscitation accordingly often prevents early cardiovascular collapse.

TABLE 1: Determinants of perfusion endpoint in resuscitation.

Macrocirculatory endpoints	• Mean arterial pressure • Cardiac output
Microcirculatory endpoints	• Lactate • Mixed and venous oxygen saturation • Central venous-arterial CO_2 gradient
Clinical assessment of perfusion	• Capillary filling time • Urine output

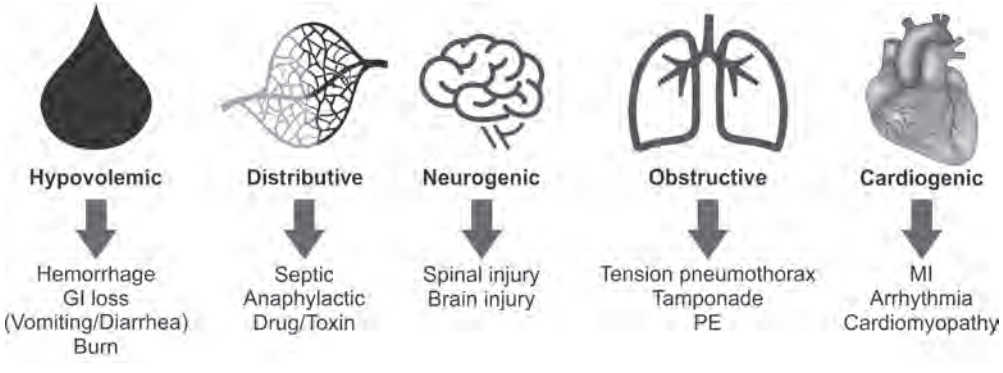

FIG. 1: Types of shock.

Mean Arterial Pressure

Mean arterial pressure, defined as: "MAP ¼ diastolic pressure 1/3 (systolic pressure–diastolic pressure)", is a common endpoint used to guide resuscitation worldwide. It is available between brackets under the blood pressure on most monitors and interpretable. MAP might not be a reliable parameter to follow during fluid resuscitation because of issues that are not uncommon with blood pressure cuffs (too large, too small, and wrong position) and no formal MAP goal that exists yet. Although initially during resuscitation a MAP > 65 and a MAP > 85 in patient with high ICP as head trauma patients are rough goals. In addition, it does not provide information regarding oxygenation at cellular level. During resuscitation in emergency room usually we target mean arterial blood pressure (ABP) of>65–70 mm Hg. In certain condition due to altered physiology and hemodynamic different MAP is targeted (**Table 2**).

Sepsis

The surviving sepsis campaign defines sepsis-related hypotension as a systolic blood pressure of <100 mm Hg, a 40 mm Hg decreases from baseline, or a MAP of <70 mm Hg. A MAP ≥ 60 mm Hg is believed to be needed to maintain adequate tissue perfusion. A MAP ≥65 mm Hg is recommended in patients with severe sepsis and septic shock by the Surviving Sepsis Campaign Guidelines Committee. Current guidelines recommendation to stabilize septic patient is to start with empiric crystalloid fluid bolus of 30 mL/kg to increase the intravascular filling pressure and CO. For fluid refractory hypotension, vasopressor therapy should be initiated. Despite normalization of MAP after proper management, lactic acidosis may persist (cryptic sepsis shock). So, more endpoints to guide septic shock resuscitation are needed.

Hemorrhagic Shock

Resuscitation initially should focus on hemorrhage control combined with rapid perfusion restore by volume reexpansion. In trauma patient without head injury, damage control resuscitation is a commonly implanted strategy that tolerates moderate hypotension to prevent excessive hemorrhage and the need for fluid administration until definitive hemorrhage control is provided. In such condition, resuscitation with balanced blood product administration, either a 1:1:1 ratio or whole blood over intravenous crystalloid therapy, is preferred. Current guidelines recommended a target systolic blood pressure of 80–90 mm Hg until major bleeding has been managed with no definitive evidence to support a specific MAP-based strategy.

TABLE 2: Mean blood pressure (MAP) targets during resuscitation in special clinical conditions.

Higher MAP target (85–90 mm Hg)	***Lower MAP target (55–60 mm Hg)***
Traumatic brain injury	Polytrauma (damage-controlled resuscitation)
Cerebrovascular accident	Hemorrhagic shock
Chronic hypertension	
Hypertensive nephropathy	
Eclampsia	

Cardiac Output

Cardiac output is defined as heart rate times the stroke volume. Normal CO is 4–8 L/min. CO is an important endpoint because it is frequently impaired in all types of shock and has been associated with poor outcomes in patients with cardiogenic shock, sepsis, and trauma, it also predicts fluid responsiveness. CO can be measured at the bedside through a variety of invasive like pulmonary artery catheter and noninvasive measures like bedside echocardiogram that are available in almost all EDs. Inotropic support should be considered in shocked patient with low CO who has adequate intravascular volume with evidence of poor perfusion. Dobutamine is often the inotrope of choice in most ED setting, but it must be used with caution because these agents can cause significant hypotension. Accordingly, most patients in cardiogenic shock need to start on vasopressor therapy first to avoid developing further hypotension secondary to inotropes. Echocardiography as endpoints remains poorly defined and there is limited data to guide standard practice in resuscitation, in addition it does not provide continuous data during resuscitation.

Point-of-care Ultrasound

Assessing intravascular volume status is a macro endpoint that can be evaluate easily at the bedside. The rapid ultrasound in shock (RUSH) protocol is used to evaluate critical patients in shock, to help further classify the type of shock they have. It evaluates via a series of scans the pump (heart), the tank [inferior vena cava (IVC)] and the pipes (aorta). The issue with bedside US is that its operator dependent, if you do not have the proper training and qualification to do it, you might end up with the wrong interpretations that miss leads further management. For more information on the RUSH protocol, please refer to the designated chapter.

MICROCIRCULATORY ENDPOINT

In many shock states, there is a loss of hemodynamic consistency where an improvement in systemic hemodynamics occurs without similar improvement in microcirculatory blood flow and end organ perfusion. Commonly available laboratory markers such as lactate, mixed venous oxygen saturation (SvO_2)/central venous oxygen saturation ($ScvO_2$), and central venous-to-arterial carbon dioxide gap ($PvaCO_2$) are helping to assess the end organ perfusion status.

Lactate

Lactate is a marker of anaerobic metabolism secondary to regional hypoxia and impairment in delivery of oxygen. Normal levels in resting healthy individuals 0.5–2 mml/L. It is easily drawn and measured in arterial or venous blood gas. It is well established that initial lactate correlates with clinical outcome and time to correction of increased lactate is associated with increased mortality rate. Despite reassuring hemodynamic vital signs, the patient with cryptic septic shock when lactate elevation > 4 mm/L has mortality risk similar to those presented with hypotension and should receive careful resuscitation. Data suggest that lactate may provide a useful resuscitation endpoint; however, specific lactate goals have not been defined yet. Alternate etiology of lactate elevation such as medications, adrenergic surge, and delayed clearance can cause hyperlactatemia as in hepatic and renal injury,

so correlating with the clinical presentation is very important, especially if elevated lactate is the only abnormality.

Mixed and Central Venous Oxygen Saturation

The oxygen content (CaO_2) of the arterial blood coming out from left ventricle to aorta is determined by following formula: $CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0003 \times PaO_2)$ where SaO_2 is the arterial oxygen saturation and PaO_2 is the partial pressure of oxygen in arterial blood. In optimum condition, the CaO_2 is about 20 mL/100 mL of arterial blood which is distributed to the different part of body. In steady state, about 25% of delivered oxygen is utilized by the different body tissues and deoxygenated blood is returned to right atrium and pulmonary artery. *The saturation of this deoxygenated blood in pulmonary artery is termed SvO_2*. Nowadays, as pulmonary artery catheter is not used commonly in intensive care unit (ICU) or in ED sampling of central venous catheter is done as surrogate of SvO_2 and is termed $ScvO_2$. $ScvO_2/SvO_2$ represents the balance between the tissue demand and the tissue utilization of oxygen. The acceptable value of SvO_2 in resting state is 75–80%. The $ScvO_2$ measures the saturation of blood in superior vena cava (SVC) unlike in SvO_2 which measures the mixed blood from both IVC and SVC In pulmonary artery. As the splanchnic oxygen extraction is normally lower than the brain; the oxygen saturation of $ScvO_2$ is 2–3% lesser than SvO_2. Steady state $ScvO_2$ is 65–70%. $ScvO_2$ can be continuously measured and monitored during resuscitation by infrared oximetry based on mass spectrophotometry using special proprietary central venous catheters available in market. There are various factors which alter $SvO_2/ScvO_2$ value (**Table 3**). Achieving $ScvO_2$ >70% during septic shock, resuscitation has been recommended as a part of early goal directed therapy and has been associated with 16% increased survival when compared to control group.

Mixed venous oxygenation saturation and $ScvO_2$ are representative of oxygenation extraction by tissue. SvO_2 is measured using a pulmonary artery catheter, and most accurately gives total body oxygenation extraction because it is a true mixed venous sample. $ScvO_2$ is measured with a central line catheter, it is often higher than SvO_2, since it is only measuring regional oxygen extraction for the upper part of the body. The normal range for $ScvO_2$ is 65–75%. $ScvO_2$ of <60% has been associated with major adverse cardiac events in patients with acute decompensated heart failure requiring inotropes and shown to be predictive of poor outcomes. Unfortunately, normal and supranormal values do not guarantee adequate tissue oxygenation. If the $ScvO_2$ levels of >90% suggest poor oxygen utilization. Diseased tissue may not be able to extract oxygen, so venous return may have high O_2 content despite persistent cellular hypoxia, or significant microcirculatory shunting which is associated with a high mortality. Studies have shown benefit in cardiac, trauma, and sepsis patients when used as endpoints of resuscitation, but, it has not been shown to independently predict survival rate. Unfortunately, no benefit has been seen in studies comparing lactate and $ScvO_2$-based resuscitation protocols. SvO_2 and $ScvO_2$ are not commonly used in the ED during early resuscitation.

TABLE 3: Common conditions altering mixed venous oxygen saturation.

Factors increasing $SVO_2/ScvO_2$	***Factors decreasing $SVO_2/ScvO_2$***
Increase tissue oxygen supply: • Vasodilatory shock • Hyperbaric oxygen therapy	*Decrease tissue oxygen supply*: • Cardiogenic shock • Hemorrhagic shock • Severe anemia
Decrease tissue oxygen utilization	***Increase tissue oxygen utilization***
• Anesthesia • Hypothermia • Cytopathic hypoxia	• Hyperthermia • Shivering • Exercise • Septic shock

Central Venous-arterial CO_2 Gradient

The inability of a normal or high $ScvO_2$ to determine adequate organ perfusion has led clinicians to look for other markers of regional tissue hypoxia and metabolic abnormalities especially in septic shock. The venous-to-arterial carbon dioxide gradient has been considered as an alternative test to determine if the patient has achieved adequate CO along with adequate microcirculatory flow and perfusion. It is calculated by subtracting the arterial pCO_2 from the central venous pCO_2 ($ScvO_2$). In multiple studies, a $PcvaCO_2$ gap that is <6 mm Hg, has been found to be associated with a higher cardiac index, better lactate clearance, and improved microcirculatory perfusion. In an opposite manner, a Pcv-aCO_2 gap that is >6 mm Hg can reliably reflect critical hypoperfusion and the need for further resuscitation.

CLINICAL ASSESSMENT OF PERFUSION

In patient with shock, tissue microvascular hypoperfusion can be evaluated at bedside using indicators of skin perfusion, measuring capillary refill time and urine output that are both easily applicable method in many circumstances, cost-effective and it has been used for predicting unfavorable outcomes in critically ill adult patient.

Capillary Refill Time

Capillary refill time is defined as a marker of peripheral perfusion that worsens during circulatory failure. It is the duration of time needed for the patient fingertip to regain color after direct pressure is applied and maintained over 10 seconds to cause blanching. A normal CRT in a healthy patient is <3.5 seconds. Failure to normalize at 6 hours of resuscitation is predictive of worsening shock and values >5 seconds despite hemodynamic optimization suggest a significant risk of progressive organ failure. That indicate further resuscitation is required.

Urine Output

Urine output often is used as a marker of acute kidney injury but also to guide fluid resuscitation in critically ill patients. Although decrease of urine output may be associated to a decrease of glomerular filtration rate due to decreased of renal blood flow or renal perfusion pressure. Consider Foley catheter placement for accurate measurement (normal values: >0.5 mL/kg/h). During the resuscitation phase of

shock, interventions to improve urine output should focus on intravascular fluid optimization, achieving microcirculatory goals, and avoiding unnecessary nephrotoxic agents.

Approach to a Patient in Shock

Standard history and physical examination are crucial to be obtained on every sick patient in the ED as an initial assessment. Then, after a patent airway and adequate oxygenation are ensured, it is important to establish access to the circulation. Peripheral large bore intravenous lines are the first options for venous access. If the peripheral access is difficult, central venous catheterization provides a reliable means of fluid resuscitation. In addition, cannulation of the intraosseous (IO) as a temporizing method is a fast and easy access for the unstable patients presenting without intravascular access. Empiric fluid administration typically is the first line of therapy in all hypotensive patients. Patients presented with hemorrhagic shock are an exception as large volumes of crystalloids will further dilute hemoglobin, platelet, and clotting factors that worsen the general condition of the patient. Instead, blood product should be used. After immediate priorities such as airway and respiratory compromise have been addressed and managed, a rapid assessment of endpoints of resuscitation is required to provide valuable information to guide further resuscitation and volume administration. Start assessment of endpoints of resuscitation by targeting macrocirculatory endpoints at the bedside to address intravascular volume status using point of care ultrasound and MAP. Then, microcirculatory endpoints need to be evaluated using clinical assessment of capillary refill time and urine output. In addition to requesting other laboratory markers (lactate, SvO_2/$ScvO_2$), and $PvaCO_2$) to ensure adequate systemic DO_2 and end organ perfusion.

SUMMARY

Resuscitation is the process of treating shock to restore normal physiology. There are multiple different ways to monitor resuscitation efforts in these patients, no one method is superior. Rather, a combination of approaches must be used based on patient condition, individual, and institutional protocols. Patient in shock frequently present to the ED and the emergency physician must recognize the shock state early and aggressively start resuscitation, using well-defined endpoints. Resuscitation efforts should focus on correction of macro circulatory endpoints such as MAP and point of care US with specific goals dependent on the type of shock and individual patient response. Afterward, microcirculatory endpoints such as peripheral lactate, SvO_2 or $ScvO_2$, and $PvaCO_2$ should guide resuscitation optimization. Finally, clinical endpoints such as capillary refill time and urine output provide valuable information at the bedside and should continue to be part of the resuscitation plan for monitoring and to assist in guiding proper interventions.

MULTIPLE CHOICE QUESTIONS

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Extracorporeal Membrane Oxygenation

51 CHAPTER

Basar Cander

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a modified cardiopulmonary bypass form providing artificial respiration and/or mechanical circulatory support in critically ill patients in intensive care units (ICUs). It is a mechanical cardiopulmonary form that can provide prolonged life support in patients unresponsive to conventional management. Conventional cardiopulmonary bypass devices provide support for patients undergoing surgery for minutes to hours, while ECMO provides support for days to weeks for patients with respiratory, cardiac, or combined cardiopulmonary failure. Indications for ECMO have been extended for longer use in ICUs and for both heart and lung transplants and lung resections in unstable patients. Venovenous ECMO (VV-ECMO) typically provides support for patients with isolated respiratory failure, while venoarterial ECMO (VA-ECMO) is used in both cardiac and cardiopulmonary failure.

As of 2016, >78,000 ECMO was implanted with >19,000 being in adult patients. There was a 433% increase in ECMO cases between 2006 and 2011 in the United States of America. Successful ECMO applications in diseases such as H1N1 influenza, advancements in ECMO technology, and published randomized clinical trials have contributed to this increase.

This chapter begins with historical development of ECMO and continues with description of the technical aspect of ECMO. The indications, contraindications, and complications of ECMO are included. In addition, ECMO practices in special patient groups such as children, the elderly, pregnant women, and obese are discussed. Finally, ECMO practices in COVID-19 that is a current global pandemic are explained and future projections for ECMO are evaluated.

HISTORICAL DEVELOPMENT OF EXTRACORPOREAL MEMBRANE OXYGENATION

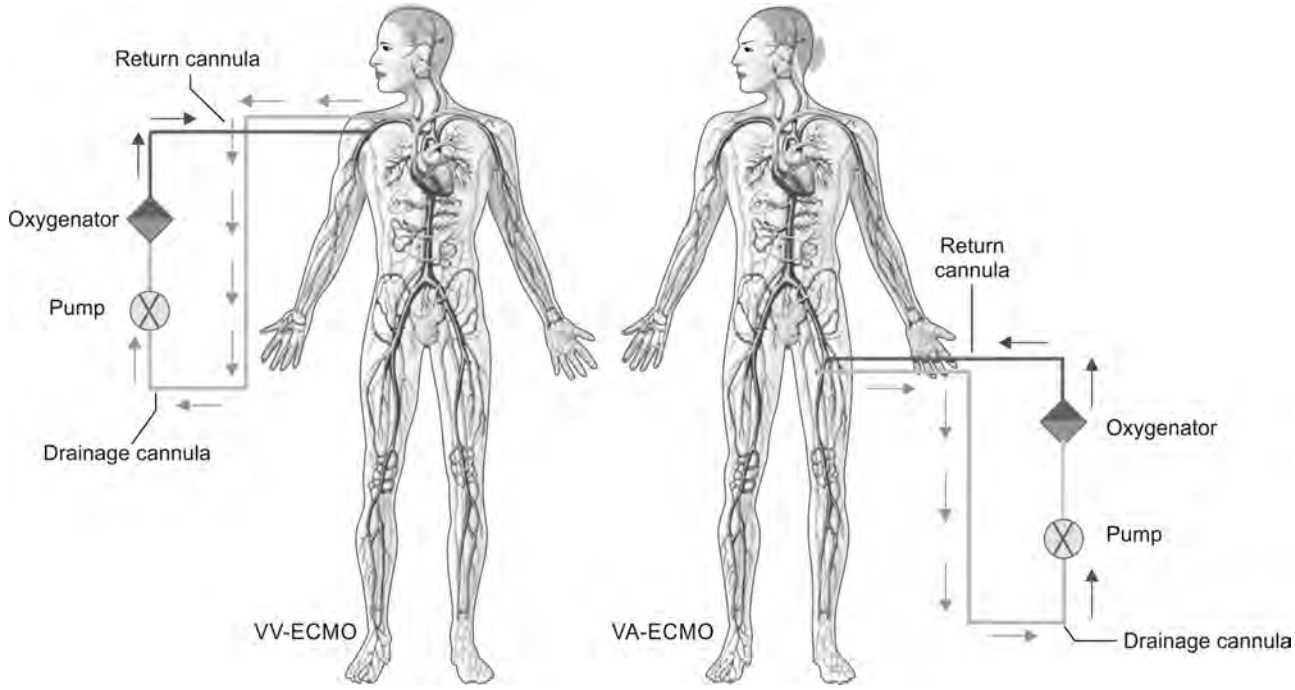
In 1944, Kolff et al. noticed that the blood was oxygenated as it passed through the cellophane chambers of the artificial kidney they developed. This concept was then applied by Gibbon who used artificial oxygenation and perfusion support for the first successful heart surgery in 1953. Direct exposure of the blood to gas in the heart-lung machine of Gibbon caused significant hematologic damage and this limited the use of this machine for only 2–3 hours. In 1969, Dorson et al. used a membrane oxygenation for cardiopulmonary bypass in infants. Whereas in adults, prolonged ECMO support was used for the first time in 1972 for severe respiratory failure. The interest in ECMO has decreased after it was demonstrated that this method is not superior over conventional ventilator support in 1990s, but the use of ECMO flourished again after CESAR study (2009), which randomized patients with severe respiratory failure treated with extracorporeal support between an expert high-case-volume center and a nonspecialized center, and showed a higher improvement in the rates of mortality and severe disability 6 months later in the expert center.

EXTRACORPOREAL MEMBRANE OXYGENATION TECHNIQUES

There are currently two main ECMO modes. VV-ECMO is indicated for severe, but potentially reversible respiratory failure. VA-ECMO provides hemodynamic support and is used for cardiac and/or pulmonary failure. Typical schematic illustration of VV-ECMO and VA-ECMO is shown in **Figure 1**.

Venovenous Extracorporeal Membrane Oxygenation

In VV-ECMO, the blood is drained from the vena cava or right atrium and returned to the right atrium. Alternatively, the drainage cannula is inserted into the jugular vein and the blood is returned to the cannula in the femoral vein. The use of double lumen enables blood drainage and returns functions from the same venous access, providing a greater patient mobility. With this ECMO type not hemodynamic support, but only respiratory support is provided and is used in patients with acute respiratory failure. Satisfying results of the CESAR trial and the successful use of ECMO in severe acute respiratory distress syndrome (ARDS) cases during 2009 influenza pandemic have increased popularity of VV-ECMO in acute respiratory failure.



(VA-ECMO: venoarterial extracorporeal membrane oxygenation; VV-ECMO: venovenous extracorporeal membrane oxygenation)

FIG. 1: Typical schematic illustration of VV-ECMO and VA-ECMO supports. ***(For color version, see plate 3)***

Venoarterial Extracorporeal Membrane Oxygenation

The main function of VA-ECMO is oxygen and carbon dioxide gas exchange as well as providing hemodynamic support. In VA-ECMO, the blood is drained from the right atrium and returned to the arterial system through the femoral, axillary, or carotid artery by bypassing the heart and lungs. The characteristics of VA-ECMO are exclusion of pulmonary circulation. VA-ECMO can be classified as central or peripheral according to the cannulated vessels. VA-ECMO is used in patients with cardiogenic shock or cardiac arrest. The improvement potential of oxygenation is less with VV-ECMO compared to VA-ECMO. However, this ECMO mode decreases right ventricular strain with pulmonary pressures through a similar mechanism.

EXTRACORPOREAL MEMBRANE OXYGENATION COMPONENTS

A typical ECMO circuit consists of a blood pump, membrane oxygenator, conduit tubing, heat exchanger, drainage, and return cannulas. ECMO circuit drains the blood from the venous system and returns the newly oxygenated blood in the membrane to the patient. The main difference between VV-ECMO and VA-ECMO circuits is cannula types and insertion sites.

Pump

The function of the blood pump is to pump blood of the patients to the oxygenator membrane, generating flow in the system. ECMO pump collects the blood from the body via an access site. The pump is usually positioned in the drainage cannula line between patient and membrane oxygenator. The blood flows from the centrifugal pump of the device toward the oxygenator component. ECMO pump is controlled by a console and runs with rotation per minute in order to provide blood flow through the patient's system. Presently, there are two pump types: (1) Roller, and (2) Centrifugal pumps. Roller pump generates a unidirectional and continuous blood flow through the progressive compressions of the segments of the drainage cannula tubing system. Whereas, a centrifugal pump provides a unidirectional and continuous blood flow through the magnetic field generated by the rotation of an axis coupled with a disk. Centrifugal pumps have been associated with less hemolysis compared to roller pumps, and therefore the use of these pumps in adults is increasing.

Oxygenator

Oxygenator contains a fibrous material, which has the ability to provide oxygen and remove carbon dioxide. Oxygenator serves as an artificial lung that exchanges oxygen (to blood) and carbon dioxide (from blood) instead of the native lungs of the patient. Gas diffusion occurs between the patient's blood and fresh blood flow through the oxygenator membrane, providing oxygenation of the venous blood and removal of carbon dioxide. The composition of fresh blood flow is determined by adjusting the inspired oxygen fraction (FiO_2) in the gas mixer. When the blood passes through both main components of the system, it returns to the body from another access site. In recent years, new generation oxygenators that eliminate disadvantages of the old ones have been developed. In these polymethylpentene oxygenators, the need for red blood cell and platelet transfusion is reduced, gas exchange is improved and the durability is better than the previous oxygenators.

WEANING

Weaning from ECMO support is conditioned by the recovery of organ dysfunction and the resolution of indication for

ECMO support. Weaning from VV-ECMO due to acute hypoxic or hypercapnic respiratory failure can be initiated when the patient can satisfactorily maintain gas exchange with acceptable mechanical ventilation parameters. Whereas weaning from VA-ECMO depends on the improvement of cardiac function. Predictors indicating recovery of cardiac functions include maintenance of continuous arterial pulse pressure at least for 24 hours, echocardiography showing improvement of systolic function [left ventricular ejection fraction (EF) ≥ 20%] and adequate arterial oxygenation.

INDICATIONS

Venovenous-ECMO is mostly used in patients with moderately decreased cardiac functions, and is the technique of choice in patients with hypoxemic respiratory failure and hypercapnic respiratory failure. VA-ECMO form is indicated in patients with heart failure that may or may not require pulmonary support.

Venovenous Extracorporeal Membrane Oxygenation Indications

Venovenous-ECMO indications are classically divided into two as hypoxemic respiratory failure and hypercapnic respiratory failure. According to ELSO; the main three indications for VV-ECMO are: (1) Bacterial pneumonia, (2) Viral pneumonia, and (3) Postoperative or trauma-related ARDS.

Venoarterial Extracorporeal Membrane Oxygenation Indications

Venoarterial-ECMO is indicated in the case of cardiogenic shock in which the patient has low cardiac output and tissue hypoperfusion despite hemodynamic optimization using volume replacement, inotrope, vasopressor, vasodilator agents, and/or intra-aortic balloon pump. According to ELSO; the main four indications for VA-ECMO are: (1) Cardiogenic shock, (2) Cardiomyopathy, (3) Congenital heart disease, and (4) Myocarditis. VV-ECMO and VA-ECMO indications are given in **Table 1**.

TABLE 1: Indications for VV-ECMO and VA-ECMO.

VA-ECMO	*VV-ECMO*
Cardiogenic shock	ARDS respiratory failure
Acute coronary syndrome	Primary graft dysfunction after lung transplant
Myocarditis	Pulmonary embolism
Post-cardiac arrest	Traumatic lung damage
Pulmonary hypertension	
Cardiomyopathy	
Primary graft dysfunction after heart transplant	
Traumatic cardiac injury	

(VA-ECMO: venoarterial extracorporeal membrane oxygenation; VV-ECMO: venovenous extracorporeal membrane oxygenation)

CONTRAINDICATIONS

According to the ELSO consensus, there is no absolute contraindication for the use of ECMO, but risks and benefits of ECMO support should be individually evaluated for each patient. However, there is some situation where ECMO benefits can be questioned and considered contraindication. These may include uncontrolled active hemorrhage, incurable cancer, and irreversible central nervous system dysfunction. VV-ECMO and VA-ECMO contraindications are given in **Table 2**.

COMPLICATIONS

The risk for potential complications is high due to the nature of ECMO. The common complications of ECMO include hemorrhage and embolic events; infection, sepsis, and multiple organ failure; pressure injury from impaired skin integrity due to immobility of the patient and organ or tissue malperfusion. The most common complication during ECMO is hemorrhage, ranging between 10% and 30%.

In addition, technical complications are frequently encountered in patients managed with ECMO support. In a retrospective analysis of 265 adult ARDS patients treated with ECMO, reinsertion of ECMO system was needed in 31% of the patients due to technical problems (worsened gas exchange, device-induced coagulation disorders, and suspicion of infection in ECMO circuit). In the same study, the most common technical complications were reported as the formation of progressive clot in the oxygenator membrane

TABLE 2: Contraindications for VV-ECMO and VA-ECMO.

	VA-ECMO	*VV-ECMO*
Relative	Organ dysfunction	Mechanical ventilation in high setting
	Advanced age	Advanced age
	Prolonged mechanical ventilation	Prolonged mechanical ventilation
	Obesity	Obesity
	Peripheral vascular disease	Peripheral vascular disease
Absolute	No chance of organ recovery and not appropriate candidate for transplant	No chance of organ recovery and not appropriate candidate for transplant
	Multiple organ failure	Multiple organ failure
	Prolonged CPR	Malignancy (advanced or metastatic)
	Malignancy (advanced or metastatic)	Severe brain damage
	Severe brain damage	
	Severe aortic regurgitation	

(CPR: cardiopulmonary resuscitation; VA-ECMO: venoarterial extracorporeal membrane oxygenation; VV-ECMO: venovenous extracorporeal membrane oxygenation)

(51%), sudden clot formation in the oxygenator membrane or blood pump (35%), and acute mechanical failure of ECMO system (10%).

EXTRACORPOREAL MEMBRANE OXYGENATION IN SPECIAL PATIENT GROUPS

Children

There are important differences in ECMO applications in pediatric patients compared to adults. These include indications, setup of ECMO circuit, and cannulation sites. According to the last ELSO report; 71% of ECMO cases were children and 47% of the entire cohort were newborns. Because of the lack of robust data, ECMO decision in pediatric patients is challenging. The most common indications for pediatric ECMO include congenital defects (left ventricle outlet obstruction, right ventricle outlet obstruction, and septal defects), cardiomyopathy, myocarditis (viral, bacterial, and aspiration), and ARDS. About 13% of all ECMO cases were performed in patients with cardiac arrest with the highest rate being in neonates by 36%. VA-ECMO is typically applied in the femoral vessels in adults, while this is not the case in children. Neck cannulation enables uninterrupted chest compression during pediatric ECMO support.

Long-term neurological outcomes after ECMO in pediatric patients are still a research topic. In a review of pediatric patients with respiratory failure treated with ECMO support between 2002 and 2012, survival was found as 57% despite comorbidities. However, this rate was 72% in patients without comorbidity. In that study, predictors of poor prognosis were determined as a patient age under 18 years, hepatic or renal failure, immune dysfunction, diagnosis of fungal pneumonia, and pertussis or ARDS secondary to sepsis.

Heparin coating of pumps, oxygenators and artificial surfaces have resulted in a higher biocompatibility and lower complication rates. In addition, improvements in anti-coagulation and bleeding control will make ECMO safer for children.

Elderly

The number of studies on the use of ECMO in elderly is limited. In addition, indications for the use of ECMO in this population are still not clear, and the use of VA-ECMO in elderly patients is controversial. However, the importance of ECMO for cardiopulmonary resuscitation (CPR) is expected to rise as geriatric population increases.

Advanced age has been reported to be a well-known predictive factor of survival for ECMO. Possible reason for this is the increase in comorbidities with ageing. However, some studies have reported that VA-ECMO was effective in elderly patients and yielded survival rates similar to young patients. In a study by Lee et al. investigating the impact of age on survival of the patients with cardiac failure treated with ECMO support, mortality rate was higher in ≥65 years of patients, but after adjusting for comorbidities, age was no longer an independent risk factor of mortality. However, pre-ECMO low serum bicarbonate and high serum creatinine serum levels were reported to be independent predictors of VA-ECMO mortality related to age. In addition, Narotsky et al., reported that advanced age was not an independent factor of short-term and long-term survival among patients receiving VA-ECMO support.

Pregnant Women

Intensive care unit admissions vary between 0.7 and 13.5 per 100 deliveries in peripartum patients, and mortality rate is 3.3% in high-income countries and 14% in low-moderate income countries. Mortality has been reported as about 40% in pregnant or postpartum women with ARDS or cardiac arrest who were admitted to ICUs.

The use of ECMO during pregnancy or postpartum period has been rarely reported since it is thought to increase the risk of developing maternal or fetal hemorrhage. The literature about ECMO support during pregnancy is limited with case reports, case series, and systematic reviews. According to these reports, peripartum patients receive ECMO support for respiratory and cardiovascular indications, the main etiology is ARDS among the respiratory indications, while the most common cardiovascular indications are reported as pulmonary embolisms and peripartum cardiomyopathy. Again according to the same studies, mortality rate is lower in peripartum patients requiring VV-ECMO compared to those receiving VA-ECMO support.

Moore et al., conducted a comprehensive literature review about the use of ECMO support during pregnancy and reported overall maternal survival as 78% and fetal survival as 65%. In contrast, in a literature screening by Ong et al., case reports on ECMO support during pregnancy period were reviewed and maternal survival was found as 91% and fetal survival as 79%.

Obese

In general, a circuit flow indexed to weight or body surface area is needed to sustain rest and recovery of the lungs in patients with severe hypoxia. In addition to the difficulties in the cannulation, obesity poses an important challenge in obtaining an adequately indexed flow. In addition, increased risk of comorbidities such as diabetes mellitus, hypertension, and coronary artery disease causes an additional difficulty for ECMO support. Therefore, there are drawbacks in many centers about the use of ECMO support in obese patients. However, outcomes have not been reported sufficiently in this patient group. Furthermore, accumulating evidence indicates that obesity has a protective effect against critical diseases. This may explain why obesity is not associated with worse results in patients with ARDS who are managed conventionally.

In the literature, there is data supporting the use of ECMO support in patients with critical weight. In a multivariate analysis by screening ELSO registry between 2002 and 2006, Brogan et al. reported that body weight was significantly higher in the survivor patients. Al-Soufi et al., investigated the relationship between body weight and results in all patients supported with VV-ECMO between 2005 and 2011 and concluded that body weight was not correlated with increased mortality. However, since body weight was used as a parameter in both studies rather than body mass index, no sufficient conclusion could be drawn about the use of ECMO support in obese patients.

Extracorporeal Membrane Oxygenation in COVID-19

During the 2009 influenza A (H1N1) pandemic, ECMO treatment was found to be beneficial, and the mortality rate was

21% in patients with H1N1-related ARDS who received ECMO support, which has been increased the use of ECMO support. Again in a cohort study conducted about the same pandemic, the mortality rate was 23.7% in patients with H1N1-related ARDS who received ECMO support, while this rate was 52.5% in patients who were not treated with ECMO. In a retrospective study conducted on Middle East respiratory syndrome-related coronavirus (MERS), it was highlighted that ECMO should be used as a rescue treatment, and the mortality rate was found to be lower in ECMO group compared to the conventional group (65% vs. 100%).

According to a new report published in JAMA, 26.1% of 138 COVID-19 patients were admitted to the ICU, and 61.1% had ARDS. According to this report, the rate of mortality from COVID-19 was found as 4.3%. So far there is no COVID-19 specific treatment. According to an interim guidelines formulated by the World Health Organization (WHO), ECMO should be considered as rescue treatment for COVID-19 with refractory hypoxemia despite lung preserving ventilation. However, experience with the use of ECMO support in COVID-19 patients is highly limited. In a study by yang et al., 31 of 52 critically ill adult patients diagnosed with COVID-19 and treated in the ICU died on the 28th day. Six patients received ECMO support and five of these patients died. In another study by Guqin et al. 10 of 48 ARDS patients with laboratory confirmed COVID-19 received ECMO support. Two of them were discharged with clinical improvement, three died and the remaining five patients were still on ECMO support at the time of the study.

According to ELSO, as of June 1, 2020, ECMO support was used in 1,371 patients with confirmed diagnosis of COVID-19 pneumonia, and among these patients 390 (55%) of 706 patients who survived were discharged. There are many factors that may influence outcomes of ECMO treatment in COVID-19 pneumonia. These factors may include the duration of mechanical ventilation, severity of the underlying disease, experience of the trained medical personnel, and ECMO equipment. However, it should be remembered that medical staff who performed ECMO support can be easily infected by the virus.

FUTURE PROJECTIONS

It is obvious that as ECMO technology develops and the experience of the implementing teams increases, and this application will be used more widespread. With the development of technology in the future, more compact ECMO circuits will prevent femoral cannulation, and invasive mechanical ventilation will be minimized, thus, rehabilitation of patients and ambulation will be more feasible. With the smaller circuit components and more efficient gas exchange membranes, portable extracorporeal gas exchange devices will be developed, which will enable a potential paradigm shift in the field of artificial lung.

Despite the increased popularity of ECMO in cardiopulmonary diseases, there are numerous questions on the patient groups in which this support should be provided. Large-scale randomized controlled studies are needed about the use of this technology and for comparison ECMO with the other treatment options in cardiovascular failure. In these studies, cost-benefit analysis should be made in order to better understand the economical impacts of ECMO, which is a resource intensive intervention. In the lack of quality data, ECMO cannot be adequately included in basic cardiac and pulmonary practice guidelines.

SUMMARY

Extracorporeal membrane oxygenation is a method that can be indicated for the management of patients with cardiac and/or respiratory failure and is applied by multidisciplinary experienced teams. Advances in ECMO technology have led to increasing use of this technique in respiratory and cardiac failure. Although there are various arguments recommending the use of ECMO from a physiopathological point of view, further studies are needed to determine the patient eligible for this method and the optimal starting time of ECMO support. More data and stronger evidence to be obtained on this subject will provide a better understanding and extension of ECMO indications.

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52 CHAPTER

Procedural Sedation and Analgesia

Devendra Richhariya, Bhawana Sharma

INTRODUCTION

There is an ever-increasing patient population including children and elderly, requiring sedation and analgesia when being treated in the emergency department. Emergency department is the place where sedation and analgesia are provided for unscheduled procedures. In procedural sedation and analgesia processes (PSA), various anxiolytics, sedatives, hypnotics, and/or dissociative medication are being used. These agents provide amnesia, decreased awareness, increase patient comfort and safety during diagnostic and therapeutic procedures in emergency department. Also, during the PSA, various methods of airway protection such as airway adjuncts or endotracheal intubation are not required. "Procedural sedation is a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures." Before further discussion, one should know the various levels of sedation and analgesia. On the basis of effect on various body function, sedation levels are divided into minimal, moderate, deep sedation, and general anesthesia (**Table 1**).

- *Mild sedation*—also termed as "anxiolysis" where patient response is normal but slow airway, breathing, and circulation remain normal and need no support.
- *Moderate sedation*—patient response is purposeful to verbal/physical stimuli, airway breathing and circulation parameter are maintained and usually need no support.
- *Dissociative sedation*—patient response is variable and trance-like state airway, breathing and circulation parameters are maintained and usually need no support. Dissociative sedation is a type of moderate sedation. Dissociation is a state in which the cortical centers are prevented from receiving sensory stimuli, but cardio-pulmonary activity and responses are preserved.
- *Deep sedation*—patient responds only after repeated stimuli, airway and breathing may be suppressed but circulation is generally maintained.
- *General anesthesia*—patient not arousable even by painful stimulus, airway support required because of breathing impairment, circulation may impair.

TABLE 1: Different levels of sedation, recommendation for monitoring and their effects on bodily functions.

Level of sedation	*Responsiveness*	*Airway*	*Spontaneous ventilation*	*Cardiovascular function*	***Monitoring*** (conscious level, heart rate, blood pressure, oxygen level)
Minimal sedation/ anxiolysis	Normal response to verbal stimulation	Unaffected	Unaffected	Unaffected	Record HR, RR, BP every 15 min, and continuous oxygen saturation
Moderate sedation/analgesia (conscious sedation)	Purposeful response to verbal or tactile stimulation	No intervention required	Adequate	Usually maintained	Continuous monitoring of every parameters
Deep sedation/ analgesia	Purposeful* response following repeated or painful stimulation	Intervention may be required	May be inadequate	Usually maintained	Continuous monitoring of every parameter
General anesthesia	Unarousable even with painful stimulus	Intervention often required	Frequently inadequate	May be impaired	Continuous monitoring of every parameter

(BP: blood pressure; HR: heart rate; RR: respiratory rate)

SEDATION POLICY AND GUIDELINES

Institution- and evidence-based policy should be in place in a hospital, which allows the emergency physician to create appropriate sedation plan for each patient. Emergency physician who is trained in providing the sedation, performing the procedure and the nurse who is trained in monitoring the patient is appropriate for practice in emergency department. Both physician and nurse are able to do the immediate resuscitation. Leadership of the emergency department, both physician and nurses should develop the policies where scope of nursing practice is determined where the nurse can also safely administer sedation in resource-limited setting.

INDICATIONS IN EMERGENCY DEPARTMENT

In emergency department, various types of sedation may be indicated for different procedures depending upon the urgency, invasiveness, and painful procedure. The need for sedation is sometimes more urgent than a full preprocedural evaluation (**Table 2**).

PRESEDATION PATIENT EVALUATION

Despite careful planning and performance, the depth of sedation needed or achieved cannot always be predicted. It is therefore important to prepare for managing deeper levels of sedation than anticipated. Most of the agents used can produce variable levels of sedation, so pay particular attention to dosing and to the patient's responses to the medications.

Risk Assessment

Complications are primarily determined by the interaction of the depth of sedation and the patient's current medical condition. One of the most common tools to assess patient's underlying clinical condition is the American Society of Anesthesiologists' *physical status classification system*. Class I—patient is healthy and no associated comorbidities; Class II—patient having mild or controlled disease such as mild asthma, obesity-controlled diabetes, and pregnancy; Class III—severe systemic disease moderate to severe asthma, pneumonia, and end-stage renal disease (ESRD); Class IV—life-threatening illness such as sepsis, severe cardiac dysfunction, and DIC; and Class V—polytrauma multiorgan dysfunction.

TABLE 2: Indications for sedation in an emergency department.

Type of sedation	*Indications*
Emergent	Cardioversion for life-threatening arrhythmias, neuroimaging for head trauma, reduction of fractures or dislocations with soft tissue or vascular compromise, care of contaminated wounds, or intractable pain
Urgent	Stable fractures, abscess incision and drainage, care of clean wounds, foreign body removal, and laceration repair
Nonemergent	Removal of a soft tissue foreign body, placing splints on fractures that require minimal manipulation, or changing splints on fractures that have already been reduced

Patient Assessment

Focused history is important to establish fasting state, prior experiences with sedation or anesthesia, current medications, and allergies. Focused physical examination reveals any potential difficult airway or cardiopulmonary compromise. A potentially difficult airway should be anticipated when the following findings or conditions are present—short neck, micrognathia, large tongue, trismus, morbid obesity, a history of difficult intubation, or anatomic anomalies of the airway and neck. At a minimum, difficult airway equipment should be present and available.

Airway Assessment Procedures for Sedation and Analgesia

If respiratory compromise develops during sedation/analgesia, positive pressure ventilation, with or without tracheal intubation, may be necessary. This may be more difficult in patients with atypical airway anatomy. Also, some airway abnormalities may increase the likelihood of airway obstruction during spontaneous ventilation. Some factors that may be associated with difficulty in airway management are listed here.

- *History*:
  - Previous problems with anesthesia or sedation
  - Stridor, snoring or sleep apnea
  - Advanced rheumatoid arthritis
  - Chromosomal abnormality (e.g., trisomy 21)
- *Physical examination*:
  - *Habitus*: Significant obesity (especially involving the neck and facial structures)
  - *Head and neck*: Short neck, limited neck extension, decreased hyoid-mental distance (<3 cm in an adult), neck mass, cervical spine disease or trauma, tracheal deviation, and dysmorphic facial features (e.g., Pierre–Robin syndrome)
  - *Mouth*: Small opening (<3 cm in an adult), edentulous, protruding incisors, loose or capped teeth, dental appliances, high and arched palate, macroglossia, tonsillar hypertrophy, and nonvisible uvula
  - *Jaw*: Micrognathia, retrognathia, trismus, and significant malocclusion

Cardiorespiratory conditions increase the complication rate. Most agents can cause vasodilation and hypotension, particularly in patients with pre-existing hypovolemia. Drugs or alcohol intoxication or reduced level of consciousness increases the risk of hypoxemia and hypoventilation. If possible, delay procedural sedation in intoxicated patients until mental status improves.

PREPARATION

Current Practice Guidelines

- *Preprocedure fasting*: In urgent or emergent situations where complete gastric emptying is not possible, do not delay moderate procedural sedation based on fasting time alone.

- *Routine capnography*: Capnography may be used as an adjunct to pulse oximetry and clinical assessment to detect hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone in patients undergoing PSA in the emergency department. Capnography includes all forms of quantitative exhaled carbon dioxide analysis.
- *Number of personnel required*: For minimal and moderate levels of sedation, one emergency physician simultaneously administering sedation and performing the procedure with a nurse monitoring the patient appears to be an appropriate practice. However, for deep sedation, two physicians, one to perform sedation and monitor the patient and the other to perform the procedure.

Equipment

Sedation area must have all size-appropriate equipment for airway management and resuscitation. An ideal list is provided in **Table 3**.

Monitoring

There are two types of monitoring: (1) Interactive and (2) Electronic. *Interactive monitoring* is the direct observation of the patient to assess the depth of sedation and observe for hypoventilation or apnea, upper airway obstruction, laryngospasm, vomiting, or aspiration. Thus interactive monitoring requires an unobstructed view of the patient's face, mouth, and chest wall. *Electronic monitoring* uses equipment to assess arterial oxygenation, ventilation, blood pressure, and cardiac rate and rhythm. Moderate and deep sedation require constant observation and continuous monitoring.

Pulse oximetry is not a substitute for monitoring ventilation. Quantitative capnography may be used as an adjunct to pulse oximetry and clinical assessment to detect hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone in patients undergoing PSA in the ED. Capnography during procedural sedation allows the early recognition of adverse events.

Monitoring of vitals including heart rate, blood pressure, and pulse oximetry must be taken and recorded legibly before beginning sedation and after each dose of medication, upon completion of procedure, beginning of recovery period, and upon discharge. For mild sedation, intermittent measurements are sufficient. For moderate and deep sedation, it is recommended that blood pressure should be assessed every 5 minutes and heart rate and pulse oximetry should be continuously monitored. Patients are at the highest risk of hypoxia and hypoventilation during the period immediately after IV medication administration (until the peak effect of the medication has been reached) and during the immediate postprocedure period (when external stimuli are discontinued and the stimulating pain of the procedure has subsided).

TECHNIQUE FOR PROCEDURAL SEDATION AND ANALGESIA

Preprocedure Analgesia and Selection of Sedative Agents

Preprocedure administration of analgesics such as opioids makes the patient more comfortable during painful procedures. Fentanyl 1–2 μg/kg often required to control the pain. Sedatives should be administered after time of peak action of analgesics in nonurgent to semiurgent procedures as it decreases postprocedure analgesic requirement and oversedation may result, if analgesic medications are given after sedation. Shorter-acting agents are preferred to drugs with a longer duration of action to minimize postprocedure respiratory depression. Various factors should be considered while choosing the appropriate agents and doses are patient age, comorbidities, and sedation target level (**Table 4**).

Oxygen Supplementation

The use of supplemental oxygen throughout procedural sedation is a common emergency department practice. The

TABLE 3: Emergency equipment for sedation and analgesia.

Basic airway management equipment (age- and size-appropriate)	*Advanced airway management equipment*	*Emergency medications*	*Pharmacologic antagonists*
• Sources of compressed O_2 (tank with regulator or pipeline supply with flowmeter) • Source of suction • Suction catheters • Yankauer-type suction • Face masks • Self-inflating breathing bag-valve set • Oral and nasal airways • Lubricant	• Supraglottic airway devices • Laryngoscope handles (tested) • Laryngoscope blades • Endotracheal tubes • Stylet • Gum-elastic bougie	• Epinephrine • Ephedrine • Vasopressin • Atropine • Nitroglycerine • Lidocaine • Glucose (IV or oral) • Diphenhydramine • Hydrocortisone, methylprednisolone, or dexamethasone • Benzodiazepines • B-blocker • Adenosine	• Naloxone • Flumazenil • Amiodarone

Other equipment *(age- and size-appropriate)*: *Gloves, tourniquets, alcohol wipes, sterile gauze pads, intravenous catheters, intravenous tubing, intravenous fluid, assorted needles for drug aspiration, intramuscular injection, appropriately sized syringes, tape*

TABLE 4: Drugs for procedural sedation.

Drugs	*Dose*	*Onset of action*	*Effectiveness*	*Comments*
Propofol	• 0.5–1 mg/kg • Repeat dose 0.25–0.5 mg/kg • In elderly 0.25–0.5 mg/kg	<1 min	<10 min	• Good for orthopedic reduction as rapid onset and short duration of action • Respiratory depression may occur • Do not provide analgesia
Ketamine	1.0–1.5 mg/kg over 1 min and repeat dose 0.5–1 mg/kg and for only analgesia 0.1–0.3 mg/g	<1 min	10 min	• Act as both sedative an analgesia, safer in comorbid conditions, provides cardiorespiratory stability • Avoid in psychiatric illness
Etomidate	• 0.1–0.2 mg/kg repeat dose 0.05 mg /kg	<1 min	<5 min	Useful for short procedure and cardioversion, minimum cardiac, and respiratory depression
Ketamine +Propofol (ketofol-single syringe)	0.5 + 0.5 mg	<1 min	<10 min	• Ketamine adds analgesic properties. Blunt propofol induces hypotension, good for prolonged procedure • Longer time for recovery if ratio increased
Midazolam	• 1–2.5 mg repeat dose 0.5–2.5 mg, repeat dose in every 3 min • For elderly dose—0.05 mg/kg	<5 min	30–60 min	• Useful for longer procedures • Not provides analgesia, so combined with analgesic • Cardiovascular and respiratory depression
Fentanyl	0.5–1.5 µg/kg repeat dose is the same every 2–3 min. In elderly dose is 0.25 µg/kg	<2 min	30–60 min	• Monotherapy used for minimal sedation • Respiratory depression may occur
Alfentanil	• 10 µg/kg • Repeat dose also same • Reduced doses are used in elderly	<1 min	<10 min	• Fast onset and short duration of action • Increased risk of apnea
Remifentanil	• 0.16 µg/kg/min infusion or 1 µg/kg bolus • Less doses in elderly	Immediate	10 min	• Fast onset and short duration of action • Increased risk of apnea

benefit is that enhanced oxygen reserves permit a longer period of normal oxygenation in the event of apnea or respiratory depression. The disadvantage is that supplemental oxygen therefore negates oximetry as an early warning device. Two studies of emergency department propofol sedation without supplemental oxygen have reported desaturation rates of 11.6% and 31%. These rates are higher than the 5–7% similarly observed in studies with supplemental oxygen. A randomized controlled trial showed no apparent benefit to supplemental oxygen during emergency department moderate sedation; however, this question has not been similarly studied for deep sedation. In the case of apnea, a preoxygenated patient will tolerate a longer period of apnea without requiring assisted ventilation, with the associated risk of gastric insufflation. Thus, although unproven, the administration of supplemental oxygen with propofol seems prudent, particularly when the patient's respiratory status can be monitored with capnography, in addition to pulse oximetry.

Sedation Management

Observe and monitor the patient until the peak effect of the initial sedative dose has been reached. If necessary, titrate with additional medications to the desired sedation level. Once the patient has achieved the target sedation level, the actual procedure may begin. If the patient begins to regain alertness before completion of the procedure, additional sedative doses may be required. However, additional sedative doses given to extend procedural sedation are associated with an increased risk of respiratory depression. As larger cumulative doses of the drug are given, the half-life of each bolus will increase. After the patient recovers from sedation, analgesics are administered as needed, for patient comfort.

Complications

Reported rates of complication during procedural sedation in emergency department vary from 0.1 to 4%. Factors associated with an increased rate of complications include age >65 years, level of sedation, premedication with fentanyl, use of short-acting agents and procedural sedation, and analgesia performed at night, when PSA could be administered by physicians with varying levels of training and experience and when consultant-level supervision is not always physically present.

Serious adverse events include the need for assisted ventilation, endotracheal intubation, or treatment of hypotension or cardiac dysrhythmias. Minor adverse events resolve spontaneously and include sedation to a deeper level than intended, transient hypoxia, or emesis. Complications can occur unexpectedly, so careful preparation, appropriate procedural monitoring, and careful selection of the target

TABLE 5: Aldrete score—assessment of the patient recovery and safety for discharge.

Activity	*Respiration*	*Circulation*	*Consciousness*	*Oxygen saturation*
Score 2: Moves all extremities voluntarily/on command	*Score 2*: Breathes deeply and coughs freely	*Score 2*: BP + 20 mm Hg of preanesthetic level	*Score 2*: Fully awake	*Score 2*: SpO_2 > 92% on room air
Score 1: Moves 2 extremities	*Score 1*: Dyspneic, shallow or limited breathing	*Score 1*: BP + 20–50 mm Hg of preanesthetic levels	*Score 1* : Arousable on calling	*Score 1*: Supplemental O_2 required to maintain SpO_2 > 92%
Score 0: Unable to move extremities	*Score 0*: Apneic	*Score 0*: BP + 50 mm Hg of preanesthetic levels	*Score 0*: Not responding	*Score 0*: SpO_2 < 92% with supplemental O_2
Aldrete score: A score of ≥9 is appropriate for safe discharge.				

sedation level will minimize the rate of occurrence and severity of adverse events.

Follow-up and Patient Instructions

At the completion of sedation and the procedure, patients should be monitored until they return to baseline mental status and cardiopulmonary function. A structured assessment, such as the *Aldrete score* (**Table 5**), can be used to assess the patient's recovery and safety for discharge. The duration of observation before discharge is variable. It depends on the quantity of sedatives given, the patient's response, the duration of the procedure, and the occurrence of any adverse events. Most adverse events occur during procedural sedation itself, typically within a few minutes of sedative administration. The occurrence of adverse events > 5 minutes after completion of the procedure is rare (<1%). Patients should be instructed to return if they develop respiratory complaints or nausea or vomiting. The follow-up interval required for patients who undergo emergency department procedural sedation is usually related to the procedure rather than the sedation itself.

SUMMARY

Noninvasive and minimally invasive procedures are performed not only in operating room but also in emergency department; for various procedures sedation, analgesia, or both may be required for interventional or diagnostic procedures. Systematic assessment and care are required for PSA. The requirement of patient may be an antianxiety drug, pain medicine, immobilization, simple reassurance, or a combination of these interventions. The procedures performed in emergency department may be painful or painless so, sedation management can range from minimal sedation, to the extent of deep sedation. Procedural sedation in emergency department usually requires single agents or combinations of multiple agents to reach desired effects of analgesia plus anxiolysis. For successful imaging, patient immobility is the key. Immobility can be achieved by moderate to deep sedation or minimal anesthesia. On the other hand, moderate sedation, deep sedation, and minimal anesthesia can be all utilized for emergency department procedures.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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53 CHAPTER

Pain Management in Emergency Department

Radhika Rani Chandra, Devendra Richhariya

INTRODUCTION

Pain is an unpleasant and emotional experience, originating in normal or potential damaged tissues. Pain is the most common presenting complaints (75–85% as primary complaints) in emergency department and most undertreated condition also. In our experience, in most of the cases, treatment of pain improves the patient satisfaction. *Pain management is urgently indicated in* acute subarachnoid headache, acute myocardial infarction, acute aortic dissection, acute pancreatitis, acute appendicitis, acute renal and ureteric colic due to calculus, ectopic pregnancy, anal fissure, trauma with head injuries, trunk and limb fractures, joint dislocations, electrical and thermal burns, acute rheumatoid arthritis in joints, analgesia during chest tube insertion, and reducing fractures and dislocations. Pain should be assessed by various available scales and which is also helpful in documenting the drug response. *It is important to note the potential causes for pain control failure in emergency department,* e.g., failure to assess pain, failure to document pain, failure to implement pain guidelines, and failure to meet patient expectation. Emergency physician should have good knowledge of the analgesics and anesthetics, their contraindications, side effects, administration methods, and monitoring requirements. Uncontrolled pain is a medical emergency and considered as quality parameter also.

Various terminologies are used related to pain:

- *Allodynia*—pain from stimulus that normally not give rise pain.
- *Amnestic*—drugs that inhibit formation of memories.
- *Local anesthesia*—drugs that make area insensitive to pain by injecting agent locally.
- *Analgesia*—agents that cause pain relief.
- *Hypnotic*—agents that induce onset of sleep.
- *Nociceptor*—pain sensitive receptor which is also responsible for pain transmission.
- *Noxious stimulus*—potentially damaging stimulus
- *Procedural sedation*—agents that used during painful procedure that causes sedation and amnesia.
- *Somatic pain*—localized in the body tissues such as nociceptive pain and neuropathic pain
- *Psychotic pain* is pain with no known physical cause.
- *Acute pain* is protective mechanism that alerts the individuals to harmful objects, sudden in onset, and relief after removal of its mediators that stimulate receptors, acute pain stimulates, autonomic nervous system causes increased heart rate and respiratory rate, elevated blood pressure, pallor or flushing, dilated pupils, diaphoresis, increase in blood sugar, and gastric acid secretion decrease in gastric motility. Acute pain also causes fear, anxiety, and general sense of unease.
- *Chronic pain* develops gradually, persistent or intermittent chronic pain can produce depression and sleeping disorders.

PATHOPHYSIOLOGY

Pain is spontaneous physiologic response to noxious stimuli which is expressed (pain) by various behavioral, cognitive, and sociocultural parameters. Pain experience by any individual is variable and depends on various factors such as present and past medical history, cognitive state, emotional maturity, and patient surrounding environment. So assessment of pain by another person is generally inaccurate and for quantification of pain, self-reporting is considered gold standard. Nociceptors, C fibers, and A-delta fibers of peripheral nervous system respond to noxious stimuli and initiate sensation of somatic pain, by sending neuronal discharge to dorsal horn of the spinal cord (**Fig. 1**). All the inputs from the various peripheral nerves and sensory stimuli are integrated, modulated, and transmitted to brain (hypothalamus, thalamic nuclei, limbic system, and reticular activating system from the spinal cord) from the spinal cord. In the brain, again processing and integration are done and then perception of pain is generated. Visceral pain pathway is more complex than somatic pain (easily localized) and that's why poorly localized. There are four types of opioid receptors are present in spinal cord and brain (delta, kappa, mu, and nociception) and opioid analgesic work by binding to these receptors. Stimulation of μ1 receptor causes supraspinal analgesia. Stimulation of μ2 receptors causes euphoria miosis respiratory depression, and decreases GI motility also. Delta receptor stimulation produces analgesia. Kappa receptors stimulation produces dysphoria dissociation, delirium, and diuresis. None of the opioid receptor is associated with addiction.

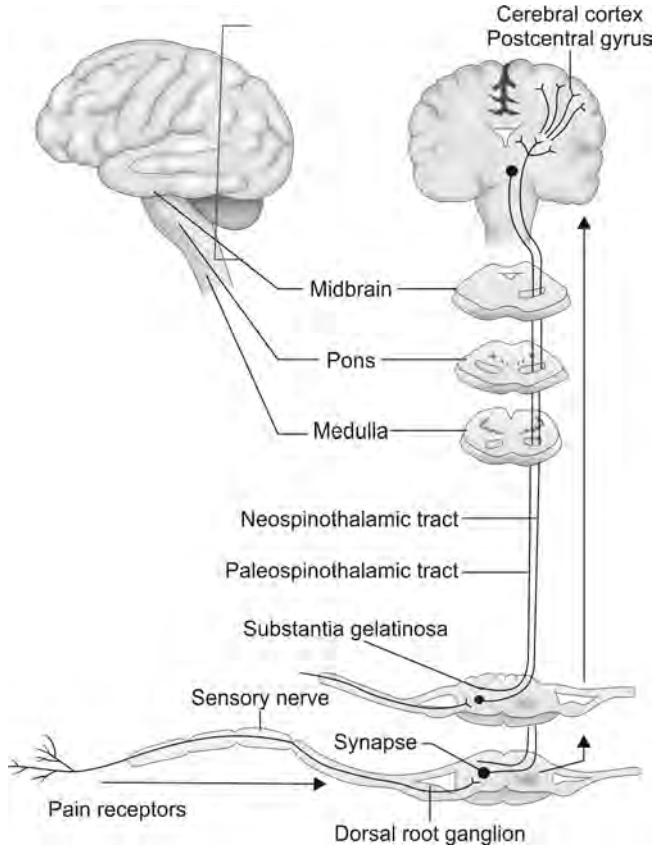


FIG. 1: Pathophysiology of pain.

ASSESSMENT OF PAIN IN EMERGENCY DEPARTMENT

A simple and straightforward method should be adopted when dealing with assessment of acute pain and as a symptom of trauma or disease. Intensity of pain and location of the pain are the main two components in the assessment of pain in clinical practice. However, other important aspects of acute pain, in addition to pain intensity at rest, need to be defined and measured when acute pain treatment is planned. Assessment and treatment of chronic pain or long-lasting pain is more challenging. Multiple tools have been developed for different types and subtypes of acute as well as chronic pain in order to assess qualitative aspects of pain and its impact on function. Multiple studies indicate that pain assessment still a challenge because pain is a subjective, personal, and private experience. Assessment of pain is more challenging for emergency physician if they find difficulty, in communicating with the patient those suffering with cognitive impairment and dementia.

The main objectives of assessment of pain are:
- Recognition of pain and measurement of its intensity
- Treatment adapted to the intensity, the patient and the pathology
- Systematic and regular reassessment permitting an appreciation of the efficiency of the treatment

Assessment and documenting pain required in order to improve management of pain. The points to be considered while assessing pain are:
- Cognitive ability
- Environment (hospital)
- Anxiety
- Cause of pain (e.g., postoperative)

A pain assessment should be performed during admission of a patient. Points to consider:
- Pain history
- Location of pain
- Intensity of pain
- Cognitive development and understanding of pain

When to assess pain?
- Pain scores should be documented for all patients at least once per shift in flow sheet.
- Patient with pain should have pain scores documented more frequently.
- Patient who is receiving oral analgesia should have pain scores documented at least 4 hourly during waking hours.
- Patient noncomplex analgesia such as intravenous opioid and/or ketamine, epidurals, or regional analgesia should have hourly pain and sedation scores documented.
- Document assessment of pain before and after analgesia, and also document effect of analgesia

Assessment of Chronic Pain

Assessment and management of chronic pain are more demanding and rewarding because chronic pain has a major impact on physical, emotional, and cognitive function, on social and family life. A comprehensive assessment of chronic pain requires documentation of (1) history of pain, (2) physical examination, and (3) appropriate diagnostic tests. The pain specific history must be taken about location, intensity, pain modifiers, and possible pathophysiological and etiological issues.

(1) Site of the pain, (2) intensity is the pain, (3) description of the pain (e.g., burning, aching, stabbing, shooting, and throbbing). (4) How did the pain start? (5) What is the time course of the pain? (6) Relieving and aggravating factors of the pain? (7) How does your pain affect your sleep? Your physical functions? Your ability to work? Your family life? Your social life? (8) What treatments have you received? Effects of treatments? Any adverse effects? (9) Are you depressed? (10) Are you worried about the outcome of your pain condition and your health? Physical examination—general physical examination, pain specific evaluation; neurological examination; musculoskeletal system examination; psychological assessment. Several reliable and valid assessment tools are developed for *chronic pain assessment* are:
- The brief pain inventory
- The McGill pain questionnaire and the short-form McGill pain questionnaire
- The Massachusetts general hospital pain center's pain assessment form
- Neuropathic pain screening tools

ASSESSMENT TOOLS FOR PAIN

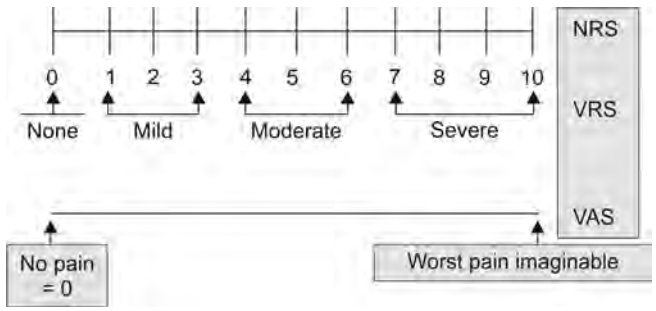
Assessment of Intensity of the Pain

The well-known *Visual Analog Scale (VAS) and Numeric Rating Scale (NRS)* for assessment of pain intensity, well known and are sensitive in assessing acute pain. VAS and NRS are both superior to a four-point *Verbal Categorical Rating Scale (VRS).* They function best and display patient's subjective feeling of

present pain intensity. These scales may be used to record average pain over the last 24 hours, or during the last week. These tools can be used to assess functional impact of pain and also used to assess "unpleasantness" of pain. A study using a large number of patients and simultaneous recordings of pain intensity on VAS, NRS, and VRS scales demonstrated the superiority of the VAS and NRS over VRS (**Fig. 2**). For children, *FLACC (Face, Legs, Activity, Cry, and Consolable) scale* (0–7 years) (**Table 1**) and children >7 years, *Wong–Baker Faces Pain Scale* pain scales (**Fig. 3**) with happy and unhappy faces are well validated. Behavioral pain scale (**Table 2**) is used for assessment of pain in mechanically ventilated, unconscious, or comatose patient. Various pain scales are summarized in **Table 3**.

PHARMACOLOGIC THERAPY FOR PAIN

Drug therapy is the mainstay of pain management in emergency department. Knowledge of appropriate pharmacologic agents for managing the intensity of pain is the key. Ideal pharmacologic agent should be easy to administer with appropriate quality and safety measures. Pain is also associated with anxiety, "suffering" components and loss of control over functions. Adjunctive drug therapy such as anxiolytics should also be also supported by reassurance, and providing information about the problem to the patient. Stepwise approach can be adopted in which pain management is started with low potency drug even if pain is acute and intensity is more. Assess the pain after specific period and escalate the therapy. The stepwise approach makes the patient suffering for prolong period of time. So, another approach is select the appropriate drug therapy initially on the basis of mild, moderate, and severe intensity pain. Mild-to-moderate intensity pain is treated with nonsteroidal anti-inflammatory drugs (NSAIDs) (nonopioids). Severe nociceptive pain should be treated with systemic opioids. Parenteral NSAIDs may control the pain of biliary and renal colic but combination of NSAIDs with opioids analgesics gives better results. Some adjuvants drug therapy is also required along with opioids which reduces the side effects and also reduces the dose requirement of opioids (**Table 4**). Antidepressants and anticonvulsants are also used to treat the pain especially neuropathic pain of postherpetic trigeminal neuralgias (**Table 5**). Topical administration of medication especially at the injury site or inflammation provides pain relief with minimum systemic drug absorption and lower incidence of adverse drug reaction (**Table 6**). In short, the implementation of analgesia is based on two steps—Step 1: Pain relief as quickly as possible, it continues until the goal is not reached; and Step 2: Maintaining the pain relief with appropriate prescriptions.



(NRS: numeric rating scale; VAS: visual analog scale)

FIG. 2: Commonly used one-dimensional pain intensity scales: The 11-point NRS, the VAS from no pain (¼0) to worst pain imaginable [¼10 (or 100)] and the four-point categorical verbal rating scale (VRS).

TABLE 1: FLACC—Pediatric Pain Scale for age 0–7 years.

Parameters	*0*	*1*	*3*
Face	No expression	Occasionally grimace	Frequent to constant quivering chin
Legs	Normal position/ relaxed	Uneasy restless tense	kicking/leg drawing
Activities	Lying quiet	Squirming shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry	Moans whimpers	Crying steadily
Consolable	Content relaxed	Reassurance hugging	Difficult to console
Interpretation: 0 = no pain, 1–3 = mild pain, 4–7 = moderate pain, 8–10 = severe pain			
FLACC—F: face, L: leg, A: activities, C: cry, C: consolable			

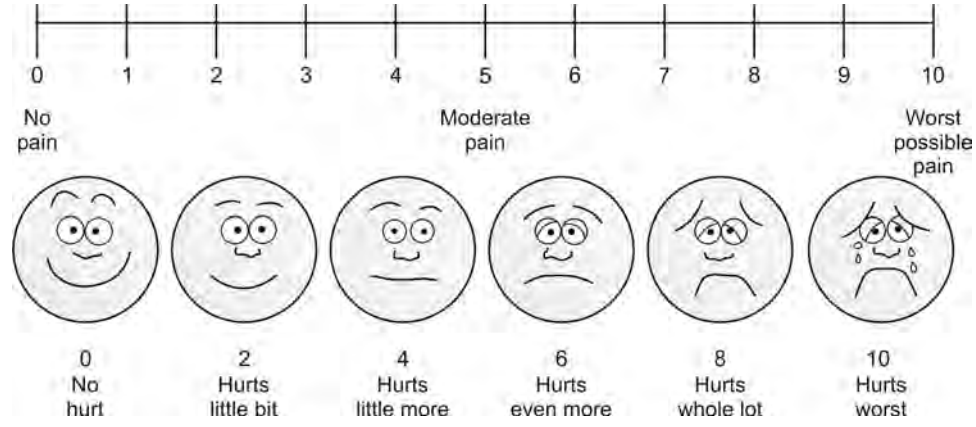

0 1 2 3 4 5 6 7 8 9 10
No pain
Moderate pain
Worst possible pain
0 No hurt
2 Hurts little bit
4 Hurts little more
6 Hurts even more
8 Hurts whole lot
10 Hurts worst

FIG. 3: Wong–Baker Faces Pain Scale (Age > 7 years).

TABLE 2: Behavioral pain score for unconscious/comatose mechanically ventilated patient.

Facial expression	Relaxed	1
	Partially tighten (brow lowering)	2
	Fully tighten (eyelid closing)	3
	Grimacing	4
Upper limb	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation most of time	2
	Fighting with ventilator	3
	Unable to control ventilation	4

Precautions

Overdoses and adverse effects can be avoided by choosing appropriate initial dose and titrating it till desired effects then maintenance therapy can continue. Respiratory depression and decreased level of consciousness can occur excessive dose without titration. Short duration of hypotension may occur with first dose of medication due to histamine release. Initial dose should be decreased in with comorbidities such as altered mental status hemodynamic instability, respiratory problems, and polytrauma.

Pain management in elderly is a challenge because they are more sensitive to analgesic effects of opioids, higher peak and longer duration of effects. Elderly are more at risk of adverse effects due to comorbidities and associated polypharmacy. Elderly are the more prone for sedation respiratory depression and cognitive and neuropsychiatric symptoms, thus initial IV opioids dose can be reduced to half.

TABLE 3: Pain scales.

Pain scale name	***Description***	***Validity***	***Comments***
Alder Hey Triage Pain Score (emergency care triage of pediatric patients)	Observational scale completed by staff, five items each scored 0–2 with total score 0–10 possible	Validated for inter-rater variability1	Easy to administer, takes about 10 min, patients need not be able to communicate
Behavioral Pain Scale (BPS) (critically ill-sedated adult patients)	Observational scale completed by staff, scores from 3 to 12	Validated for inter-rater variability and reliability	Validated for use with patients with a low level of consciousness due to head trauma
Brief Pain Inventory (BPI) (adult cancer patients	Self-report of pain intensity (sensory dimension) and how pain interferes with patient's life (reactive dimension)	Validated and translated into numerous languages	Has been validated for use in patients with chronic and nonmalignant pain and osteoarthritis
Clinical Global Impression (CGI) (psychiatric patients)	Observational assessment of patient's global function before and after study medication; it measures psychopathology	Validated and reliable	Easy to administer
Critical Care Pain Observation Tool (CPOT) (Nonverbal critically ill adults)	Observational scale of behaviors, facial expressions, body movements, and muscle tension	Moderate to high inter-rater reliability and significant correlations between CPOT and self-reported pain scales 7; sensitivity 86%, specificity 78%	For intubated patients, compliance with ventilator is assessed; for nonintubated patients, vocalization is assessed
COMFORT Scale [children unable to report pain (has been evaluated in patients age 12–36 months)]	Observational care completed by staff evaluating alertness, anxiety, respiratory response, crying, movement, muscle tone, and facial tension	High inter-rater reliability	Requires staff training
Visual Analog Scale (VAS) (adult pain patients)	Self-report by patient who selects a point on a 100-mm line that indicates pain level; in some cases, a percentage may be used (0 is "no pain" and 100% is "worst pain imaginable")	Validated, familiar, and among the most frequently used pain scales in the US	Easy to administer, fast, and easy for patients to understand but measures pain intensity only
Verbal Rating Scale (VRS) (adult and pediatric pain patients)	Self-report by patient to verbal questions of healthcare professional, asking them to describe their pain using five categories (no pain, mild pain, moderate pain, severe pain, and unbearable pain)	Correlates highly to VAS	Measures pain intensity only and is subject to variations depending on how each patient understands "mild," "moderate," and "severe" pain

Continued

Continued

Pain scale name	Description	Validity	Comments
FACES (Wong-Baker) [pediatric patients (age 3–7) treated for acute pain in emergency department]	Self-report using 6-item ordinal scale made up of 6 faces showing no pain (smiling face) to worst pain imaginable (grimace)	Validated with good agreement between FACES and visual analog scale	May also be used for adults when there is a language barrier
Numerical Rating Scale (NRS) (adult and pediatric pain patients)	Self-report on scale of 0–10 with 0 meaning "no pain at all" and 10 "the worst pain imaginable"	Reliable and validated	Widely used minimal training required, easy for patients to understand; measures pain intensity only
Dallas Pain Questionnaire (DPQ) (adult patients with chronic spinal pain)	16-item self-report measuring pain intensity, function, anxiety, depression, and social interest	Good external reliability and internal consistency	DPQ is divided into two sections called "factors"; factor 1 represents functional activities, factor 2 emotional capacities
Descriptor Differential Scale (DDS) (ALERT and nonimpaired adults)	Self-report in 12-item questionnaire	Good reliability and is sensitive to even small changes in pain intensity	Easy for patients to use but requires some training for healthcare team to interpret
Lequesne-Algofunctional Index (adult pain patients with circadian types of pain)	Self-report in 10-item questionnaire that puts pain in temporal context (pain at night, upon rising) and situations (pain standing, pain walking, and so on)	Validated	Easy to administer, takes about 10 min, and is well suited for pain that fluctuates over course of day
Mankowski Pain Scale	Self-report on 0–10 scale with descriptions to help better quantify pain	Validated for chronic pain patients	Developed by Andrea Mankowski, a chronic pain patient
McGill Pain Questionnaire (MPQ) (adults with various pain syndromes)	Self-report, 20 items grouped as sensory, affective, evaluative, and miscellaneous; patients score each 0–5. The Pain Rating Index (PRI) is the sum of the rank values	Validated and designed to better capture the subjective experiences of pain	Also rates the Present Pain Index (PPI) as a separate scale (0–5)
Neck Pain and Disability Scale (NPDS) (adults with cervical pain syndromes)	Self-report of 20 items as visual analog scales with descriptors, describing different aspects or behaviors associated with the neck	Reliable, internally consistent, correlates well with other scales	
OSWESTRY Disability Index (adults with low back pain)	Self-report of pain intensity and function (disability)	Validated and correlates highly with the Roland-Morris Disability Index	Fast and easy to administer, easy for patients to understand
Palliative Care Outcomes Scale (PCOS) (adult palliative cancer patients)	Two nearly identical tools: a self-report by the patient and corresponding observational report by staff; documents patient's well-being over past 3 days in physical, psychological, and spiritual domains	Validated with good internal reliability; good agreement between patients and staff on many items	May be useful in better determining prospective care for end-of-life patients
Pediatric Pain Questionnaire (PPQ) (pediatric pain patients ≥6 years)	Self-report on visual analog scale of present pain, worst pain intensity, and disease severity	Good correlation between PPQ and healthcare professionals' observations	Easy to administer
Roland-Morris Back Pain Questionnaire (adults with low back pain)	Self-report, 24-item checklist in which patients are asked which statements apply to them that day; all items have equal weight (1 point) and score is total	Validated and correlates highly with the OSWESTRY Disability Index	Short, simple, easy to use; each item on the scale begins, "because of my back pain…"
Support Team Assessment (STAS) (adults in palliative care)	Self-report and corresponding observational report (to be completed by family members or healthcare professionals)	Measures prospective outcomes	When observational scales were compared to self-reports, observations by healthcare professionals were closer to patient self-reports than observations by family members

Continued

Continued

Pain scale name	*Description*	*Validity*	*Comments*
Checklist of Nonverbal Pain Indicators (CNPI) (cognitively impaired adult patients)	Observational test completed by staff based on specific behaviors, restlessness, vocalization	Inter-rater reliability 93%	Requires staff training
Discomfort in Dementia (DS-DAT) (adults with dementia or Alzheimer's disease)	Observational 9-item tool for completion by staff over 5-min assessment period	Inter-rater variability exists in 3 of the 9 items	Requires staff training to administer accurately
Edmonton Symptom Assessment System (palliative care patients, typically end-of-life cancer patients)	Twice-daily assessment using 8 visual analog scales to be completed by patient alone or by patient with assistance (from nurse or family member)	Validation evidence is not robust	Data from the 8 scales are transferred to a graph; the sum of all scores is the "symptom distress score" has been translated into several languages

TABLE 4: Pharmacologic management of pain.

Opioids analgesic therapy		
Drugs	***Initial dose for adult***	***Comments***
Morphine	• 2–6 mg intravenous • 10 mg IM/SC	Nausea vomiting transient hypotension
Fentanyl	50–100 µg IV	Less CV depression than morphine
Meperidine (pethidine)	• 25–50 mg IV • 50–100 mg IM/SC	With MAO inhibitors may precipitate serotonin syndrome if taken within 14 days
Tramadol	50–100 mg in 100 mL NS IV over 30–45 min as infusion	CNS side effects are common
Opioid agonist-antagonist analgesic		
Butorphanol	1 mg IV or 2 mg IM every 4 h	Sedation dizziness nausea
Pentazocine	30 mg IV/IM/SC every 4–6 h	CNS side effects
Adjunctive medications with opioid		
Ondansetron	4–8 mg IV/PO	Can prolong QT interval
Prochlorperazine	5–10 mg IV/IM/PO	Can cause extrapyramidal reactions
Promethazine	25–50 mg IV/IM	Can cause extrapyramidal reactions
Metoclopramide	5–10 mg IV/IM/PO	Can cause extrapyramidal reactions
Nonopioids analgesics		
Acetaminophen (paracetamol)	• 325–1,000 mg PO every 4–6 h • >50 kg 1 g IV every 6 hourly • <50 kg 15 mg/kg IV every 6 hourly	• Liver dysfunction • Maximum dose not >3 g/day
Aspirin (acetylsalicylic acid)	325–650 mg every 4 hourly	GI irritation, mucosal bleeding, platelet dysfunction tinnitus, CNS toxicity
Ibuprofen (NSAIDs)	400–800 mg PO every 4–6 hourly	GI upset, platelet and renal dysfunction. Bronchospasm
Naproxen (NSAIDs)	250–500 mg PO every 8–12 h	GI upset, platelet and renal dysfunction. Bronchospasm
Indomethacin (NSAIDs)	25–50 mg PO every 8 hourly	GI upset, platelet and renal dysfunction. Bronchospasm

(CNS: central nervous system; CV: cardiovascular; GI: gastrointestinal; MAO: monoamine oxidase inhibitor; NSAID: nonsteroidal anti-inflammatory drug)

Care must be taken while using the opioids and other analgesic in patient with impaired hepatic and renal functions because most of them are metabolized by kidney and liver. Hydromorphone and fentanyl are preferred choice in renal dysfunction patient. Low-dose analgesics in severe hepatic dysfunctions minimize the risk of overdose.

Patient with respiratory dysfunction, e.g., chronic obstructive pulmonary disease (COPD), cystic fibrosis, and various neuromuscular disorders affecting respiratory functions (muscular dystrophies and myasthenia gravis) are monitored carefully as they are at risk of severe respiratory depression after opioids analgesics.

TABLE 5: Drug therapy for neuropathic pain.

Drugs	*Initial dose*	*Maximum dose*	*Uses*
Amitriptyline	25–50 mg PO (evening)	10–50 mg/day, maximum 150 mg/day	For chronic pain
Carbamazepine	100 mg PO twice/day	• 200–400 mg PO twice/day • Maximum 1,200 mg/day	Trigeminal neuralgia
Oxcarbazepine	300 mg PO/day	450–1,200 mg PO twice/day	Trigeminal neuralgia
Gabapentin	• For neuropathic pain 300 mg PO three times/day • For postherpetic neuralgias 300 mg PO on day 1 then • 300 mg PO twice/day on day 2,300 mg PO thrice/day • (1,800–3,600 mg/day) maximum 3,600 mg/day		• Neuropathic pain • Postherpetic neuralgias
Pregabalin	50 mg PO three times/day or 75 mg PO twice daily	• 150 mg PO twice/day or 100 mg PO three time/day • Maximum 600 mg/day	• Neuropathic pain • Postherpetic neuralgias
Duloxetine	30 mg PO once daily	Maximum 60 mg PO/day	Diabetic neuropathy

TABLE 6: Topical agents for pain management.

Agents	*Comments*
Diclofenac	1% gel or 1.3% topical patch, can be apply on knee ankle elbow shoulder joints up to 4 times/day
Ibuprofen	5% gel can be applied 4 times/day on affected area
Ketoprofen	2.5% apply on affected area until absorbed 2–4 times/day
Lidocaine	5% gel and 5% topical patch apply thick layer over affected area. In 30–60 min numbness will develops. Use patch only once for 12–24 h
Capsaicin	• 0.025 and 0.075% cream and 0.1% gel 8% patch • Apply cream and gel on affected area and rub until get absorbed • Patch only for postherpetic neuralgias
Methyl salicylate	10% patch apply only one patch at a time on affected area only for 8–12 h, maximum 2–3 patch/day

ANESTHETIC AGENTS IN PAIN MANAGEMENT

Local Anesthesia

Pain arising from the acute injury and the procedures in the emergency department can adequately be controlled by local anesthetic. Route of administration of local anesthetic may be topical, subdermal, or infiltration around the peripheral nerves (regional anesthesia).

Esters and amides are the two classes of the local anesthetics (**Table 7**), affect the smaller nerve fibers and act by reversible blocking the sodium channels and inhibit the propagation of nerve impulse. Reduction in pain and temperature occurs first followed by loss of touch, deep pressure sensation, and motor functions in the last. Appropriate selection of anesthetic agents is important and depends on their onset of action, duration of anesthesia, and potential systemic toxicity by local anesthetics. Systemic toxicity of local anesthetics is dose related and sodium channel blockade primary affect brain and heart. Toxicity may range from minor neurological symptoms to refractory seizure and cardiovascular collapse. Neurological toxicity seizure should be treated with benzodiazepine. Cardiac depression and or cardiac arrest should be treated with intravenous 20% lipid emulsion specially bupivacaine (high lipid solubility)-induced toxicity (20% lipid emulsion 1.5 mL/kg over 1 min followed by 0.25 mL/kg continued for 10 min after hemodynamic stability occurs). Standard resuscitative measures should be applied for cardiac arrest, and smaller doses of epinephrine are recommended and vasopressin and lidocaine should be avoided. Prilocaine and benzocaine result in cyanosis, if methemoglobin concentration exceeds 1.5 g/dL. Prilocaine and benzocaine can cause oxidation of ferrous iron of normal hemoglobin into ferric form creating the methemoglobin.

Topical Anesthesia

There are three major situations for use of topical anesthesia before any dermal instrumentation (*on intact skin), intact mucosa* and before wound repair *on open skin.* For suturing of any dermal laceration, effect of topical anesthesia is almost equivalent to local anesthesia. Mixture of lidocaine 2.5% + prilocaine 2.5% was the first topical agent used for intact skin. Liposome-encapsulated tetracaine, liposome-encapsulated lidocaine, and tetracaine gel are as effective as lidocaine and prilocaine mixture. For open dermis, mixture of lidocaine, epinephrine, and tetracaine is used (lidocaine 4% + epinephrine and tetracaine 0.5%).

Intradermal and Subdermal Anesthesia

Intradermal injections of local anesthesia are painful, produce visible wheals, and raise the surface and useful for removing the cutaneous lesion. Subdermal injection is less painful, slower onset of action, and most common method used in emergency department for delivering local anesthesia in suture of clean laceration or as a field block in contaminated wound.

TABLE 7: Local anesthetic agents.

	Agents	*Concentration for subdermal use*	*Concentration for regional anesthesia use*	*Onset (min)*	*Comments*
Amides	Bupivacaine	0.50–0.75%	0.25–0.50%	2–10 min	High lipid soluble and high protein binding
	Levobupivacaine	0.25%	0.50%	10–20 min	High lipid soluble and high protein binding
	Lidocaine	0.5–1.0%	1–2%	<1 min	Medium lipid soluble and medium protein binding
	Mepivacaine	0.5–1.0%	1–2%	3–20 min	Low lipid soluble and medium protein binding
	Prilocaine	4%	NA	5–6 min	Medium lipid soluble and medium protein binding
Esters	Procaine	0.25–0.50%	0.5–2.0%	5 min	Low lipid soluble and low protein binding
	Chloroprocaine	1–2%	1–2%	5–6 min	Low lipid soluble and low protein binding
	Tetracaine	NA	0.2–0.3%	6–7 min	High lipid soluble and high protein binding

REGIONAL ANESTHESIA (PERIPHERAL NERVE BLOCK)

Regional anesthesia is a technique in which local anesthesia is infiltrated adjacent to peripheral nerve (also known as nerve block). Regional anesthesia or nerve block is used for complicated fracture and dislocation, laceration, debridement, and abscesses. Serious complication by regional anesthesia is reduced with adopting careful technique. Adequate anesthesia reduces patient anxiety, and provides greater patient satisfaction. Regional anesthesia on extremities and for laceration repair provides better pain control than subdermal infiltration of anesthetic. Regional anesthetic also eliminates wounds distortion caused by large volume subdermal injection. Pain associated with peripheral nerve block can be reduced by applying topical anesthetics before the procedure.

Local anesthetic for peripheral nerve block should be selected on the basis of onset of clinical effect, duration of analgesia, and toxicity risk. Lidocaine is most popular agents while bupivacaine, levobupivacaine provides longer duration of action. Peripheral nerve block requires (lidocaine—10–20 min and bupivacaine 15–30 min) time to achieve optimal analgesia. Pain and temperature are affected first followed by deep pressure and motor function in the last.

In emergency department, regional nerve block is performed by landmark technique but anatomic variation is the major disadvantage in this technique. Thus two other techniques, peripheral nerve stimulator (using electrically insulated needles) and ultrasound guidance are used to locate the peripheral nerve. Ultrasound-guided procedure shortens the procedure time, reduces the risk of vascular injury, and enables the blocks with using lower anesthetic dose. Using the high-frequency linear array transducer nerve appear as white honeycomb structure in short axis and hyperechoic in long axis. Needle can be visualized as hyperechoic bright white structure in short and long axis both helpful in injecting the anesthetic agents around the target nerve.

NONPHARMACOLOGIC INTERVENTION FOR PAIN

Role of nonpharmacologic intervention for pain is limited in emergency department. Application of hot or cold packs, immobilization, and limb elevation of injured limbs are common nonpharmacologic intervention in emergency department. Other technique can be applied after discharge from the emergency department, e.g., cognitive behavioral technique for mild pain and anxiety. In such technique, reassurance, explanation, and relaxation breathing exercises are used. Nonpharmacologic interventions are the important adjunct in managing the moderate to severe pain. Skilled person can teach these techniques to patient. Other less commonly used techniques are transcutaneous electrical nerve stimulation and acupuncture in which no need for IV access and no systemic effects occur.

SUMMARY

Pain is the most common presentation in emergency department. Pain management should be priority. Over the last decade, various methods for assessment of pain and management strategies are developed. Adequate pain treatment in emergency improves the quality and patient satisfaction. Every emergency physician should be expert in efficient and effective management of painful condition.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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Point-of-care Ultrasound in Resuscitation

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CHAPTER

Won-Jun Kuk, Mohamed Moheb El Abd, Tiffany Fong

INTRODUCTION

Shock is a life-threatening condition defined by the inadequate oxygenation and perfusion of tissues relative to their metabolic demand. Hypotension is frequently correlated, but its presence is not required to make a diagnosis of shock. A number of conditions may lead to shock, and while they are all associated with high rates of morbidity and mortality, they differ in their management strategies. Because prolonged shock and hypotension have been linked to poorer outcomes, the early identification of shock etiology and initiation of the most appropriate interventions are vital in the care of such patients. Shock has traditionally been categorized into four subtypes:

1. *Hypovolemic shock* is caused by the loss of intravascular volume. This may result from traumatic hemorrhage; nontraumatic hemorrhagic conditions such as gastrointestinal bleeding or ruptured ectopic pregnancy; or volume loss from vomiting, diarrhea, poor oral intake, increased insensible fluid losses, or renal losses (e.g., diabetes insipidus or hyperosmolar hyperglycemic syndrome).
2. *Distributive shock* is a state of relative hypovolemia from the pathologic redistribution of intravascular volume. This is frequently seen in sepsis, due to both vasodilation and increased vascular permeability that decrease effective circulating volume. Anaphylaxis and neurogenic shock are additional examples.
3. *Cardiogenic shock* is caused by a critical reduction in cardiac function and forward flow, leading to end-organ hypoperfusion. Cardiac dysfunction may be related to myocardial disorders (e.g., acute coronary syndrome, cardiomyopathy, and myocarditis), dysrhythmias (both tachycardias and bradycardias), and mechanical causes (e.g., valvular dysfunction, thrombi, and tumors).
4. *Obstructive shock* results from an obstruction of the heart or great vessels. It is the rarest cause of shock, but requires immediate intervention directed at the specific underlying cause. Examples include pericardial tamponade, massive pulmonary embolism, and tension pneumothorax. Though early identification and treatment of the etiology of shock are important to reduce morbidity and mortality, this is often a challenging task. Point-of-care ultrasound (POCU) has emerged as an important tool to support clinical decision making at the bedside. A sonographic physiologic assessment for shock, often described as the *RUSH examination* (rapid ultrasound in shock), has gained popularity. This framework organizes the potential etiologies of shock into three broad, sonographically assessable systems that drive hemodynamics, simplified as:
   i. *The pump*: Cardiac function
   ii. *The tank*: Intravascular volume status
   iii. *The pipes*: Vascular emergencies in the venous and arterial system

Careful evaluation of these components can enable clinicians to quickly identify the underlying etiology of shock in patients with undifferentiated hypotension and subsequently allow early initiation of the most appropriate treatment.

STEP 1: PUMP

The first step in approaching a patient in shock will be determining their cardiac status, otherwise termed "the pump." This evaluation has three key questions which can be rapidly assessed with a focused transthoracic bedside echocardiogram:

- Is there a pericardial effusion compressing the heart, causing mechanical obstruction to forward flow and leading to obstructive shock (i.e., cardiac tamponade)?
- What is the global contractility of the heart? Does the left ventricle have reduced ejection fraction, suggestive of cardiogenic shock, or is the heart hypercontractile, suggesting hypovolemic or distributive shock?
- Is there right heart enlargement that may suggest a massive pulmonary embolism causing an obstructive shock?

The focused echocardiography is performed with the phased array transducer. It comprises four views: (1) Parasternal long-axis, (2) parasternal short-axis, (3) apical four-chamber, and (4) subxiphoid. **Figure 1** demonstrates probe positioning. The parasternal views are obtained with the transducer placed just left of the sternum; the probe marker faces the patient's right shoulder for the long-axis view, then is turned 90° to the left shoulder to obtain the short-axis view. The probe may need to be adjusted across several intercostal spaces to determine the optimal window of visualization. The apical four-chamber

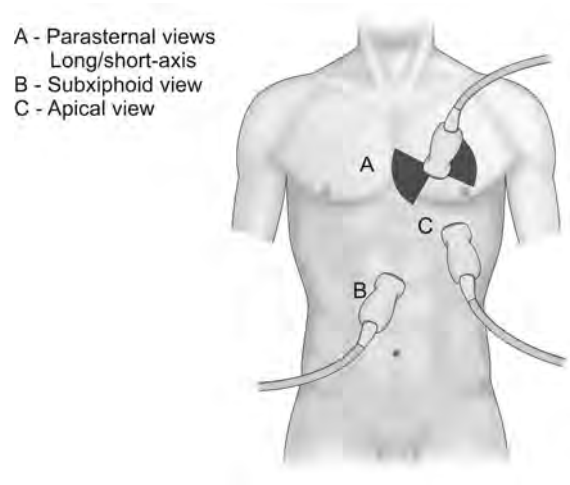


FIG. 1: Sonographic views for "pump" evaluation.

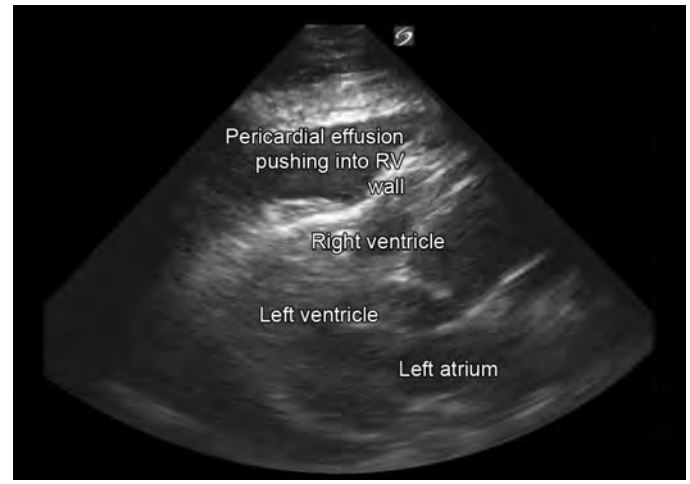


FIG. 2: Parasternal long-axis view of pericardial tamponade with the effusion collapsing the right ventricular wall during diastole.

view is best evaluated by placing the probe below the nipple line at the point of maximal impulse (PMI) with the probe marker facing the patient's left. The subxiphoid view is obtained with the probe flat against the abdomen inferior to the xiphoid tip of the sternum with the marker facing the patient's left. These four views each offer a different perspective of the heart to assist the clinician in answering each of the focused questions above.

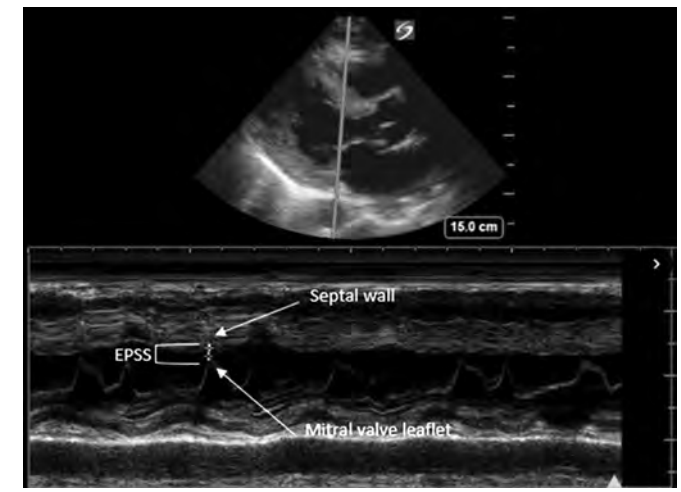
Pericardial Effusion

The first step is to evaluate for a pericardial effusion. Studies have shown that emergency physicians can reliably identify the presence of pericardial effusion even with limited training. Effusions can vary in echogenicity and appear anechoic if they contain blood or simple fluid, or more echogenic if blood is clotted or in complex effusions. Effusion size can also vary from a thin stripe layering posteriorly or inferiorly in dependent portions of the pericardial space to larger effusions that can wrap circumferentially around the heart. The pericardium is a thick, fibrous structure, which can allow even relatively smaller effusions to produce tamponade physiology when accumulation is acute and rapid. On the other hand, chronic pericardial effusions can grow to significant volumes as the pericardium stretches to adjust to the slow increases in volume, and thus avoid hemodynamic collapse.

If a pericardial effusion is identified, the next step will be to assess for tamponade physiology. Cardiac tamponade results when the pericardial effusion exerts sufficient pressure to restrict the heart from fully expanding and filling during diastole. The right side of the heart is a lower pressure system and is therefore more vulnerable to external pressure than the left side of the heart. Therefore, tamponade physiology can be assessed by evaluating for collapse of the right atrium during systole or right ventricle during diastole. This will appear as an inward deflection of the free wall of the right-sided chambers, sometimes described as "a man jumping on a trampoline" (**Fig. 2**). Finally, the inferior vena cava (IVC) should also be evaluated. Because tamponade is an obstructive process that reduces forward flow, the IVC will become plethoric as right heart filling pressures increase.

Global Left Ventricular Contractility

The next step is to assess the global contractility of the heart, or the ejection fraction. This can be achieved by "eyeballing"



(EPSS: E-point septal separation)

FIG. 3: Normal EPSS measurement in parasternal long-axis view.

or visually estimating left ventricular (LV) contractility through observation of the excursion of the endocardium and thickening of the myocardium through systole and diastole. Cardiac contractility can be broadly categorized as normal, reduced, severely reduced, or even hyperdynamic (an above normal ejection fraction where the LV walls may be seen completely contracting into the ventricular cavity). While these determinants may appear subjective, studies have shown that emergency physician estimates of LV contractility correlated well compared to those measured by cardiologists, with a correlation coefficient of 0.86.

In addition, using a parasternal long-axis view, the operator can observe the movement of the anterior leaflet of the mitral valve toward the interventricular septum during diastole, termed the E-point septal separation (EPSS). Good LV contractility is implied by a mitral leaflet that opens vigorously during diastole, and closely approaches (or even touches) the septal wall. This can be visually estimated or objectively measured using M-mode. In the parasternal long-axis view, an M-mode cursor is placed at the tip of the anterior mitral valve leaflet. The M-mode tracing will produce characteristic waves of the leaflet motion, allowing measurement of the distance between the valve during its maximal opening and

the interventricular septum (**Fig. 3**). As cardiac contractility decreases, this distance between the tip of the mitral valve leaflet and septum will increase. The EPSS is normally <7 mm. An EPSS >1 cm correlates with lower ejection fraction.

Knowledge of LV contractility is vital to medical decision-making during resuscitation. A reduced ejection fraction is helpful in diagnosing a cardiac etiology of shock (e.g., acute coronary syndrome and/or cardiogenic shock). A hypercontractile or hyperdynamic heart can be seen in distributive and hypovolemic shock. Furthermore, knowing the squeeze of the pump provides valuable data related to the heart's ability to tolerate additional fluid. Finally, repeated bedside echocardiograms can be used for therapeutic monitoring. Demonstration of improvement or deterioration after intervention may provide guidance for additional treatments.

Right Ventricular (RV) Strain

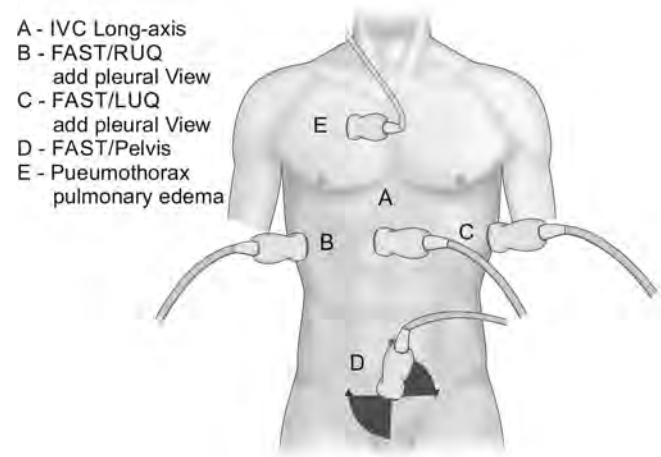
The third goal in evaluation of the pump is to identify evidence of right heart strain. In a normal heart, the LV is larger and more muscular than the right ventricular (RV) due to its role pumping against the higher pressures of the systemic vasculature. On echocardiogram, a normal ratio of LV to RV size is 1:0.6. Any condition that increases the pressure within the pulmonary vascular circuit can cause dilation of the right heart, causing the RV to appear equal to or even larger in size than the LV. Further evidence of right heart strain is visualization of the interventricular septum pushing from the RV into the LV cavity. This can be visualized on a parasternal short-axis view and is called the "D-sign," as flattening of the interventricular septum causes the LV to take on the appearance of the capital letter "D" (**Figs. 4A** and **B**).

The classic cause of acute right heart strain is a large pulmonary embolism. A thrombus causes obstruction in the pulmonary vascular circuit, acutely raising pulmonary pressures. Of note, chronic lung illness such as pulmonary hypertension, chronic obstructive pulmonary disease (COPD), and chronic effects of recurrent smaller pulmonary emboli can also cause right heart strain. While acute, chronic, and acute-on-chronic right heart strain may be difficult to distinguish, a dilated RV that is also hypertrophied suggests the influence of a chronic process. In acute right heart strain, the ventricle does not have time to compensate, and thus ventricular hypertrophy should not be seen.

STEP 2: TANK

The second step in the evaluation of shock is determining the intravascular volume status, or "the tank." This step is further broken down into three components (**Fig. 5**):

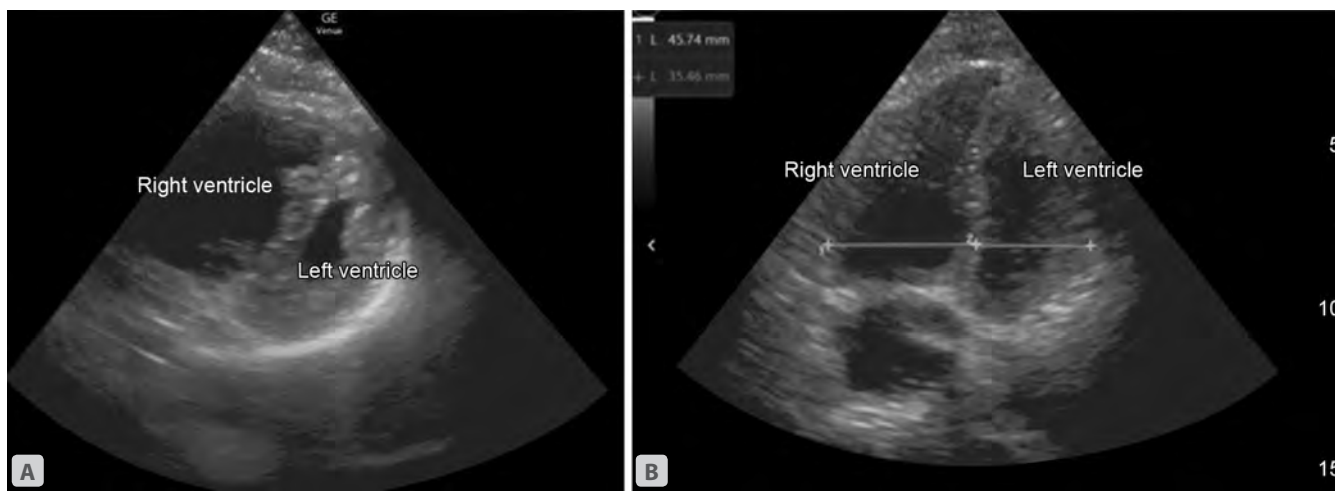
- *Fullness of the tank*: The IVC is evaluated to estimate volume status. The internal jugular vein (IJV) has also been described as a surrogate for jugular venous pressure and volume status.
- *Leakiness of the tank*: Focused assessment with sonography for trauma (FAST) assesses for any intra-abdominal or intrathoracic bleeding or fluid loss that decreases effective intravascular volume. Lung ultrasound evaluates for pulmonary edema.



(FAST: focused assessment with sonography for trauma; IVC: inferior vena cava; LUQ: left upper quadrant; RUQ: right upper quadrant)

FIG. 5: Sonographic views for "Tank" evaluation.

Source: Perera P, Mailhot T, Riley D, Mandavia D. The RUSH Exam: Rapid ultrasound in shock in the evaluation of the critically lll. Emerg Med Clin North Am. 2010;28(1):29-56.



FIGS. 4A AND B: Right heart strain (A) "D-sign" in the parasternal short-axis caused by high RV pressures flattening the interventricular septum. (B) Apical four-chamber view showing a dilated RV that is larger in size than the LV.

- *Tank compromise*: Lung ultrasound is performed to evaluate for a pneumothorax, which can increase intrathoracic pressures and cause decreased venous return to the heart.

Fullness of the Tank

The first step in evaluating the patient's intravascular volume status is to assess the IVC. Historically, central venous pressures (CVP) have been used as a surrogate for a patient's volume status, but have not been shown to predict volume responsiveness. Sonographic measurements of the IVC, including vessel size and collapsibility, have been shown to accurately and noninvasively estimate volume status while also correlating well to CVP. More recent literature suggests more nuance in interpretation of IVC ultrasound and some limitations of this as a tool for volume assessment. However, IVC may be most reliable at the extremes of size (flat vs. plethoric).

The IVC can be visualized by a low frequency transducer in a longitudinal orientation in the epigastrium, just right of midline. The IVC runs parallel to the aorta and can be distinguished by its thinner walls and respiratory variation. Furthermore, visualization of the IVC can be confirmed by anatomic landmarks, including its convergence with the right atrium and the hepatic veins. Two features of the IVC will be assessed—size and respirophasic variation.

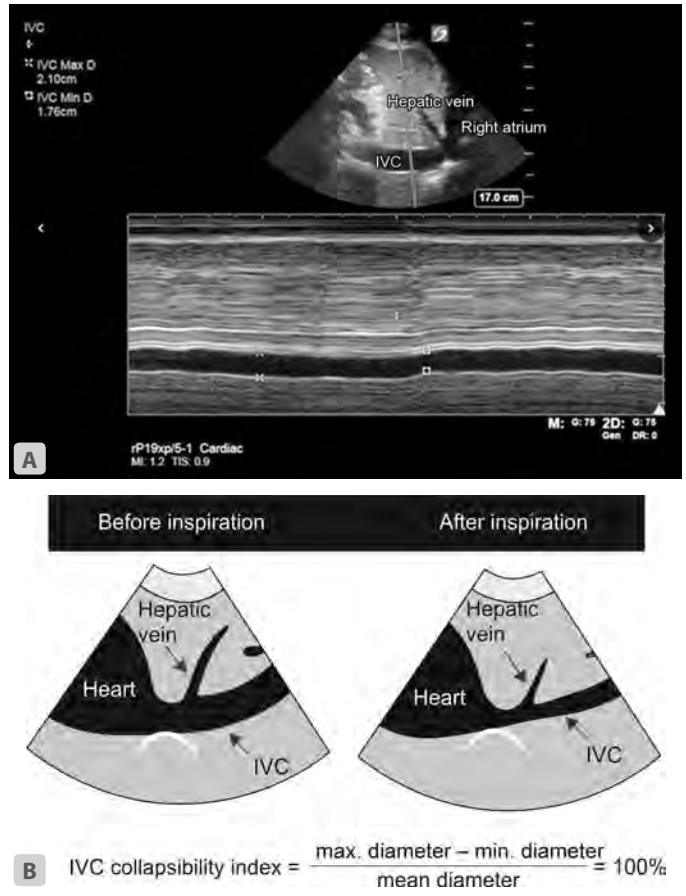
In spontaneously breathing patients, inspiration will cause IVC collapse due to negative pressure generated in the chest. This can be objectively measured in M-mode by placing the cursor approximately 2 cm distal to the junction of the right atrium and IVC, and graphically documenting the changes in vessel caliber through the respiratory cycle (**Figs. 6A** and **B**). The IVC diameter can be determined by measuring the wall-to-wall distance at the same location.

A patient with a small caliber IVC (<2 cm in diameter) and an inspiratory collapse >50% is associated with a decreased CVP, and suggests an underlying hypovolemic or distributive shock. Conversely, a patient with a larger caliber IVC (>2 cm in diameter) and an inspiratory collapse <50% is roughly associated with an increased CVP, suggesting an underlying cardiogenic or obstructive shock.

Unfortunately, it may be difficult to evaluate the IVC in some patients due to body habitus or bowel gas. In these patients, a transhepatic coronal view (with transducer placed at the right mid-axillary line) may be obtained, using the liver as an acoustic window. In addition, sonographic evaluation of jugular venous distention can be performed. The IJV is identified using a high-frequency linear array transducer with the patient's head elevated to 30° (**Fig. 7**). The IJV is evaluated in the short-axis to determine its diameter, and then in the long-axis to determine its respiratory collapsibility as well as the point on the neck where the walls of the vessel meet. Distended IJV diameter, minimal respiratory variation, and closing levels more superiorly toward the angle of the jaw suggest an elevated CVP. The opposite findings would suggest a decreased CVP.

Leakiness of the Tank

After assessing the patient's intravascular status, the next step is to evaluate for any abnormal "leakiness of the tank." This refers to either internal blood loss (e.g., trauma with hemoperitoneum or hemothorax) or fluid extravasation from increased hydrostatic pressures, (e.g., cardiac, renal, or hepatic failure resulting in pulmonary edema, pleural effusions, or ascites).



FIGS. 6A AND B: (A) Inferior vena cava (IVC) assessment using M-mode, (B) Calculation of IVC collapsibility index as a measure of respiratory variation of IVC diameter in spontaneously breathing patients.

Courtesy: Seif et al.

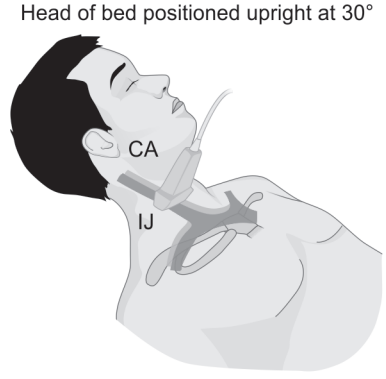
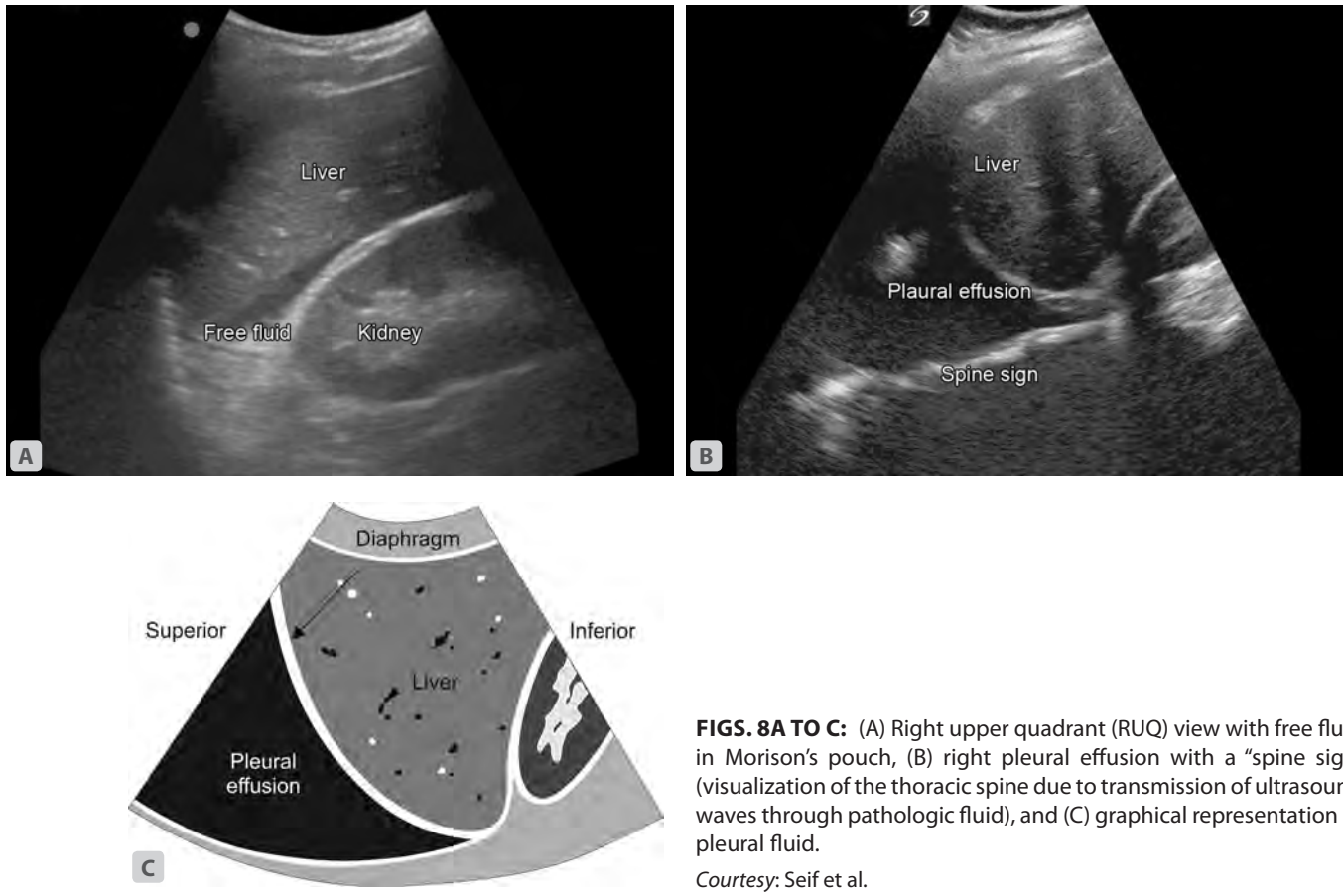


FIG. 7: Internal jugular vein sonographic assessment.

A FAST examination is performed to evaluate for fluid in the peritoneal and thoracic cavities (**Figs. 8A** to **C**). The exam assesses potential spaces in three discrete locations: (1) The right upper quadrant (RUQ), (2) left upper quadrant (LUQ), and (3) pelvis. Specifically, the RUQ view evaluates for free fluid in the space between the liver and kidney (Morison's pouch), the right paracolic gutter (near the inferior tip of the



FIGS. 8A TO C: (A) Right upper quadrant (RUQ) view with free fluid in Morison's pouch, (B) right pleural effusion with a "spine sign" (visualization of the thoracic spine due to transmission of ultrasound waves through pathologic fluid), and (C) graphical representation of pleural fluid.

Courtesy: Seif et al.

liver), the subdiaphragmatic space, and in the thorax above the right hemidiaphragm. The LUQ view evaluates the space between the spleen and kidney (splenorenal recess), the left paracolic gutter, the subdiaphragmatic space, and the left thorax above the left hemidiaphragm. The pelvis view evaluates the peritoneal recesses between the bladder and rectum in male patients, and between the uterus and rectum (pouch of Douglas) in female patients. Anechoic collections in any of these potential spaces represent free intraperitoneal fluid.

For female patients presenting with undifferentiated shock, it is important to also consider the possibility of a ruptured ectopic pregnancy. Direct visualization of an ectopic pregnancy with a transabdominal ultrasound is challenging. However, a ruptured ectopic can present with the sonographic findings of an empty uterus combined with a positive FAST. Visualization of an intrauterine pregnancy in the pelvic view significantly lowers the concern for ectopic pregnancy.

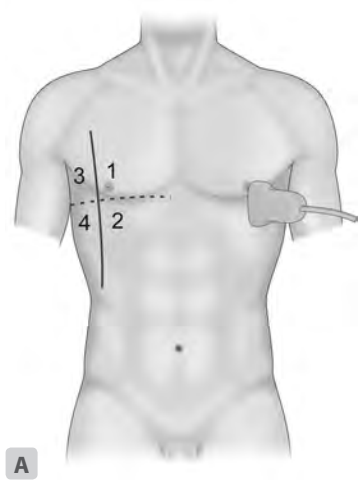
The second examination to assess for leakiness of the tank is a lung ultrasound. This focuses on identification of pulmonary edema. Using a phased array or curvilinear transducer, the thin, echogenic pleural line between two ribs is visualized. Bilateral anterior and lateral views may be obtained (**Fig. 9A** to **C**).

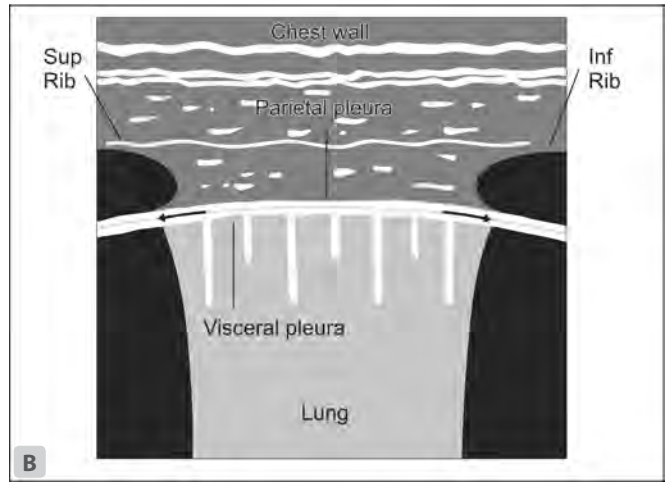
Conditions that elevate hydrostatic pressures can cause fluid accumulation in the interstitium of the lung. Extravascular lung water is detected on ultrasound by identifying B-lines or "lung rockets." B-lines are artifacts that originate from the pleural line and are caused by reverberating ultrasound energy from a focus of fluid surrounded by air. On ultrasound, they appear as thin, vertically-oriented, brightly echogenic lines that originate from the pleural line and extend into the far field of the ultrasound. The visualization of three or more B-lines in any single view is considered pathologic (**Fig. 10**). Presence of pathologic B-lines in multiple locations bilaterally is suggestive of pulmonary edema. Studies have shown that sonographic findings of pulmonary edema correlate well with signs of volume overload seen on chest radiography, and in many cases is more sensitive than X-ray.

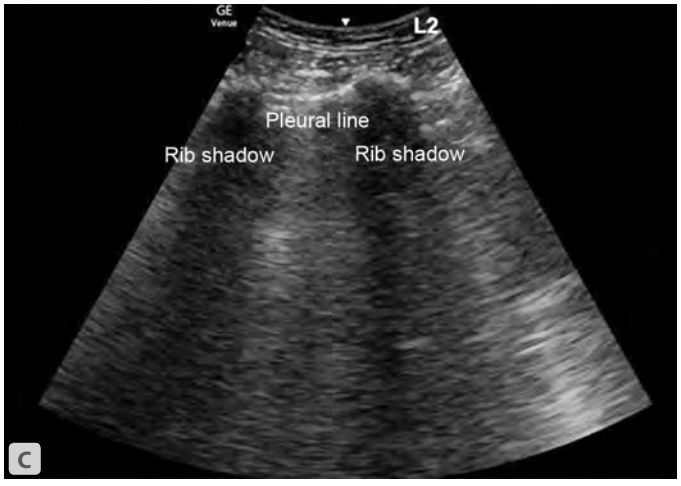
Compromise of the Tank

The final component in evaluation of the tank is to assess for a tension pneumothorax. While a high-frequency linear transducer provides the greatest detail of the pleural line, a phased array or curvilinear transducer may also be used. In the supine patient, the transducer is placed at the most anterior aspect of the thorax in the midclavicular line. In a normal lung, the visceral and parietal pleura slide against each other during respiration. This movement is described as a shimmering or "ants marching." In contrast, in patients with pneumothorax, air between the two pleural layers allows only the parietal layer to be visualized as a single stationary line.

The presence of lung sliding can also be represented graphically using M-mode. A patient without pneumothorax will have pleural sliding that displays on M-mode as "waves on a beach." The lack of motion within the chest wall produces the linear horizontal "waves" and motion of the pleura and lungs below produces the irregular, granular pattern of the "sand." In the presence of a pneumothorax, only repeating horizontal lines will be seen, signaling the lack of lung motion. This is called the "barcode" or "stratosphere" sign (**Figs. 11A** and **B**).







FIGS. 9A TO C: (A) Lung zones assessed during RUSH examination; (B) graphical representation of anatomic structures seen on lung ultrasound; and (C) normal lung ultrasound.

FIG. 10: B-lines on lung ultrasound. Three or more B-lines are considered pathologic.

STEP 3: PIPES

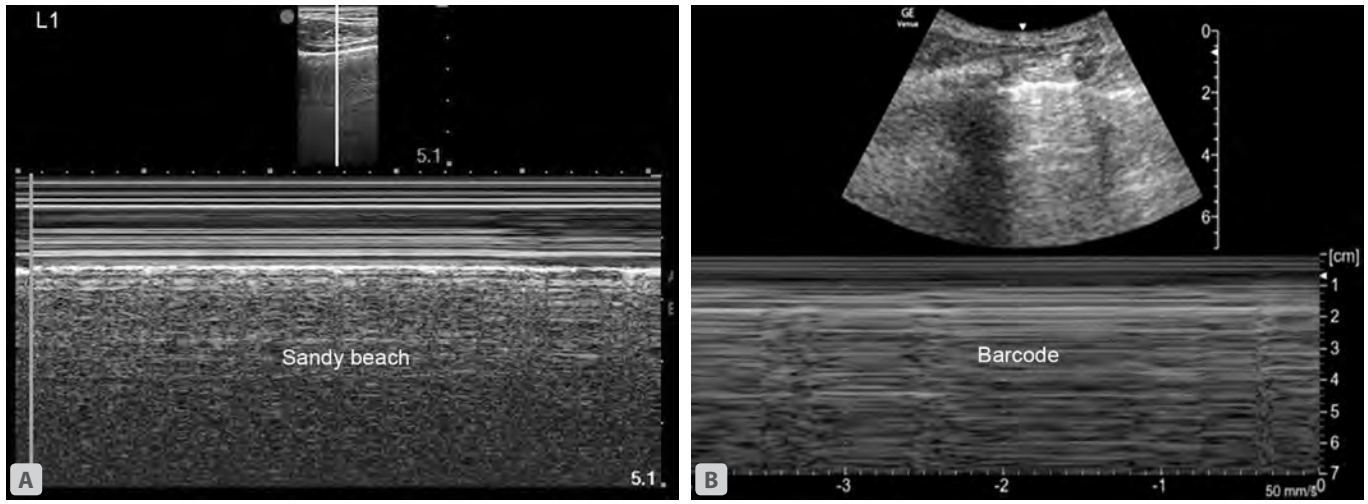
The third major system to evaluate in patients with shock is the "pipes," or the major arteries and veins of the body (**Fig. 12**). The key clinical question to answer is if these pipes are ruptured or obstructed.

Rupture of the Pipes: Aortic Aneurysms and Dissection

Sonographic evaluation begins with an arterial assessment, targeting vascular catastrophes such as abdominal aortic aneurysm (AAA) and aortic dissection as a cause of shock (**Figs. 13A** to **C**). Both can have devastating consequences and require early diagnosis and surgical management to improve outcomes.

Emergency physicians can diagnose AAA using bedside ultrasound with high sensitivity and specificity. With the patient in a supine position, a curvilinear or phased array transducer is placed in the epigastrium in a transverse orientation with the marker oriented toward the patient's right. Firm, steady pressure may be required to displace bowel gas. The aorta sits anterior to the semicircular vertebral body and appears as a round, thick-walled, pulsatile, and noncollapsible structure adjacent to the IVC. The abdominal aorta is visualized at the epigastrium to view its proximal portion, with the celiac artery or superior mesenteric artery serving as an anatomic landmark. It is followed distally until it bifurcates into the two common iliac arteries, occurring near the level of the umbilicus. Finally, the aorta can be visualized in its longitudinal axis by rotating the probe 90°.

The maximal diameter of the aorta is measured from outer wall to outer wall in the short axis. A AAA is diagnosed when



FIGS. 11A AND B: Evaluation for pneumothorax using M-mode: (A) Normal lung with "waves on a beach" and (B) pneumothorax with "barcode" sign.

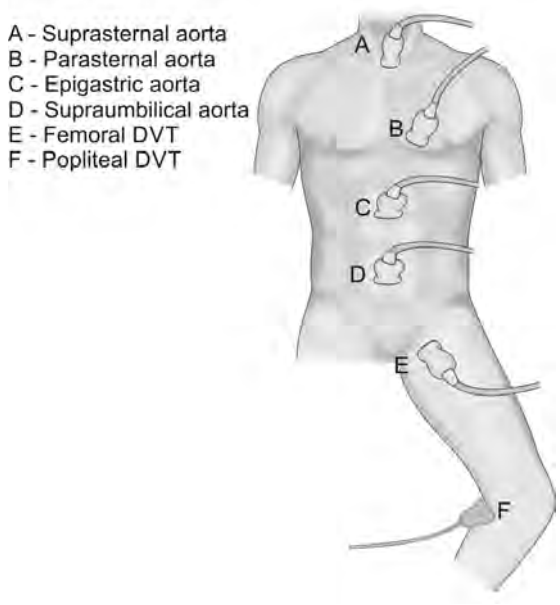


FIG. 12: Sonographic views for "pipe" evaluation.

Source: Perera P, Mailhot T, Riley D, Mandavia D. The RUSH Exam: Rapid ultrasound in shock in the evaluation of the critically Ill. Emerg Med Clin North Am. 2010;28(1):29-56.

the vessel diameter exceeds 3 cm, though rupture is more commonly seen in aneurysms measuring >5 cm. For the iliac arteries, measurements >1.5 cm are considered aneurysmal. Mural thrombus can also be observed within the lumen of the aorta. During measurement, care should be made to include the entire aorta with thrombus; if the lumen alone is measured, AAA may be missed.

An abdominal aortic dissection may be seen as an intimal hyperechoic flap inside the vessel. Though ultrasound is less sensitive than computed tomography (CT) to identify dissection, it may help to more quickly rule-in this pathology.

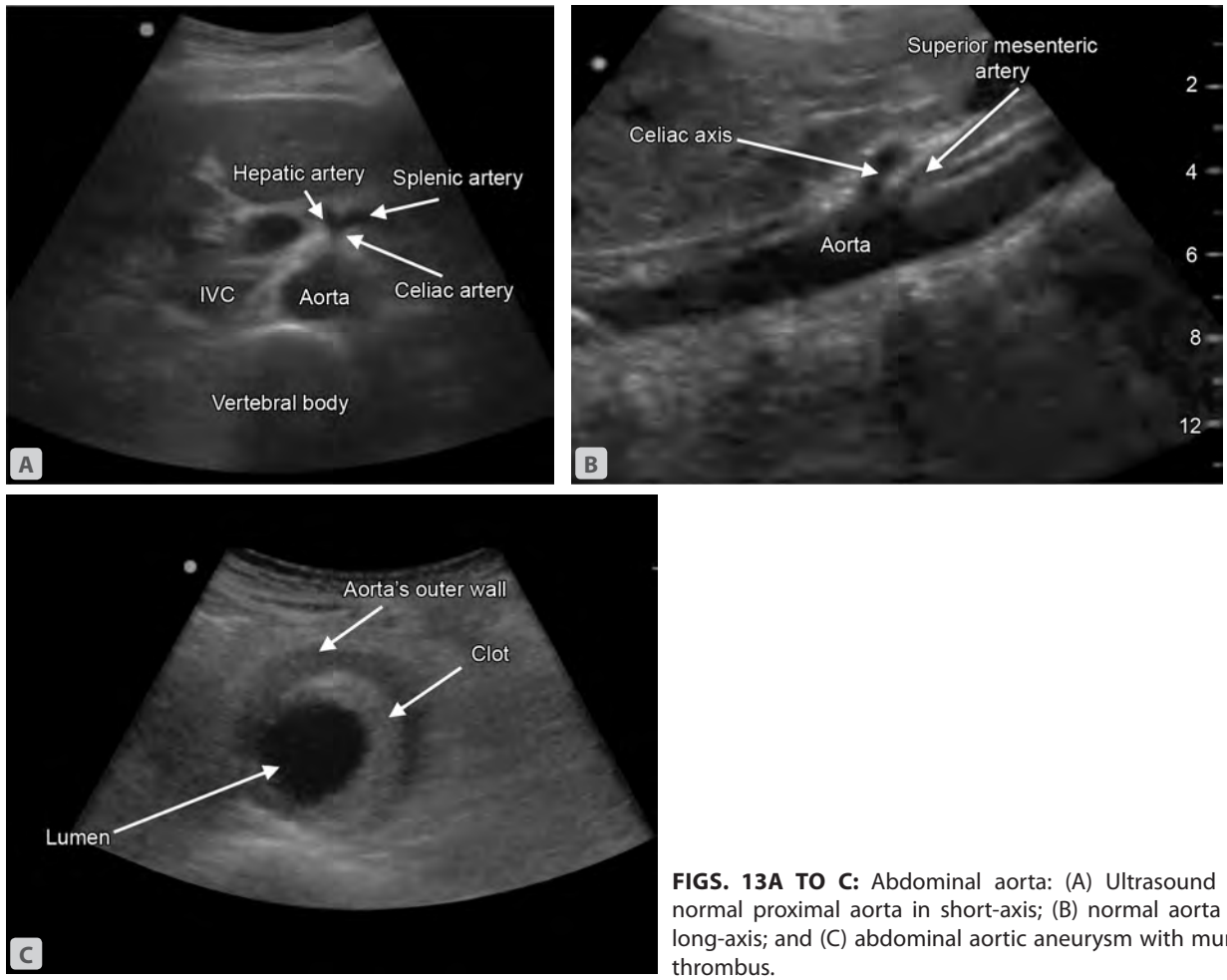
Next, the thoracic aortic is assessed. The sensitivity of transthoracic echocardiography to detect aortic dissection is poor and if clinical suspicion exists, further evaluation with more sensitive imaging modalities such as CT, magnetic resonance imaging (MRI), or transesophageal echocardiography should take place. However, bedside ultrasound may detect thoracic aortic dissections, and in those cases, lead the patient to a more expedient diagnosis of this time-sensitive condition.

Two ultrasound views may assist in this diagnosis. The parasternal long-axis view of the heart allows visualization of the aortic root. Aortic root dilation >3.8 cm is considered abnormal. The suprasternal view allows visualization of the aortic arch. This view is obtained by placing the phased array probe within the suprasternal notch and aiming the probe caudally and anteriorly (**Figs. 14A** and **B**). The presence of an intimal flap in either of these views diagnoses an aortic dissection. Pericardial effusion and evidence of aortic regurgitation may also be visible.

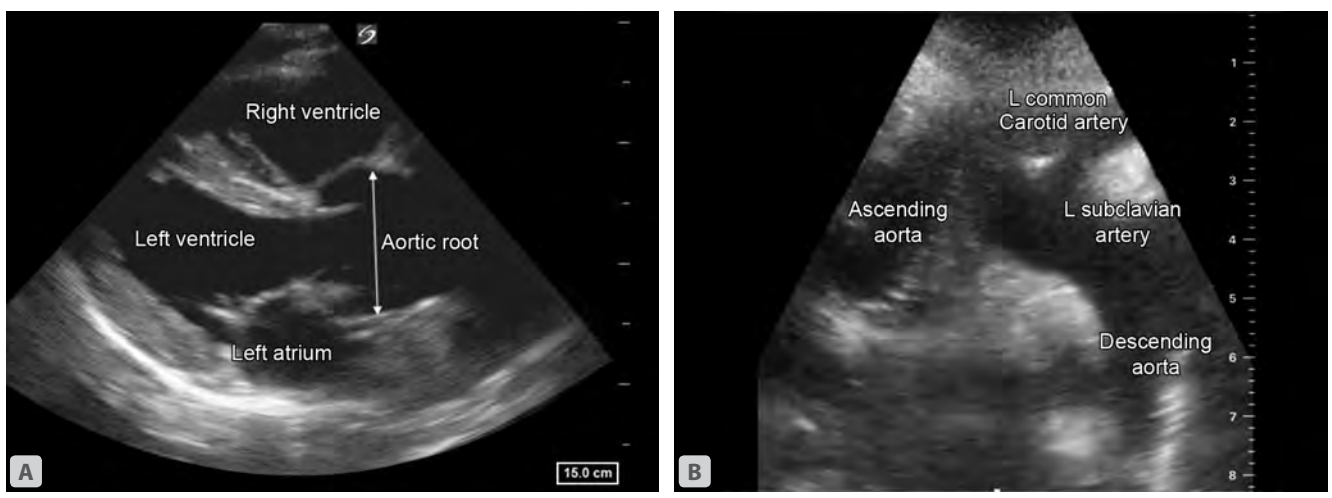
Clogging of the Pipes: Venous Thromboembolism

If a pulmonary embolism is suspected as an etiology of shock, then a lower extremity deep vein thrombosis (DVT) study should be done. The majority of pulmonary emboli originate from lower extremity DVTs (**Fig. 15**). At times, thrombus may be directly visualized on ultrasound. A well-formed blood clot may appear hyperechoic, while a fresh blood clot will appear hypoechoic. However, compression sonography is required for evaluation of DVT. A normal vein will completely collapse with compression, while a vein containing thrombus will show no compression or incomplete compression (**Fig. 16**).

A focused examination for DVT uses a high-frequency linear transducer to assess compressibility of the (1) common femoral vein, (2) proximal femoral vein, and (3) popliteal vein. This focused protocol has been shown to have high sensitivity to detect DVT.



FIGS. 13A TO C: Abdominal aorta: (A) Ultrasound of normal proximal aorta in short-axis; (B) normal aorta in long-axis; and (C) abdominal aortic aneurysm with mural thrombus.



FIGS. 14A AND B: (A) Measurement of aortic root in parasternal long-axis view; (B) suprasternal view of the aortic arch.

SUMMARY

A simplified three step assessment by point of care ultrasound during resuscitation helpful in identifying an underlying etiology of shock and appropriate intervention can be implemented (**Table 1**).

As adoption of ultrasound-based resuscitation protocols (**Fig. 17**) has become more widespread, many studies have emerged to evaluate the utility of these protocols in managing undifferentiated patients with shock or hypotension. Some studies have shown that in the hands of a highly skilled sonographer, a multiorgan POCUS evaluation can effectively

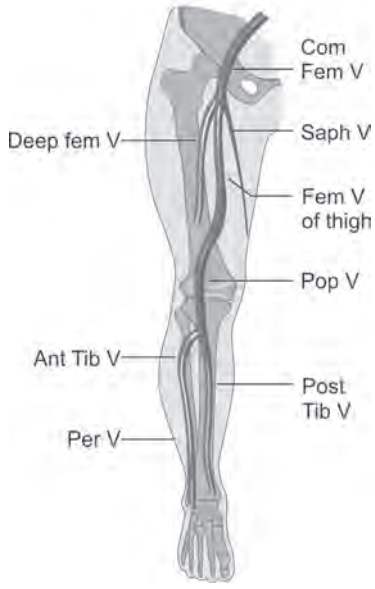


FIG. 15: Anatomic areas assessed in a focused lower extremity DVT study.

Courtesy: Seif et al.

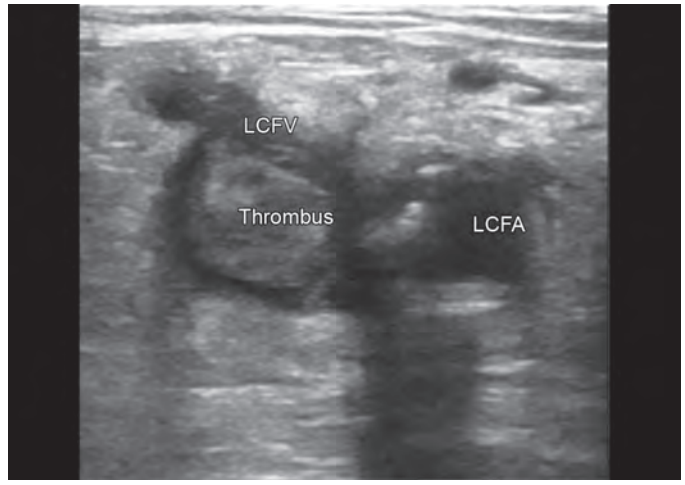


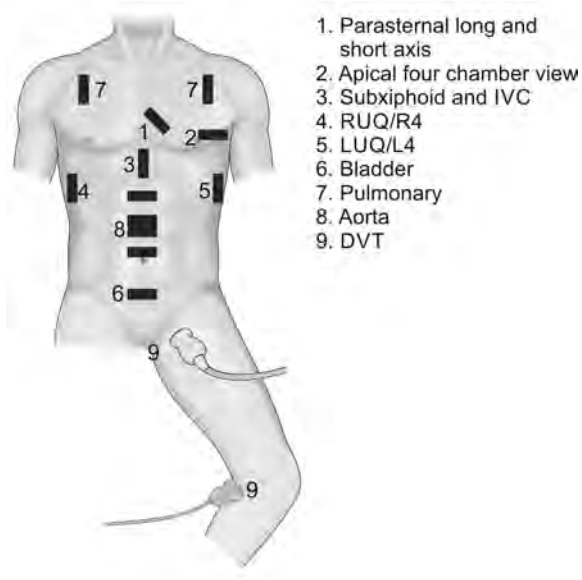
FIG. 16: DVT in the left common femoral vein. The vein is non-compressible.

TABLE 1: Sonographic findings, and categories of shock and initial management.

RUSH evaluation	*Hypovolemic shock*	*Cardiogenic shock*	*Obstructive shock*	*Distributive shock*
Pump	• Hyperkinetic heart • Small chamber size	• Hypocontractile heart • Dilated cardiac chambers	• Hypercontractile heart • Pericardial effusion • Cardiac tamponade • Right heart strain • Cardiac thrombus	• Hyperkinetic heart (early sepsis) • Hypocontractile heart (late sepsis)
Tank	• Flat IVC • Flat jugular veins • Free fluid in thorax or abdomen	• Distended IVC • Distended jugular veins • Pulmonary edema (diffuse B-lines) • Pleural fluid • Peritoneal fluid (ascites)	• Distended IVC • Distended jugular veins • Absent lung sliding (pneumothorax)	• Normal or flat IVC (early sepsis) • Focal B-lines or other sonographic findings of pneumonia
Pipes	• Abdominal aneurysm • Abdominal dissection	Normal	DVT	Normal
Initial interventions	• Fluid bolus • Hemorrhage control • Transfusion • Surgery consult	• Inotrope • Pressor • Diuresis	• Pericardiocentesis • Tube thoracostomy • Thrombolysis/ anticoagulation	• Fluid bolus • Antibiotics

diagnose shock etiology and allow initiation of the correct therapeutic intervention. However, a recent randomized control trial did not demonstrate benefits in patient-centered outcomes including survival, hospital length of stay, rates of CT scanning, inotrope use, or fluid administration. A meta-analysis reported that ultrasound was well suited to rule-in causes of shock, but was poor at ruling-out causes of shock.

These results may seem to argue against the use of POCUS during emergency department resuscitations; however, they more so reinforce the idea that POCUS should not be



(DVT: deep vein thrombosis**;** LUQ: left upper quadrant; RUQ: right upper quadrant)

FIG. 17: Recommended sequence for point-of-care ultrasound resuscitation protocol.

performed indiscriminately for patients in shock, but rather should be targeted to the clinical context of the patient. The RUSH protocol is broad, incorporating multiple ultrasound examination elements that can be time-consuming to perform. Numerous other ultrasound-based diagnostic protocols have also been described to evaluate the critically ill patient. While the underlying components comprising, these protocols are often identical, these protocols differ in their sequence of evaluation and number of elements included. The RUSH protocol should be considered a general framework for systematic evaluation of hypotension, and the sequences included should be tailored to the presentation of each patient. Furthermore, these studies neglect a significant benefit of POCUS in the management of the critically ill patient—serial ultrasound assessment to guide ongoing therapy.

Future work will require further standardization of ultrasound in resuscitation for patients with varying presentations. When used in isolation, multiorgan-based ultrasound protocols are imperfect, but as one component of a complete evaluation of a hypotensive patient, and used in conjunction with other clinical data points, ultrasound can reduce diagnostic uncertainty and provide needed guidance early in clinical decision making.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Ultrasound-guided Procedures

Richa Manglorkar, Mohaned Moheb El Abd, Tiffany Fong

INTRODUCTION

Vascular access is an essential and frequently lifesaving procedure in emergency and trauma care. Ultrasound (US) guidance for vascular access permits direct real-time visualization of the needle and surrounds structures and improves the quality and safety of needle guided procedures, including improved procedural success, reduced number of attempts, and fewer complications. The challenges of inherently poor anatomic landmarks, presence of aberrant anatomy, and weak or absent pulses in hypotensive or cardiac arrest patients can be mitigated by the use of ultrasound. Use of ultrasound guidance, particularly in central venous catheterization has become a standard of care and recommended by numerous professional societies as well as the Agency for Healthcare Research and Quality and National Institute of Health and Care Excellence as a top safety practice. As ultrasound guidance of vascular access procedures has become more widespread and clinician proficiency has increased, so has the spectrum of procedures performed under ultrasound guidance, to include peripheral veins and arterial puncture. Studies show that even with limited ultrasound training, physicians, nurses, and other healthcare personnel have been successful in learning and adopting these techniques.

PHYSICS OF ULTRASOUND

Ultrasound transducers contain piezoelectric elements that convert electrical energy into mechanical energy. This mechanical energy causes compression and rarefaction of particles, generating a sound wave. After the sound waves pass through a medium and are reflected back by an object, they are then converted back into electrical energy that is processed by a computer into the gray-scale images seen on the ultrasound display. The brightness displayed on the ultrasound system is dependent upon the strength of the reflected echoes (**Fig. 1**). Fluid-filled structures transmit most sound waves producing an anechoic or dark appearance on ultrasound.

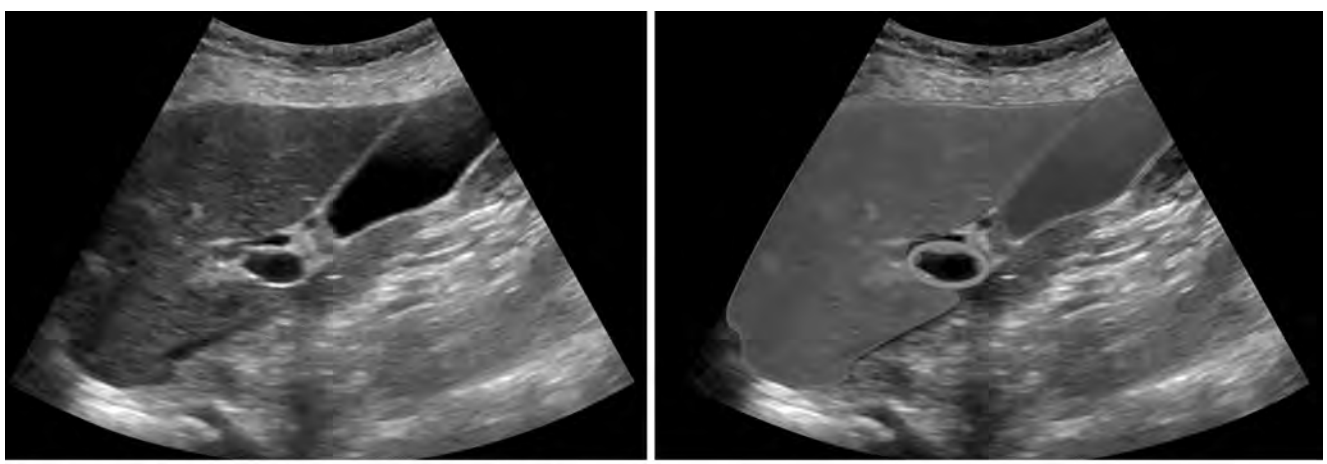

Blue: The gallbladder in longitudinal view is an anechoic structure.
Green: The walls of the portal vein represent a hyperechoic structure.
Orange: The liver parenchyma represents a hypoechoic structure.

FIG. 1: Varying echogenicity of structures seen on ultrasound. ***(For color version, see plate 3)***

Various types of fluid, including blood, bile, or urine have this appearance. Dense structures that reflect most sound waves are hyperechoic and appear as bright on ultrasound. Examples include bone, calcified structures such as gallstones, and the diaphragm and pericardium. On a spectrum between anechoic and hyperechoic materials are hypoechoic objects, displayed as shades of gray. Hypoechogenicity may be seen in solid organs such as the kidneys. Isoechoic describes structures that produce echoes that are similar to surrounding materials.

TRANSDUCERS

Three major transducers are commonly used in point-of-care ultrasound: (1) Curvilinear, (2) phased-array, and (3) linear. Each transducer has a different sound wave frequency, shape, crystal array, and application. The curvilinear probe utilizes frequencies of 2–5 MHz and allows visualization of deep solid organs such as the liver, kidney, gallbladder, and aorta. The phased-array probe utilizes frequencies of 1–5 MHz and its compact shape allows visualization of deep dynamic organs such as the heart and lungs between the ribs. The linear probe utilizes frequencies of 5–15 MHz and allows high resolution imaging of superficial structures such as veins, arteries, and nerves. This transducer is most often used for procedure guidance (**Fig. 2**).

KNOBOLOGY

Knobology refers to the functionality and manipulation of various controls on the ultrasound system. This section will review basic ultrasound controls essential to optimizing views for ultrasound-guided procedures.

Depth

Depth should be adjusted so that the structure of interest remains in the center of the screen, thus maximizing image resolution. Occasionally, it may be important to include other structures in view for landmarks or avoidance. An example is maintaining adequate depth to visualize the pleura when performing subclavian central venous catheterization to avoid pneumothorax.

Gain

Gain adjusts the level of amplification of echoes after the returning signal is received by the transducer. Increasing gain brightens images, decreasing gain darkens images. Gain should be adjusted until known anechoic (black) structures appear as dark as possible.

Color Doppler

Color Doppler assesses the presence and directionality of flow and is most commonly used for vascular structures (**Figs. 3A** to **C**). By convention, blue represents flow away from the probe and red represents flow toward the probe. This directionality may be useful in determining the difference between arteries and veins.

TECHNIQUE OVERVIEW

The technique most commonly used in ultrasound-guided vascular access procedures is direct or real-time visualization. From the time, the needle enters the skin until it reaches the target structure; its position and trajectory are visually tracked with ultrasound. This technique provides many advantages such as ensuring proper positioning of the needle tip and avoiding puncture nearby structures including arteries and nerve bundles.

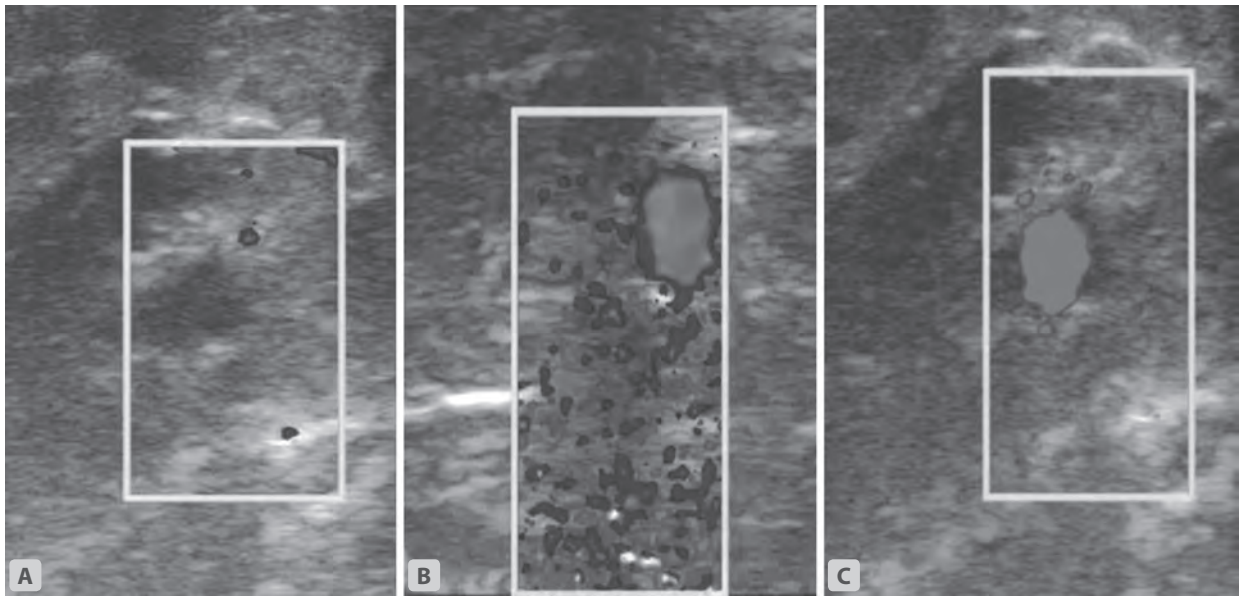
Procedural guidance may be performed using an out-of-plane technique (also known as short-axis, transverse, or cross-sectional relative to the structure of interest) or an in-plane technique (also referred to as long-axis) (**Table 1**). Each technique has its own advantages and disadvantages.

PERIPHERAL VENOUS CATHETER PLACEMENT WITH ULTRASOUND GUIDANCE

Placement of peripheral intravenous (IV) lines is an essential skill that is used in multiple settings varying from outpatient clinics to intensive care units. The ability to obtain peripheral access is an integral part of patient care. Patient factors can

From left to right:
Curvilinear probe: Low frequency, used for deep abdominal structures (i.e., liver, kidney)
Phased-array probe: Low frequency, used for deep dynamic structures (i.e., heart, lungs)
Linear probe: High frequency, used for superficial vascular structures (i.e., veins, arteries)

FIG. 2: Ultrasound transducers.



FIGS. 3A TO C: Use of color Doppler to identify vascular flow; (A) A nonvascular structure with no flow seen on Doppler; (B) A vascular structure with flow away from the probe consistent with a vein; (C) A vascular structure with pulsatile flow toward the probe consistent with an artery. ***(For color version, see plate 4)***

TABLE 1: Techniques for ultrasound-guided procedures.

	Short axis/out-of-plane technique	***Long axis/in-plane technique***
Advantages	• Arteries and veins can be simultaneously visualized • Minimal probe adjustment • Technically easier to perform	• Tip and entire length of the needle are visualized • Less likely to go through the back wall of the vessel
Disadvantages	Probe position requires adjustment for the needle tip to be visualized while advancing the needle	• More challenging to obtain long-axis view • Lose visualization of surrounding structures

make IV insertion difficult, including but not limited to body habitus, IV drug use, end-stage renal disease, and hypovolemia. Greater success successfully may be seen in such patients with the use of ultrasound guidance. Indications contraindications and requirements of supplies are given in **Table 2**.

Anatomy

- *Upper extremities*: The most commonly accessed veins for ultrasound-guided peripheral IVs are in the upper extremities. Traditional IVs placed by palpation methods are frequently performed in the dorsum of the hand, forearm, or antecubital fossa. In contrast, ultrasound-guided IVs frequently target the larger but often deeper cephalic, basilic, and brachial veins. The cephalic vein is ideal as it is a large, superficial vein located at the lateral aspect of the arm. The brachial and basilic veins run more medial along in the inner arm, making procedural positioning more difficult. Furthermore, the brachial vein runs in a neurovascular bundle that dives deep to the muscle, making avoidance of arteries and nerves more challenging.
- *Lower extremities*: The lower extremity veins may be used if vascular access in the upper extremity veins is unsuccessful. Potential targets include the greater saphenous and lesser saphenous veins.

Technique

Ultrasound-guided peripheral IV access may be performed using an out-of-plane technique using a transverse view of the vessel, or using an in-plane technique while visualizing the longitudinal course of the vessel (**Table 3**). Steps are described in **Table 4**.

Complications

Pain, arterial puncture or cannulation, hematoma, nerve injury, phlebitis, cellulitis, and extravasation.

CENTRAL VENOUS CATHETER PLACEMENT WITH ULTRASOUND GUIDANCE

Obtaining central venous access is essential in critically ill patients and can be considered in three locations: (1) the internal jugular (IJ), (2) subclavian, and (3) femoral veins. The next section will review the general approach to central venous access. Indications for central venous catheter placement are given in **Table 5**.

TABLE 2: Indication contraindications supplies requirements for catheter placement.	
Indications	• IV medications • IV fluids • Laboratory testing • Blood transfusion • Contrast administration for imaging • Difficult IV access or failure of landmark techniques
Contraindications to IV access at a particular site	• Dialysis fistula • Mastectomy or lymph node dissections • Known or visualized deep vein thrombosis • Cellulitis • Trauma or other pathology to extremities requiring surgical management
Supplies (**Fig. 4**)	• Chlorhexidine or another topical antiseptic • Gauze • J-loop extension tubing or Luer-lock/IV adapter clave • Tourniquet • Gloves (non-sterile acceptable) • Peripheral IV needle with catheter • Clear barrier adhesive dressing (one to secure the intravenous line and a second to use as an ultrasound probe cover as needed) • Sterile ultrasound gel • Saline flush • Ultrasound with high frequency linear transducer • Local anesthetic may be considered (avoid "with epinephrine" as this may constrict target vessels)

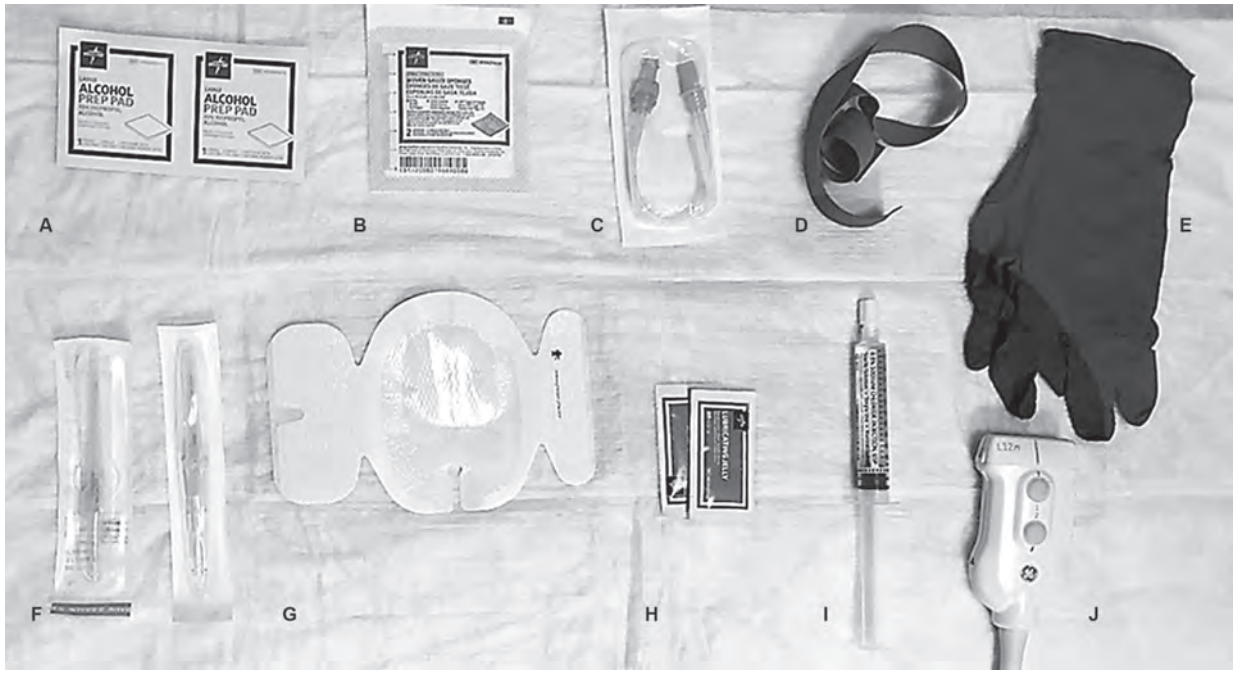


FIG. 4: Supplies required for ultrasound-guided peripheral venous access.

Procedure

Identify the vein and any nearby arteries and nerves with ultrasound. It is best to survey the anatomy prior to sterilizing the skin and sterile draping. The target vein should be compressed to assess patency. If the vein is nonpatent or noncompressible, this may indicate presence of a venous thrombosis and the site should be avoided. Spectral Doppler can be employed to assess arterial versus venous waveforms. Don proper sterile personal protective equipment and widely sterilize and drape the appropriate site. The site to be punctured is anesthetized with lidocaine. Before injection, it is important to aspirate to ensure the needle tip is not positioned in a vessel (**Figs. 5A** to **C**).

TABLE 3: Technique for ultrasound-guided peripheral IV access.

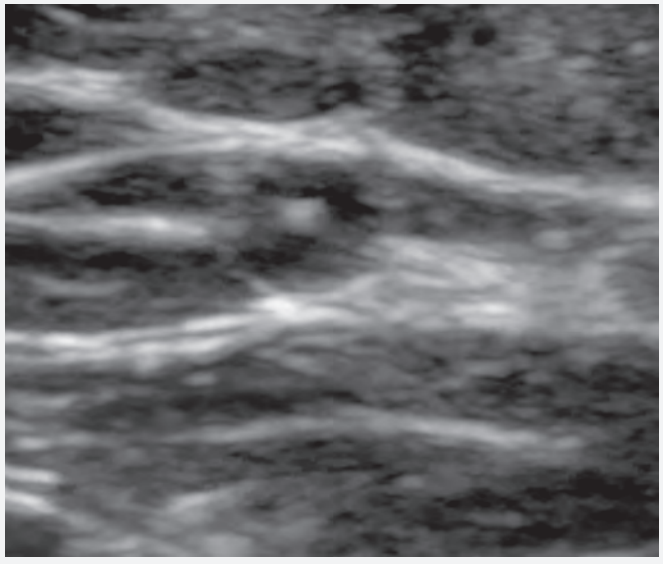
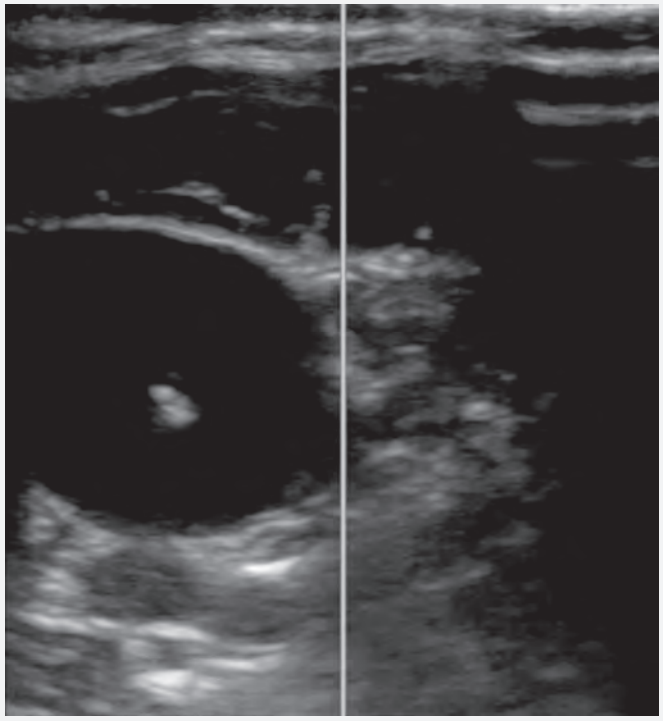
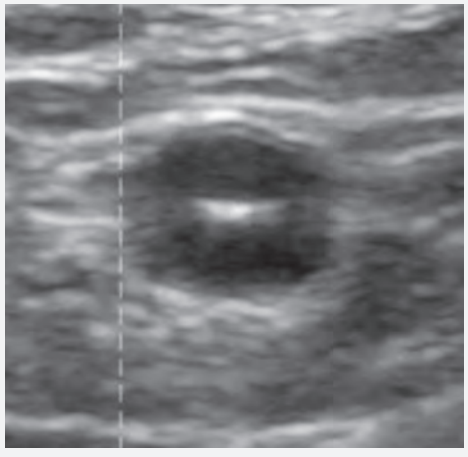
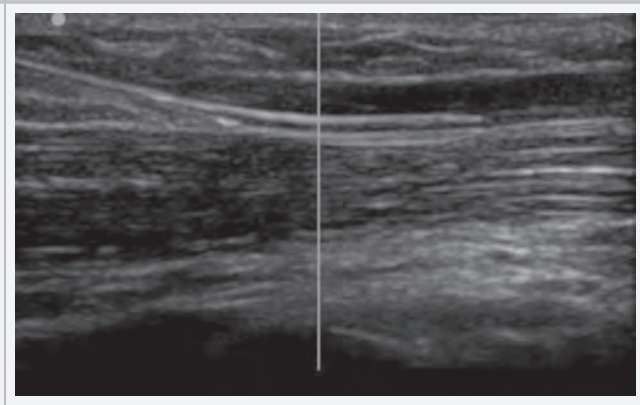
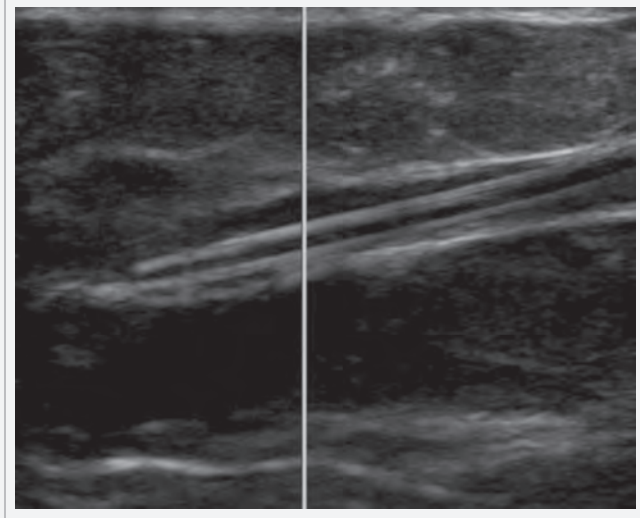
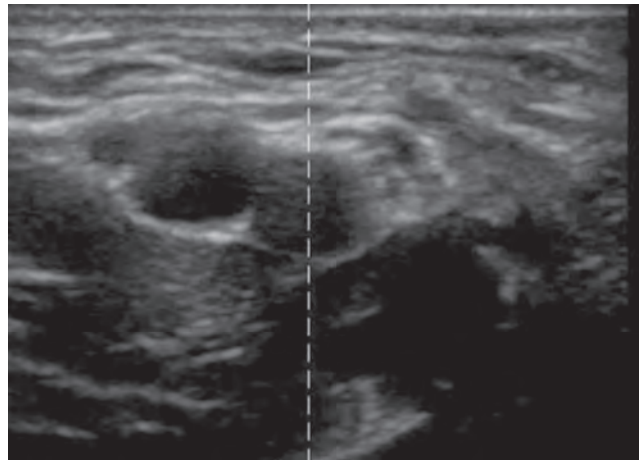
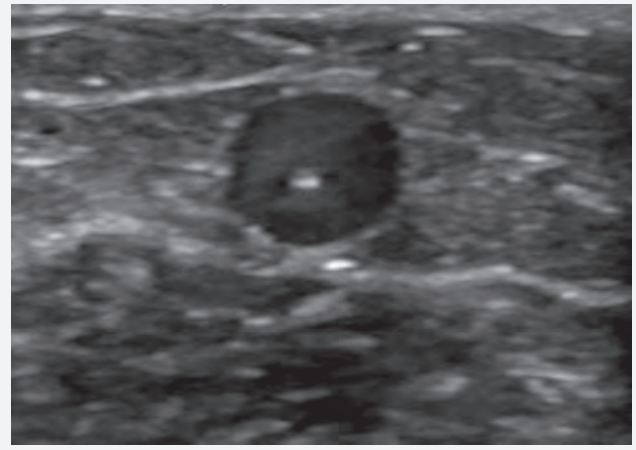
Out-of-plane (transverse) technique	*In-plane (longitudinal) technique*
  	 

TABLE 4: Transverse approach to peripheral IVs.

Step	*Comments*	*Imaging*
1. *Patient and equipment positioning*	• Place the patient in a comfortable position • Keep the patient's arm abducted to maximize space to perform the procedure • Position the ultrasound machine so that area to be punctured lies in the same visual axis as the ultrasound monitor. At times this will be on the opposite side of the patient • Adjust the height and tilt of the ultrasound display	
2. *Identify a target vein with ultrasound*	• An ideal vein is larger, more superficial, and has a linear course without branch points • Compression is performed to confirm the venous structure and to assess for patency • Note depth of vein and ensure adequate catheter length. A standard 3.18 cm (1.25 inch) IV catheter is appropriate for vein depths <1 cm. A long length IV (4.88 cm, 1.88 inches) is appropriate for vein depth >2 cm	
3. *Probe and skin preparation*	• Place a probe cover or clear adhesive barrier on the transducer and apply sterile gel • Clean procedure site with antiseptic (e.g., alcohol wipe or chlorhexidine) and place tourniquet	
4. *Probe manipulation*	• Hold the probe with the nondominant hand and needle with dominant hand • The probe marker should face the operator's left side to allow for movement of probe and movement on screen to correspond • Identify the target vessel and center it on screen	

Continued

Continued

Step	Comments	Imaging
5. *Advance the needle*	• Puncture skin at the center of the probe. The point of entry of the needle relative to the probe corresponds directly to the depth of the vessel (e.g., for a vessel that is 1 cm deep, the needle should enter the skin 1 cm form the probe) • Advance at a 45° angle, keeping the tip of the needle in view at all times. This can be achieved by advancing the probe until the needle tip disappears, and then advancing the needle until the tip is seen again • If the needle tip is not visualized, pause needle advancement, and fan the probe to identify the needle tip	
6. *Enter the vessel with the needle*	• Once the needle "tents" the top of the vessel, slowly advance until the needle tip is seen in the center of the vessel • Look for a flash of blood in the catheter • Do not puncture through the posterior (deep) wall of the vessel	
7. *Cannulate the vessel*	• Keep the needle tip steady in the center of the vessel to ensure smooth advancement of the catheter and not the needle • Gently set down the probe • Thread the catheter with the dominant hand	
8. *Remove needle, keeping the catheter in place*	Blood flow may be seen	

Continued

Continued

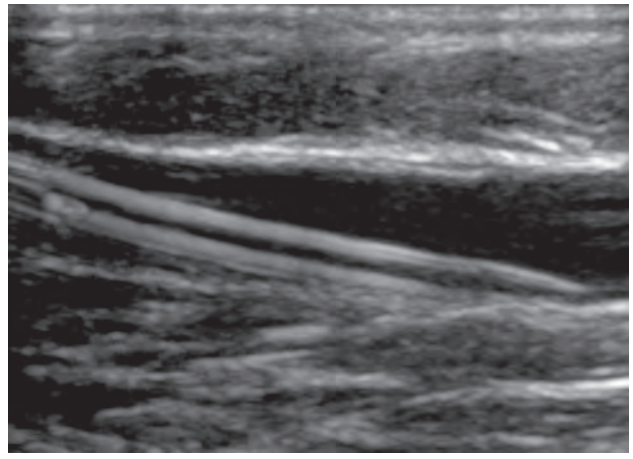
Step	Comments	Imaging
9. *Secure and confirm IV line*	• Attach J-loop/Luer lock and aspirate with saline flush to confirm blood return • Remove tourniquet. Flush with sterile saline to prevent clot • Secure IV with Tegaderm or other clear adhesive barrier	
10. *Confirm catheter placement with ultrasound*	• If no blood is seen with aspiration, re-evaluate catheter position with ultrasound • When the catheter is appropriately positioned, it will be seen in the longitudinal axis as an echogenic structure within the lumen of the vein	

TABLE 5: Indications of central venous catheter placement.

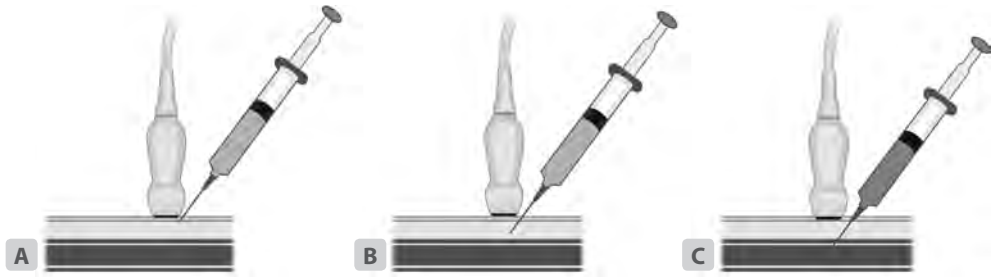
Indications	• Inability to obtain peripheral IV access • Dosing of medications that cause venous sclerosis if used peripherally (e.g., vasopressors, hypertonic saline, and high-concentration potassium) • Need for central venous procedures (e.g., transvenous pacing and Swan–Ganz catheter)
Supplies	• Ultrasound machine with high-frequency linear probe • Sterile transducer cover • Sterile ultrasound gel • Sterile gloves • Central venous catheter kit, containing necessary supplies including sterile personal protective equipment, drapes, local anesthetic solution, syringes and needles, guidewire, scalpel, dilator, catheter, suture, gauze, and clear adhesive dressing
Technique	The high-frequency linear array transducer should be used for this procedure because it allows high resolution imaging of superficial vascular structures. Similar to peripheral IV, central venous access may be performed using a transverse or longitudinal approach

Hold the ultrasound probe in the nondominant hand to obtain either a transverse or longitudinal view. With the dominant hand, pierce the skin and advance the needle, always keeping the needle tip in view on the ultrasound monitor. As with peripheral IVs, begin at a 45° angle. The depth of the vessel will inform the distance from the probe at which needle will enter the skin. For example, if the vein is 2 cm deep, the needle should enter the skin 2 cm away from the probe.

As the needle is advanced and the vessel is entered, the needle tip will be seen within the vessel lumen, as well as a flash of blood and loss of resistance of the syringe. Gently set down the transducer and stabilize the needle with the nondominant hand. Using the dominant hand, remove the syringe from the needle and immediately occlude the top using the finger of your nondominant hand to prevent an air embolism. Pick up then thread the guidewire through the needle using the dominant hand. Once the wire is properly positioned within the vessel, remove the needle over the wire while maintaining the wire's position in the vessel. Ultrasound may be used to confirm that the wire is within the vessel using both transverse and longitudinal views. After anatomic confirmation of wire placement, the catheter may be threaded over the wire, the wire removed, and the catheter secured with suture.

Complications

Similar to peripheral IVs, complications include pain, arterial puncture or cannulation, hematoma, nerve injury, phlebitis,



FIGS. 5A TO C: Ultrasound-guidance of needle advancement; (A) Needle tip starting at the skin distal to the vessel under ultrasound guidance; (B) Advancing the needle through soft tissue through toward the vein while advancing the ultrasound probe to keep the needle tip visible; and (C) Entering the vein with a flash of blood while aspirating and keeping the needle tip in the center of the vessel.

cellulitis, and extravasation. However, central lines also carry additional risk of pneumothorax, hemothorax, or thoracic duct injury (IJ or subclavian), bladder injury (femoral), noncompressible hematoma (subclavian), brachial plexus injury (subclavian), retroperitoneal hematoma (femoral), or central-line associated bloodstream infections.

Specific Sites for Central Venous Access

This subsection will review three separate sites of central venous access in more detail including (1) the IJ vein, (2) femoral vein, and (3) subclavian vein. Each site of access has special considerations regarding anatomy and procedural approach. Despite the following special considerations, all three sites follow the basic steps of cannulation that were previously outlined.

Internal Jugular Vein

- *Background*: Traditionally, IJ catheterization had been performed using anatomic landmarks, leading to failed attempts and procedural complications. The earliest description of ultrasound assistance for IJ access was published in 1984. The IJ often preferred for central venous access due to its superficial position and easy accessibility. A 2015 systematic review compared the use of ultrasound guidance to landmark techniques for IJ cannulation. This revealed a decrease in overall number of attempts, a 57% increase in first attempt success, decreased time to cannulation, and a 71% decrease in rate of complications.
- *Anatomy*: The IJ vein is vertically oriented along the lateral aspect of the neck and is contained within the carotid sheath lateral to the carotid artery and together with the vagus nerve. The IJ lies deep to the platysma, digastric, omohyoid, and sternocleidomastoid muscles. Once the IJ reaches the first rib/thorax it joins the subclavian vein to form the innominate vein, draining to the superior vena cava and ending in the right atrium (**Fig. 6**).
- *Special considerations*: To optimize the patient's position, turn the head toward the contralateral shoulder to open the anatomic space and create a more linear course of the IJ. Furthermore, the patient should be placed in Trendelenburg position (head lower than feet) position to increase venous dilation and to minimize the risk of air embolism. The IJ should be visualized in a more lateral position relative to the carotid artery (**Fig. 7**).

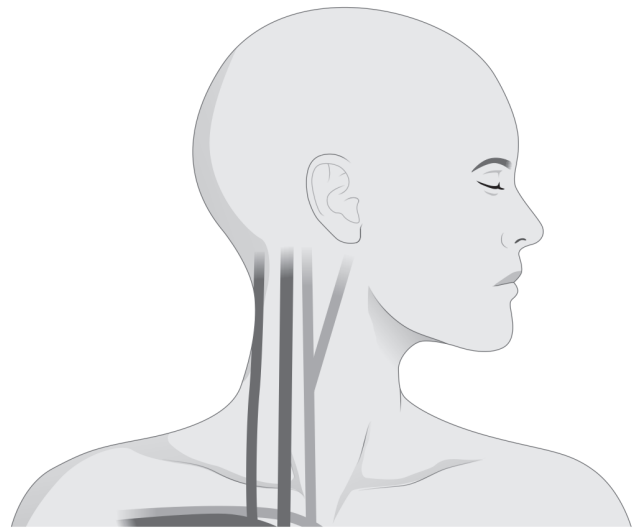
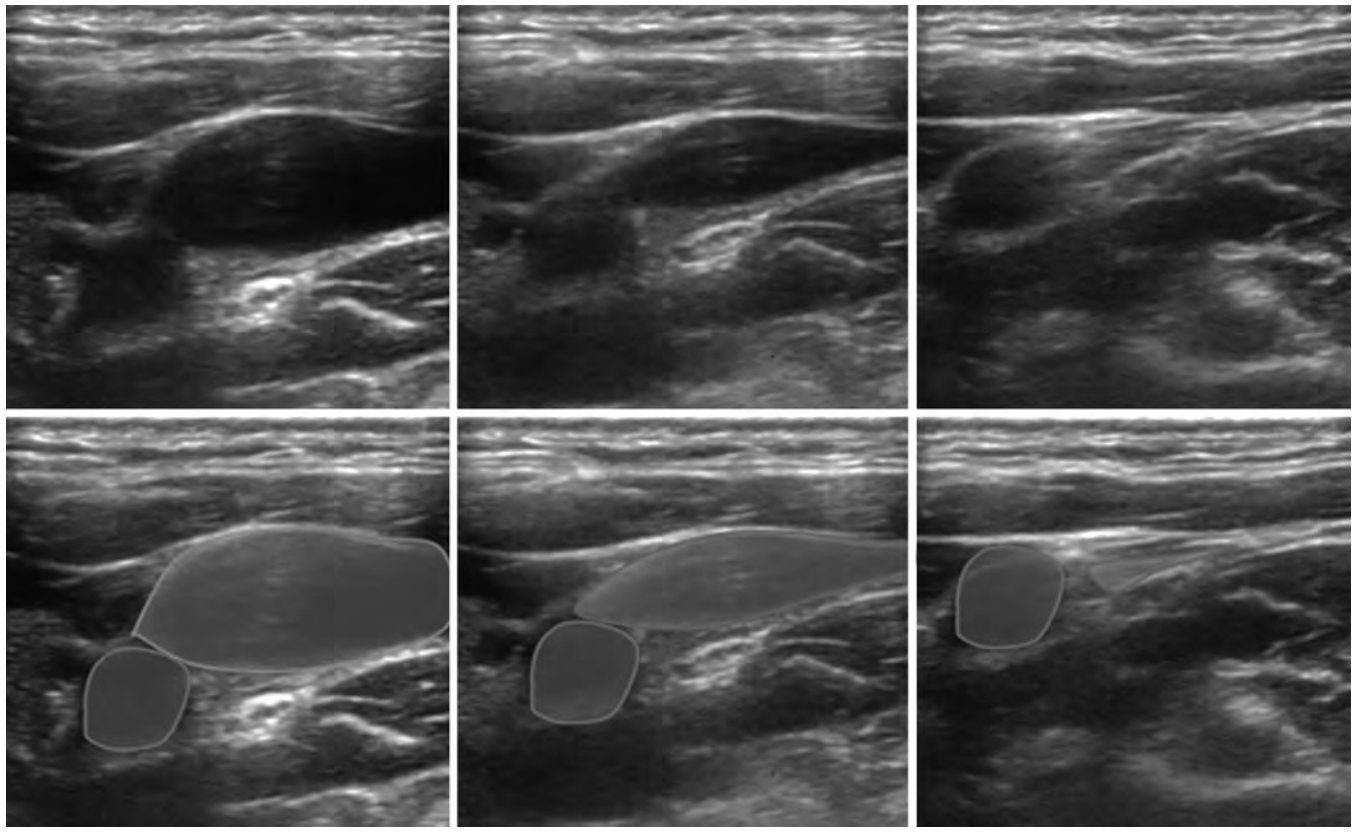


FIG. 6: Anatomy of the internal jugular and subclavian veins relative to the carotid and subclavian arteries.

Subclavian Vein

- *Background*: Subclavian central venous access offers several advantages over the IJ site, including increased patient comfort and fewer infectious complications, most notably central-line associated bloodstream infection. Because of its fixed position under the clavicle, it has less size variation than the IJ and may be easier to access in patients with hypovolemia or sepsis. However, its location under the clavicle may also create more technical challenges to accessing it, and more difficult compressibility in the event of inadvertent arterial puncture.
- *Anatomy*: The subclavian vein is formed by the confluence of the cephalic and axillary veins of the upper extremity and runs anterior to the subclavian artery. After the subclavian vein joins the IJ vein to form the innominate vein, it drains into the superior vena cava leading to the right atrium. The right subclavian vein is preferred for cannulation due to its straighter angle with the IJ and relative ease of passage into the superior vena cava (**Fig. 8**).
- *Special considerations*: The use of ultrasound guidance allows two approaches to subclavian vein catheterization.
  (i) *Infraclavicular approach*: This approach is more commonly taught and used to access the subclavian



(Blue: internal jugular vein; Red: carotid artery. Internal jugular and carotid artery shown from left to right with progressive compressibility of the internal jugular vein)

FIG. 7: Sonographic anatomy of internal jugular vein and carotid artery. ***(For color version, see plate 4)***

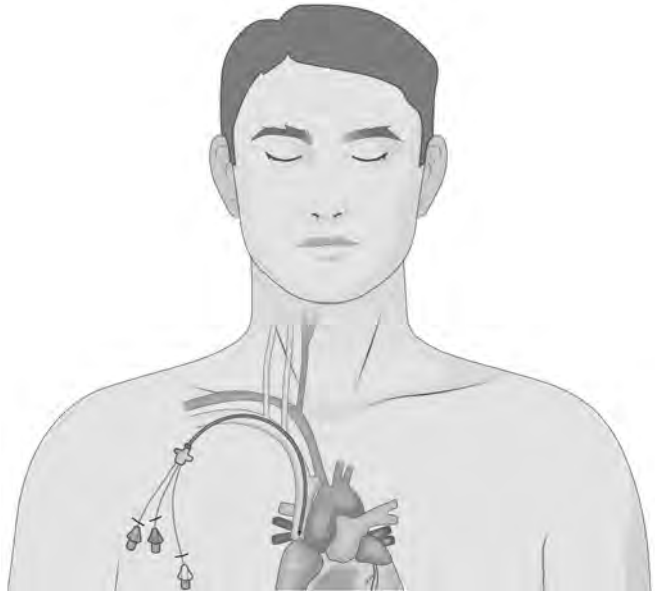
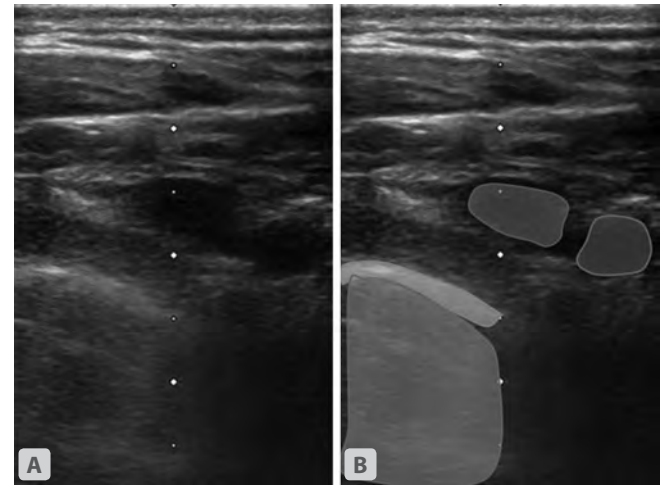


FIG. 8: Anatomy and catheter placement within the subclavian vein.



FIGS. 9A AND B: Transverse infraclavicular ultrasound view of the subclavian vessels and lung. ***(For color version, see plate 5)***

vein (**Figs. 9A** and **B**). The linear probe is placed below the clavicle in the infraclavicular fossa to obtain a longitudinal view of the subclavian vein. The subclavian vein should be cannulated at its junction with the axillary vein, in a more lateral position than with a landmark-based approach. Slide the probe along the margin of the inferior clavicle to identify the accessible portion of the vein prior to its dive deep to the clavicle. Fan the probe to identify both the subclavian vein in its long axis, and the subclavian artery posterior to it. Compress to assure vein patency and to confirm arterial and venous structures. Because of the position of the clavicle, compression may be limited and alternatives include use of color or spectral Doppler. The hyperechoic mobile pleural line will be

seen immediately below the subclavian vein. The pleural line should always be kept in view to ensure the needle tip does not puncture the pleura and cause a pneumothorax. Utilizing an in-plane approach, the needle is inserted at the lateral edge of the transducer and advanced slowly toward the subclavian vein.

(ii) *Supraclavicular approach*: The subclavian vein has a short supraclavicular course prior to merging with the IJ to become the innominate vein. This area of confluence offers a shallow and relatively larger area of vein that may be easy to access. However, this technique is more challenging and recommended for operators who have greater experience with in-plane procedures.

The supraclavicular fossa itself has space limitations, and the use of a small footprint high-frequency transducer (or endocavitary transducer) is advised. The transducer is placed on the lateral neck in a transverse plane just superior to the clavicle to identify the IJ. The IJ is traced inferiorly then angled anteriorly to visualize its confluence with the subclavian vein—this is the target site for cannulation. Fan the probe to identify both the subclavian vein in its long axis, and the subclavian artery posterior to it. Again use compression and Doppler techniques to assure vein patency and to confirm arterial and venous structures. Continuously visualize the pleura throughout the procedure to avoid lung puncture and pneumothorax. After local anesthesia, the needle punctures the skin just lateral to the probe using an in-plane approach. It is slowly advanced toward the subclavian IJ junction, just lateral to the clavicular head of the sternocleidomastoid muscle.

Femoral Vein

- *Anatomy*: The femoral vein is located within the femoral sheath medial to the femoral nerve and femoral artery. It lies inferior to the inguinal ligament, lateral to the adductor muscles, and medial to the sartorius muscle (**Fig. 10**). Moving proximally, the femoral vein becomes the external iliac vein, draining into the common iliac vein, and ultimately joining the inferior vena cava. The femoral vein generally has fewer surrounding high-risk structures.
- *Special considerations*: The patient may be placed in reverse Trendelenburg position (feet toward the ground) to increase venous dilation. Additionally, abduction and external rotation of the leg may open up the space of the femoral triangle to allow greater ease of access. On ultrasound, the femoral vein should lie medial to the femoral artery (**Fig. 11**). Select a portion of the common femoral vein below the inguinal ligament for cannulation. Attempts above the inguinal ligament can lead to intraperitoneal complications or retroperitoneal bleeding.

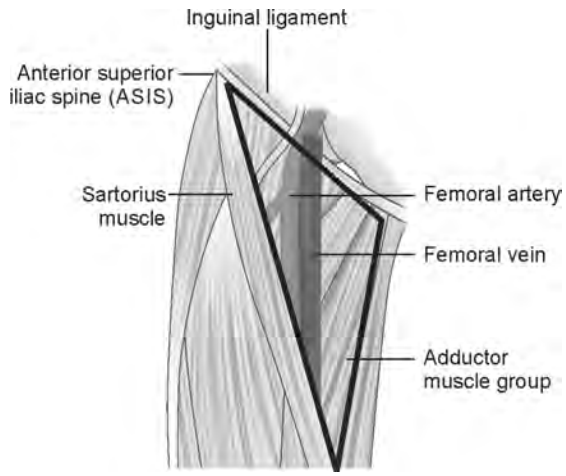


FIG. 10: Anatomy and catheter placement within femoral vein.

ULTRASOUND-GUIDED PERICARDIOCENTESIS

Background

Pericardial tamponade is a life-threatening condition characterized by accumulation of fluid in the pericardial sac resulting in high intrapericardial pressures that impair cardiac filling. Tamponade is a clinical diagnosis that should be suspected in a hemodynamically unstable patient with moderate or large pericardial effusion. Beck's triad describes the classic physical findings of hypotension, muffled heart sounds, and distension of the neck veins. However, these findings are limited to identify tamponade, with 50% of patients demonstrating just one element of the triad and as low as 0% of patients demonstrating all three elements.

Point-of-care ultrasound is a necessary tool to diagnose pericardial effusion and tamponade and to guide the life-saving procedure of pericardiocentesis. Ultrasound facilitates direct visualization of the needle approaching the pericardium and aspirating the effusion and is recommended to increase procedural success, improve survival, and minimize the potential complications.

The hemodynamic effect of pericardial effusion is dictated by both the volume and the rate of fluid accumulation. More chronic, slowly growing effusions allow larger volumes to

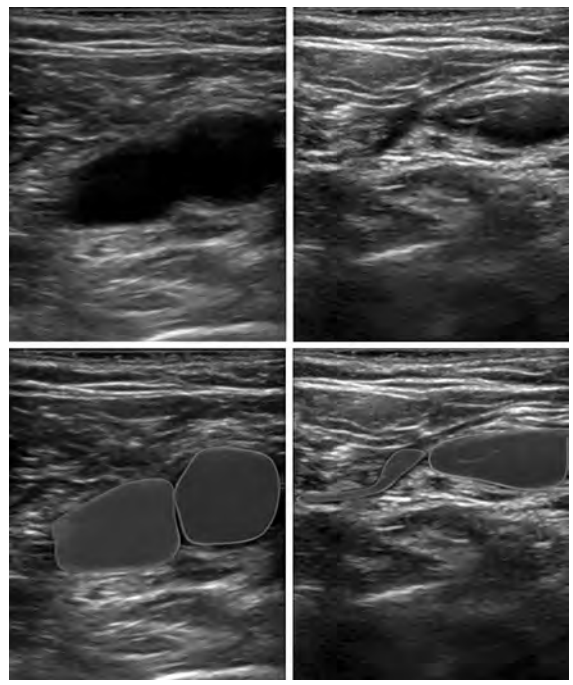


FIG. 11: Ultrasound view of a femoral vasculature with a patent femoral vein. ***(For color version, see plate 5)***

accumulate due to pericardial stretch. In contrast, rapidly expanding effusions can lead to critical increases in pericardial pressure at smaller volumes. Thus, with acute effusions, removal of relatively small amounts of fluid can have a significant hemodynamic effect.

Indications and Contraindications

Pericardiocentesis is immediately indicated when pericardial tamponade is suspected, including cardiac arrest with pericardial effusion and in hemodynamically unstable patients with moderate or large pericardial effusions. There are no absolute contraindications to pericardiocentesis when pericardial tamponade is present. Relative contraindications to emergency pericardiocentesis include coagulopathy, anticoagulant therapy, thrombocytopenia (platelet count < 50,000/mm^3), and presence of small, posterior, or loculated effusions.

Supplies

- Ultrasound system with phased array transducer
- Probe cover or clear barrier adhesive dressing
- Sterile ultrasound gel
- Chlorhexidine or other topical antiseptic
- Small syringe (10 cc) and needle (20–25 gauge) for local anesthetic
- Large syringe (20–60 cc) for pericardiocentesis
- Long 16–18 gauge needle (e.g., from central line kit) or spinal needle
- Local anesthetic (e.g., 1% lidocaine)
- *Optional*: If an indwelling pericardial drain will be placed, a kit containing a 6–8 French pigtail catheter, guidewire, dilator, introducer sheath, three-way stopcock, needles, and syringes may be used.

Anatomy and Pathophysiology

The pericardium is a dense, fibrous sac composed of visceral and parietal layers and is visualized on ultrasound as a strongly echogenic (white) border surrounding the relatively hypoechoic myocardium. The pericardial space normally contains a trace amount of serous fluid that is not prominently seen. When fluid accumulates, an anechoic (black) stripe is seen between pericardium and myocardium, first in dependent areas then circumferentially around the heart as volume of fluid increases. The epicardial fat pad may be mistaken as pericardial effusion, but may be differentiated from effusion by the presence of internal echoes (making it more hypoechoic than anechoic), and its anterior position adjacent to the right ventricle rather than dependent. In addition, left pleural effusions may mimic pericardial effusion; however, pleural effusion can be confirmed through visualization of the effusion posterior to the descending thoracic aorta in the parasternal long axis view (**Fig. 12**). Pericardial tamponade occurs when high intrapericardial pressures that exceed intracardiac pressures, and the lower pressure system of the right heart is more vulnerable. Ultrasound findings of tamponade are collapse of the right ventricle during diastole and right atrium during systole. Poor right heart filling leads to dilation and decreased respiratory variation of the inferior vena cava.

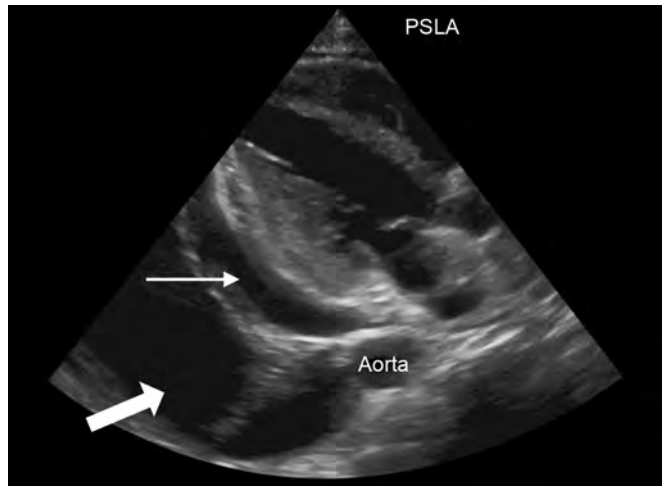


FIG. 12: Distinguishing pericardial and pleural effusion in the parasternal long-axis view. Pericardial effusion (thin arrow) tapers anterior to the descending thoracic aorta while pleural effusion (thick arrow) lies posterior to the descending thoracic aorta.

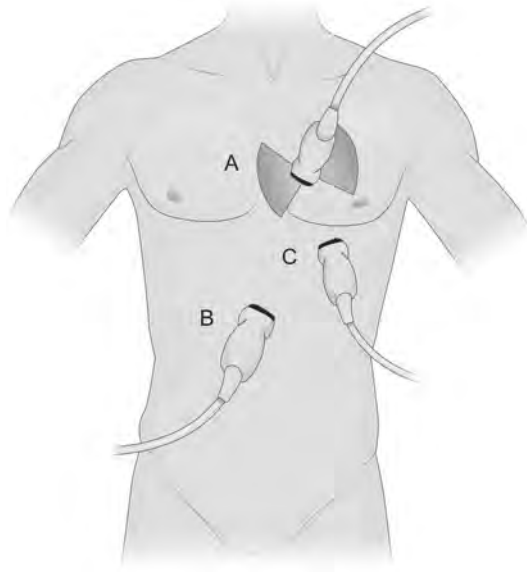


FIG. 13: Three approaches to ultrasound-guided pericardiocentesis approaches: (A) Parasternal; (B) Subxiphoid; and (C) Apical.

Preparation and Technique

Three main approaches can be used for pericardiocentesis: (1) subxiphoid, (2) parasternal, and (3) apical (**Fig. 13**). Ultrasound-guided pericardiocentesis has greater success and safety when the site of approach is selected through ultrasound visualization of the largest collection rather than a routine blind subxiphoid approach. Of note, in cardiac arrest situations, a subxiphoid approach may be preferred to allow for uninterrupted chest compressions.

The patient should have large bore IV access, supplemental oxygen provided, and remain on a cardiac monitor. Pericardial effusion and tamponade are first confirmed by ultrasound. An optimal approach is selected through identification of the largest and most accessible fluid pocket and avoidance of vital

structures. The subcostal approach is easiest in the majority of patients, while an apical approach is closest to the skin.

If time permits, a sterile cover may be placed over the transducer, the area is sterilized with chlorhexidine and covered with a sterile drape. Local anesthesia may be administered if the patient is conscious. If the patient is not in cardiopulmonary arrest, consider raising the head of bed to 30° to better localize the effusion.

Subxiphoid Approach

A subxiphoid cardiac view is obtained with the transducer flat against the abdominal wall inferior to the xiphoid process. A long 16- or 18-gauge needle is inserted between the xiphoid process and left costal margin at a shallow angle (<30°), aiming toward the tip of the left scapula. The subxiphoid approach is thought to be the easiest in the majority of patients.

Apical Approach

A view at the apex of the heart is obtained, just inferior to the left nipple in men and beneath the inferolateral left breast in women. A 16- or 18-gauge needle is inserted just adjacent to the ultrasound transducer and advanced toward the right shoulder to the cardiac apex.

Parasternal Approach

A parasternal long-axis view is obtained with the transducer placed left of the sternal border between the second and fifth intercostal spaces. The needle is inserted in-plane with the transducer at a 45° angle, directed toward the effusion. This approach offers a shorter distance from skin to effusion, and more easily avoids puncture of the liver and lung. However, there is risk of puncture of the internal thoracic artery.

In all approaches, the needle is continuously aspirated while it is advanced. Visualization of the echogenic needle will guide a trajectory toward the largest fluid pocket within pericardium. Once the pericardium is entered, fluid should be withdrawn (**Figs. 14A** to **C**). Fluid can be repeatedly removed until vital signs normalize or until no further fluid can be removed. The heart can then be visualized with ultrasound again to confirm decrease in pericardial fluid and improvement in cardiac filling and function. Resuscitation should continue to take place concurrent to the procedure. A chest radiograph should be obtained postprocedure to exclude the presence of pneumothorax.

If more prolonged drainage is necessary, a pigtail catheter may be left in the pericardial space. After pericardial fluid is aspirated using a sheathed needle, the needle is advanced additional 2 mm, the needle sheath advanced over the needle, and needle removed. Using a Seldinger technique, a guidewire is inserted through the sheath, a small skin incision is made, and the tract is dilated. Lastly, the pigtail catheter is inserted over the wire. It is very important to confirm the location of the guidewire within the pericardial space prior to dilation. If needed, further confirmation of position can be provided by injection of agitated saline or fluid with visualization of bubbling or turbulent flow in the pericardial space. If bubbling or flow is seen within the left ventricle, the needle should be withdrawn and surgery consulted.

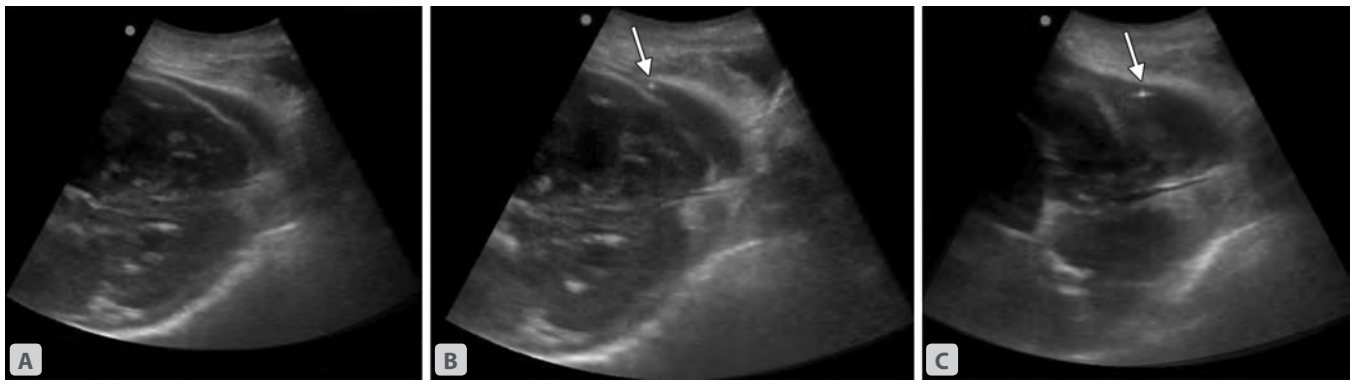
Complications

Pericardiocentesis is necessary as a lifesaving procedure, but may itself have major complications. These include worsening tamponade with cardiac arrest (if a ventricular wall or coronary artery is punctured), laceration of the coronary artery or intercostal vessels, cardiac dysrhythmias, myocardial injury, pneumopericardium, pneumothorax, puncture of the liver or abdominal viscera in peritoneal cavity, diaphragmatic injury (particularly with the subxiphoid approach), and pericardial decompression syndrome. A dry tap is another procedural risk.

ULTRASOUND-GUIDED PERIPHERAL NERVE BLOCKS

Background

Pain is the most common presentation of patients seeking care in the emergency department (ED). Safe and appropriate pain management is an important component of high quality and compassionate care. Ultrasound-guided nerve blocks have emerged as an important tool available to emergency clinicians as part of a multimodal analgesic strategy. In situations where the dosing of systemic analgesics may be limited or contraindicated, nerve blocks can serve a meaningful role (**Fig. 15**). Regional anesthesia has long been used by anesthesiologists in operative settings to provide sensory blockade for surgical procedures while avoiding the complications and side effects of general anesthesia. These nerve block techniques have similarly benefitted patients in the ED by relieving pain while reducing the need for adjunctive



FIGS. 14A TO C: Ultrasound-guided pericardiocentesis with needle tip (white arrow) seen entering the pericardial space.

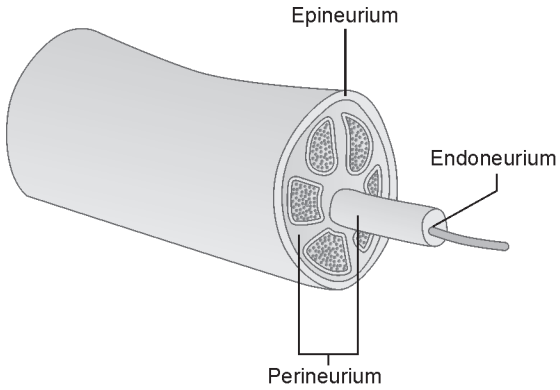


FIG. 15: Schematic representaion of peripheral nerve.

analgesics. In particular IV opioids, while commonly used, can lead to undesired and at times serious dose-related side effects, including respiratory depression, hypotension, and depressed consciousness. Furthermore, in patients with extensive injuries requiring procedural intervention, nerve blocks utilize less local anesthetic when compared to the potentially large volumes required for local infiltration, thus reducing the potential for toxicity. Unlike in the operating room, the goal of ED nerve blocks is not to provide full sensory and motor blockade, but rather to provide significant pain relief in conjunction with standard systemic analgesics, and reduce opioid-related adverse effects.

The addition of ultrasound guidance for nerve blocks permits localization of nerves, blood vessels, and key surrounding structures. It allows real-time confirmation of needle position, enabling local anesthetic to be more safely and precisely delivered to the appropriate location around the nerve. A Cochrane review reported that use of ultrasound guidance is superior to landmark and nerve stimulation methods, producing superior sensory blockade, reduced need for supplementation, and decreased complications during the performance of peripheral nerve blocks. Numerous studies support the ability of emergency physicians to learn and successfully perform ultrasound-guided nerve blocks. While a wide variety of ultrasound-guided nerve blocks have been described in the anesthesia and emergency medicine literature, this chapter will focus on five commonly performed nerve blocks for acute pain management in the ED.

Indications and Contraindications

The indications to perform an ultrasound-guided nerve block are diverse, and will be detailed in the sections describing specific blocks. Nerve blocks have broad utility for acute pain management after injury and for anesthesia during painful procedures, often as an alternative to procedural sedation or to reduce opioid requirement. Patients that may most benefit from nerve blocks include those at risk of respiratory depression (e.g., advanced age, underlying lung disease, obstructive sleep apnea, severe obesity, and polypharmacy), those with altered mental status, those with other indications for judicious opioid use (e.g., chronic opioid use and intolerance to opioid medications), and those with severe pain that is not well managed with systemic analgesics.

Contraindications to nerve blocks include allergy to local anesthetic agents, active soft tissue infection at the site of injection, injuries at risk of compartment syndrome, neurologic deficit in this distribution of the block, and inability to cooperate with the procedure. Coagulopathy or use of anticoagulants, particularly for blocks in noncompressible areas, is a relative contraindication.

Anatomy

Peripheral nerves are more easily identified by ultrasound in their short-axis. Though they may have a variable appearance depending on surrounding tissues, nerves are often echogenic, round or oval in shape, and classically have a "honeycomb" appearance. This is due to their architecture, composed of hypoechoic fascicles surrounded by more echogenic perineural and epineural connective tissue. More proximally (e.g., the brachial plexus), nerves may appear more hypoechoic; distally nerves have fewer myelinated axons and can appear more tendon-like.

It is important to adjust the transducer angle to minimize anisotropy. This is an ultrasound imaging artifact seen in musculoskeletal structures such as tendons and nerves that leads to a darker, less echogenic, and more indistinct appearance when the structure is viewed at a nonperpendicular angle. If a nerve is difficult to visualize, the transducer should be rocked or tilted to change the angle of insonation relative to the nerve thus optimizing its appearance.

Supplies

- Ultrasound system with high frequency linear transducer
- Probe cover or clear barrier adhesive dressing
- Chlorhexidine or other topical antiseptic
- Sterile ultrasound gel
- Small gauge needle (e.g., 25 g) to anesthetize the skin at injection site
- Syringe (10 or 20 cc, dependent on volume of anesthetic required), or control syringe if available
- IV extension tubing
- Blunt tip block needle (commercially available) or 20 g spinal needle
- Local anesthetic
- Gauze
- Creation of preassembled nerve block kits or storage of supplies in one central location will allow the operator to most efficiently gather the necessary materials.

Anesthetic Choice

Considerations when choosing an anesthetic agent include onset, duration, operator comfort, and local availability. Lidocaine and bupivacaine are commonly available in ED settings. For less experienced operators, lidocaine may be preferred over bupivacaine, due to its more favorable safety profile in the event of unintentional injection into vasculature. **Table 6** reviews the recommended dosing, onset, and estimated duration of action of commonly used local anesthetics in the ED (Wallace 2015).

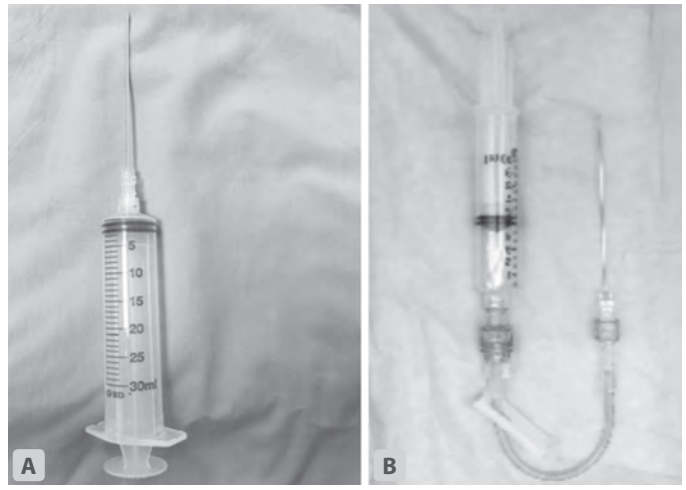
General Technique

Preparation

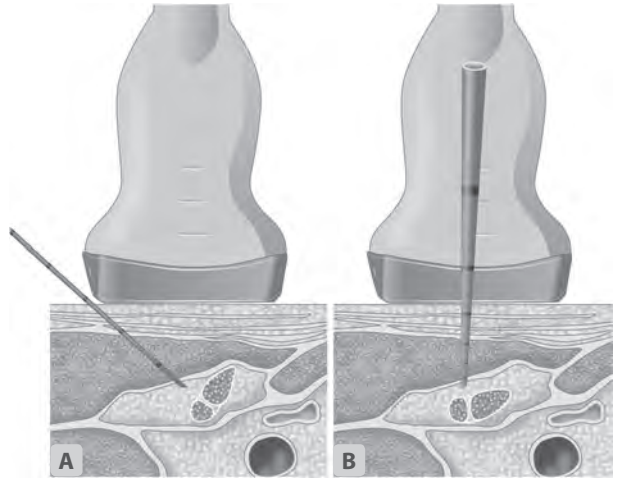
Informed consent should be obtained prior to the procedure. A discussion with relevant consulting services involved in the

TABLE 6: Dosing, onset, and duration of action of commonly used local anesthetics.

Anesthetic	*Maximum dose*	*Onset*	*Duration*
Lidocaine 1% without epinephrine	4.5 mg/kg	Rapid	60–120 min
Lidocaine 1% with epinephrine	7 mg/kg	Rapid	90–180 min
Bupivacaine 0.5% without epinephrine	2.5 mg/kg	Slow	180–360 min
Bupivacaine 0.5% with epinephrine	3 mg/kg	Slow	300–480 min



FIGS. 16A AND B: Needle and syringe setup for nerve block syringe containing anesthetic solution can be (A) connected directly to the block needle for a single-operator technique or (B) to a spinal needle through extension tubing during a two-operator technique.



FIGS. 17A AND B: In-plane and out-of-plane approaches to nerve block.

patient's care (e.g., orthopedics or trauma surgery) should take place prior to the block and consensus reached regarding appropriateness of nerve block for the presenting injury and longitudinal care plan. The presence of existing protocols for nerve blocks developed with relevant stakeholders from each department will facilitate these discussions.

The patient should have IV access and be placed on a cardiac monitor prior to the procedure. Patient positioning will be variable depending on the nerve block performed. However, ideal positioning allows the clinician to see the injection site, ultrasound display, and cardiac monitor in the same line of view. Often this is facilitated by placement of the ultrasound system on the other side of the bed contralateral to the injury.

The high-frequency linear transducer used for the procedure should be cleaned and a probe cover or clear adhesive dressing applied to the footprint of the transducer. The area is prepared with chlorhexidine and sterile ultrasound gel should be used. Once the target nerve is identified, a small gauge needle can be used to anesthetize the skin at the injection site.

The nerve block procedure may be performed with one or two operators. A single operator administering the injection on their own will use a syringe directly attached to the needle. During a two-operator technique, IV extension tubing is attached between the needle and the syringe; this allows the primary operator to have better manual control of the needle while the assistant performs the aspiration and injection once the needle tip is appropriately positioned (**Figs. 16A** and **B**). Higher volume blocks (>10 mL) may be more easily performed with two operators. Prior to starting the procedure, ensure that the block needle and tubing are primed with the anesthetic solution, as injection of air may interfere with ultrasound image quality or lead to complications.

In-plane versus Out-of-plane Approach

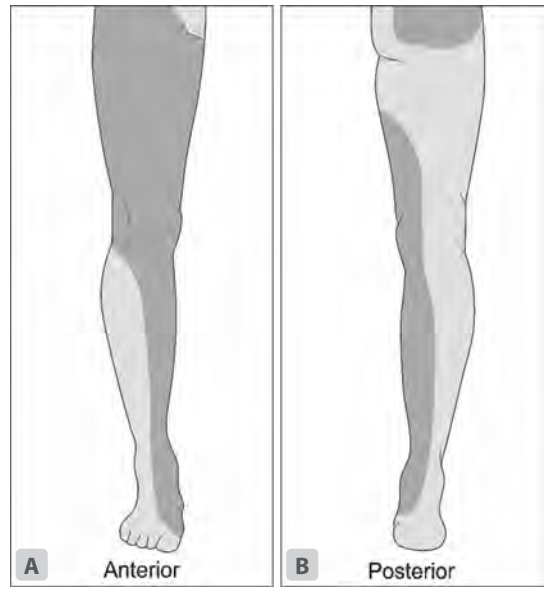
The nerve is visualized in its transverse axis and the nerve block procedure may be performed using either an in-plane (longitudinal) or out-of-plane (transverse) technique (**Figs. 17A** and **B**). An in-plane approach is generally preferred. Here, the needle is introduced under the lateral edge of the transducer, and the entire length of the needle is visualized as it approaches the target nerve. This makes the needle easier to track, and decreases the risk of injury to important soft tissue structures or puncture of the nerve itself. Use of a shallow angle may facilitate visualization of the needle. In an out-of-plane approach, the needle enters skin perpendicular to the long-axis of the transducer, and only a cross section of the needle (ideally the tip) is visualized. The out-of-plane approach is often more technically challenging. With either approach, to maximize block success and minimize complications, the operator should be aware of the position of the needle tip at all times. The needle should never be advanced if the position of the tip is uncertain. To localize the needle tip, the transducer can be tilted to scan through to the tip of the needle or rotated to better align with the trajectory of the needle. Alternatively, the needle can be withdrawn slightly to visualize tissue movement to confirm its position. Lastly, a small amount of anesthetic solution can be injected allowing identification of the needle tip at the collection of anechoic fluid. Techniques for specific blocks will be described subsequently in this chapter.

Postblock Care

The patient should remain on cardiorespiratory monitoring for at least 30 minutes following nerve block. Members of the healthcare team should be informed about the block, and

the extremity marked. Due to numbness and weakness of the blocked extremity, the patient must be cautioned to exercise care to avoid falls or injury to the extremity during the duration of nerve blockade.

Complications: Compartment syndrome, particularly after fractures, burns, or crush injury, is a feared but uncommon complication. There has been no evidence to date to suggest that nerve blocks have led to delayed diagnosis of a compartment syndrome. However, with high-risk injuries, discussion with the appropriate consulting services should take place prior to performing a nerve block. Nerve damage after a nerve block is also uncommon, and if it occurs, is usually transient or mild. The risk of nerve injury is higher if injection takes place within the epineural sheath, thus the operator should stop the injection if the resistance to injection of anesthetic solution is encountered, or if the patient reports painful paresthesia. These may suggest intraneural needle placement. A complete preblock sensory and motor examination should be performed and documented in the medical record. Local anesthetic systemic toxicity (LAST) is a rare but life-threatening complication caused by the sodium channel blockade of local anesthetic agents. The symptoms of LAST occur over a dose-dependent clinical spectrum, beginning with perioral numbness, lightheadedness, tinnitus, and audiovisual disturbances. This may progress to seizures, altered mental status, and coma, followed by dysrhythmias and cardiovascular collapse. The onset of LAST can take place within minutes if inadvertent intravascular injection occurs, or may be delayed up to 30 minutes as subcutaneous absorption takes place. For this reason, patients should be closely monitored for at least 30 minutes after the nerve block procedure. The treatment of LAST begins with supportive airway management, advanced cardiac life support (ACLS), and seizure suppression with benzodiazepines. For lidocaine toxicity, supportive management alone may be sufficient, given the shorter half-life of this drug. Lipid emulsion therapy may be required for bupivacaine or other agents with a relatively long half-life. Dosing of 20% lipid emulsion is a 1.5 mg/kg bolus followed by a 0.25 mL/kg/min infusion, continued until the patient is hemodynamically stable for 10 minutes. Prior to performing a nerve block, the operator must be aware of the availability and location of the lipid emulsion, and local protocols for administration. LAST is a devastating but avoidable compilation of nerve blocks. The operator must take care to calculate the maximum dose of anesthetic in advance of the procedure, use the lowest effective dose, and ensure aspiration before infiltration to avoid intravascular dosing.



FIGS. 18A AND B: Distribution of femoral block.

(FN: femoral nerve; FA: femoral artery; Dotted line: fascia iliaca)

FIG. 19: Ultrasound of femoral nerve.

Specific Blocks

Femoral Block Indications

The femoral block aims to anesthetize the femoral nerve (and may also block the obturator and lateral femoral cutaneous nerves) through anesthetic spread beneath the fascia iliac (**Figs. 18A** and **B**). It provides analgesia for hip fractures or dislocations, femoral shaft fractures, patellar fracture or dislocation, and anesthesia for anterior thigh or patellar laceration repairs or abscess drainage.

Anatomy and scan technique: The femoral nerve is a major branch of the lumbar plexus traveling with the femoral vessels under the inguinal ligament into the femoral triangle. To image the nerve, the patient should be in a supine position, with the hip externally rotated and abducted if possible. The transducer is placed parallel to the inguinal crease and the femoral artery and vein first identified. Slide laterally until the hypoechoic, triangular femoral nerve is visualized, deep to the fascia iliaca and immediately lateral to the femoral artery (**Fig. 19**).

The area is disinfected with chlorhexidine and the injection site should be anesthetized locally. The needle will enter the skin approximately 1-cm lateral to the ultrasound transducer, advancing medially toward the femoral nerve while maintaining visualization of the needle tip. Once the needle is below the fascia iliaca and approximately 1 cm from the nerve, aspirate to ensure the needle is not intravascularly positioned, then slowly inject 1–2 mL of local anesthetic to confirm appropriate needle placement. This will reduce the risk of intravascular injection and puncture of the nerve.

When the needle is correctly positioned, injection will result in displacement of the femoral nerve and fascia iliaca. If not, the needle should be repositioned. A total of 10–20 mL of anesthetic solution is adequate for femoral nerve blockade, though the operator should maintain awareness of the maximum weight-based dose for the patient.

Popliteal Sciatic Block Indications

The sciatic block is easily performed near the popliteal fossa and anesthetizes the lower leg distal to the knee, providing analgesia for tibia and fibular fractures, ankle fractures and dislocations, Achilles tendon ruptures, or foot injuries (**Figs. 20A** and **B**). If there is concern for compartment syndrome, this block should take place in consultation with the service that will have longitudinal care of the patient.

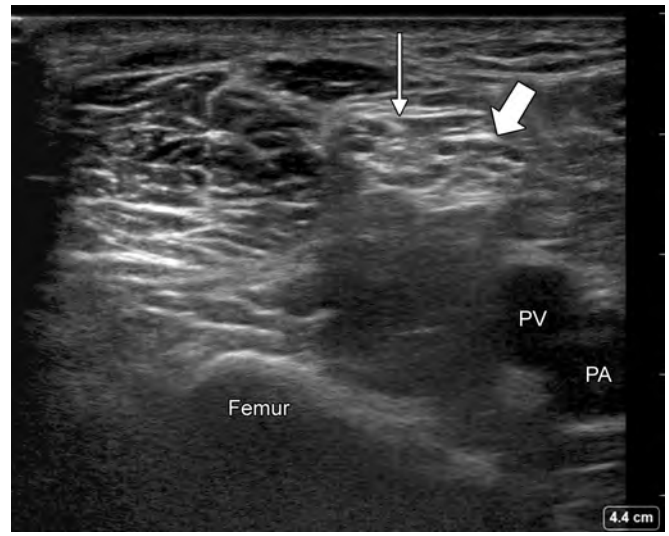
Anatomy and scan technique: The sciatic nerve is formed by the lumbosacral plexus, traverses the posterior thigh. It bifurcates into the common peroneal nerve (medial) and tibial nerve (lateral) just before entering the popliteal fossa. To image the nerve, the patient should be placed in a prone position; if this is not achievable, the patient may remain supine with leg elevated and supported with pillows/blankets to allow access to the popliteal fossa (**Fig. 21**). The knee should be mildly flexed if possible. The high-frequency linear transducer is placed at the popliteal crease, and the popliteal artery and vein are first identified. The hyperechoic and oval-shaped tibial nerve will be seen superficial and lateral to the popliteal vein; the common peroneal nerve will lie superficial and lateral to the tibial nerve. Slide the transducer proximally until the two nerves unite to form the distal sciatic nerve, usually 5–10 cm from the popliteal crease and at a depth of 2–4 cm.

The area is disinfected with chlorhexidine and the injection site should be anesthetized locally. Given the relatively superficial position of the nerve, needle entry should take place several centimeters from the probe in the lateral thigh, allowing for a shallow angle to enable visualization of the needle. The needle tip is slowly positioned just above and adjacent to the sciatic nerve where it begins to bifurcate within the common sciatic nerve sheath. Aspirate to ensure the needle is not intravascularly positioned, then slowly inject 1–2 mL of local anesthetic to confirm appropriate needle placement. Local anesthetic spread should be seen within the sheath around the nerve(s), both proximal and distal to the nerve division. A total of 15–20 mL of anesthetic solution will provide nerve blockade, though the operator should maintain awareness of the maximum weight-based dose for the patient.

Posterior Tibial Block Indications

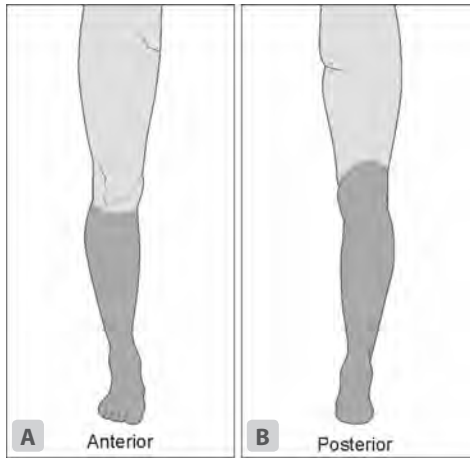
The posterior tibial nerve innervates the heel and sole of foot and provides analgesia for calcaneal fractures and anesthesia for repair of sole of foot lacerations and foreign body removal (**Fig. 22**).

Anatomy and scan technique: The posterior tibial nerve arises from the tibial branch of the sciatic nerve and is most easily visualized at the medial ankle. With the patient in a supine position and lower leg externally rotated, a high-frequency linear transducer is placed in a transverse orientation at the level of the medial malleolus. The nerve has a classic hyperechoic honeycomb appearance and can be identified just posterior to the posterior tibial artery. It may resemble nearby tendons including the tibialis posterior, flexor digitorum longus, and flexor hallucis longus. Of these structures, the posterior tibial



(Thick arrow: tibial nerve; Thin arrow: common peroneal nerve; PA: popliteal artery; PV: popliteal vein)

FIG. 21: Ultrasound of popliteal sciatic nerve.



FIGS. 20A AND B: Distribution of sciatic block.

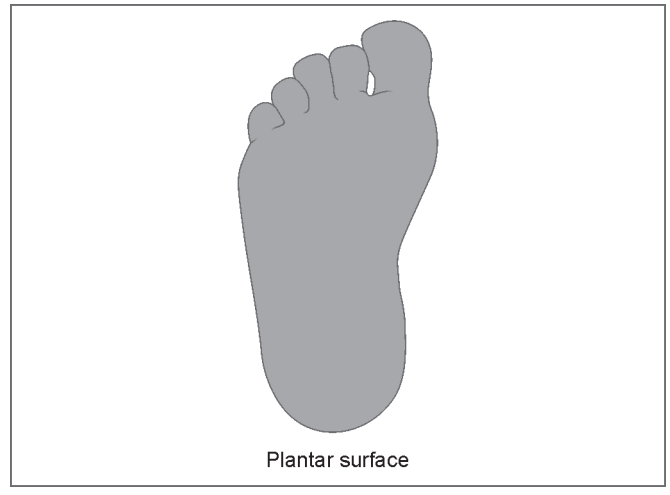


FIG. 22: Distribution of posterior tibial nerve block.

nerve is most intimately related to the artery, which can aid in its identification. To confirm, the transducer may be moved proximally—the nerve will maintain its appearance while tendons will transition into muscle (**Fig. 23**).

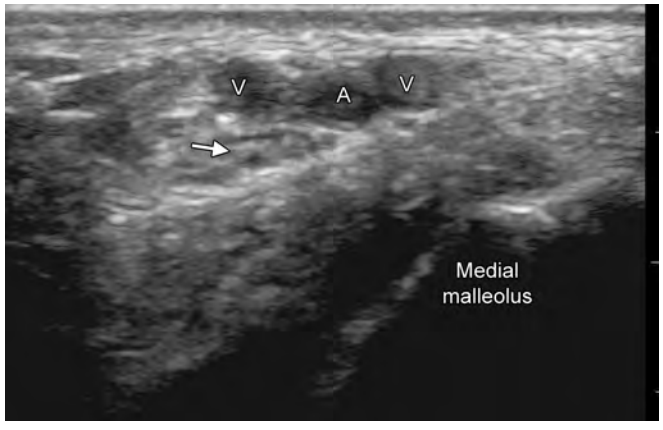
Procedure: As the posterior tibial nerve is superficially positioned, only a 1.5 inch 22- or 25-gauge needle is required. The area is disinfected with chlorhexidine and the injection site should be anesthetized locally. The needle is inserted just posterior to the medial malleolus and posterior tibial artery, directed posteriorly. Either an in-plane or out-of-plane technique may be used depending on patient positioning and ergonomics. Aspirate to ensure the needle is not intravascularly positioned. A total of 3–5 mL will be adequate for a successful block.

Interscalene Block of the Brachial Plexus Indications

The interscalene block anesthetizes cords of the brachial plexus to provide upper extremity analgesia and anesthesia for shoulder fractures and dislocations, clavicle fractures, humerus fractures, and elbow fractures and dislocations, forearm fractures, and upper extremity laceration repairs and drainage of large abscesses (**Fig. 24**). This is a more advanced nerve block due to nearby key structures (e.g., carotid artery, subclavian vessels, and pleura). In addition, this block is associated with phrenic nerve blockade leading to hemidiaphragmatic paralysis. Patients with acute or chronic respiratory disease may not be good candidates for this block. Furthermore, high volumes of anesthetic can spread to the sympathetic chain, leading to a transient Horner's syndrome.

Anatomy and scan technique: The brachial plexus originates from the ventral rami of C5-T1 and its cords can be found in the interscalene groove of the neck between the anterior and middle scalene muscles. Position should be optimized prior to the procedure with the patient supine with the head of bed elevated 30°, head turned away from the side being blocked, and a towel roll placed under the ipsilateral scapula (**Fig. 25**). The transducer is placed in a transverse orientation just below the level of the cricoid cartilage, and the carotid artery, IJ vein, and sternocleidomastoid muscle are identified. Slide laterally until the anterior and middle scalene muscles are seen, and the cords of the brachial plexus will be visualized in the groove between these two muscles as three large hypoechoic circles at 1–3 cm depth. They are frequently described as a "traffic light." Alternatively, the supraclavicular brachial plexus can first be identified above the clavicle and tracked superiorly to the interscalene groove. The goal is to place the needle tip in the tissue plane between the anterior and middle scalene muscles. Color Doppler may be used to confirm location of vascular structures.

The area is disinfected with chlorhexidine and the injection site should be anesthetized locally. The needle is inserted at a shallow angle approximately 1 cm from the transducer moving in a lateral to medial direction through the middle scalene muscle, choosing a plane that avoids puncture of the external jugular vein. Maintain visualization of the needle tip at all times. When the interscalene groove is reached, aim the needle tip between two nerve roots (to avoid nerve injury), aspirate to ensure the needle is not intravascularly positioned, then slowly inject 1–2 mL of local anesthetic to confirm appropriate



(V: posterior tibial veins; A: tibial artery; Arrow: tibial nerve)

FIG. 23: Posterior tibial nerve.

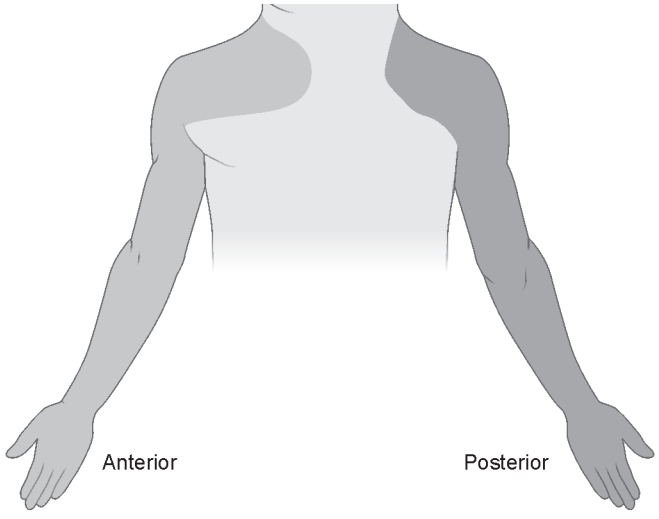


FIG. 24: Distribution of interscalene nerve block.

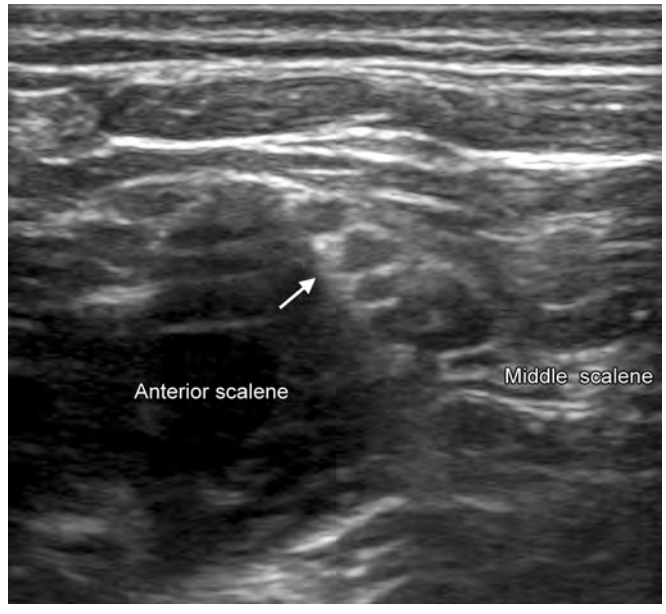


FIG. 25: Cervical plexus with C5, C6, and C7 trunks in a "stoplight" orientation (arrow), located between the anterior and middle scalene muscles.

needle placement through visualization of spread of anechoic anesthetic solution. If no fluid is seen, there should be concern for intravascular injection. Furthermore, significant resistance to injection may suggest an intrafascicular injection. After appropriate needle placement is confirmed, a total of 10–20 mL of anesthetic may be injected and needle repositioning may be needed to facilitate spread around the brachial plexus.

Axillary Block Indications

This block anesthetizes the radial, median, ulnar, and musculocutaneous nerves for analgesia of the upper extremity from the mid-arm distally, and is named for the approach and not blockade of the axillary nerve itself (**Fig. 26**). This block has a lower risk of complications relative to the interscalene block. It may be performed for elbow, forearm, wrist and hand fractures, and dislocations. Although the individual nerves can be identified on ultrasound, this is required as the spread of local anesthetic to nerves around the axillary artery can produce an effective block.

Anatomy and scan technique: Three primary branches of the brachial plexus can be seen surrounding the axillary artery in a superficial location in the proximal arm—the median, ulnar, and radial nerves. The musculocutaneous nerve may also be found in this area in the plane between the coracobrachialis and biceps muscles. The arm is abducted to 90° to allow space for transducer and needle manipulation. The transducer is placed in a transverse orientation on the upper arm just distal to the pectoralis major insertion and overlying both the biceps and triceps muscle. The axillary artery will become apparent (**Fig. 27**). Local anesthetic solution will be infiltrated around the axillary artery and spread to the median, radial, and ulnar nerve, which may not always be well visualized.

The area is disinfected with chlorhexidine and the injection site should be anesthetized locally. Using an in-plane technique, the needle is inserted from anterior directed toward the posterior axillary artery. Anesthetic solution should be first injected posteriorly to the radial nerve. Starting with an anterior injection may displace deeper structures, making them more difficult to access. After the infiltration of approximately 5 mL of anesthetic, the needle is withdrawn and redirected medially and anteriorly to reach the median and ulnar nerves. An additional 5–10 mL of anesthetic will be required here. If the individual nerves are not well seen, a simplified perivascular approach may be used with injection of 5–10 mL of anesthetic solution posterior to the axillary artery. A separate injection is required to block the musculocutaneous nerve—the needle is again withdrawn and directed to this nerve, requiring 5–7 mL of solution. Given the number of needle redirections required for this procedure, frequent aspiration is required to prevent accidental intravascular injection.

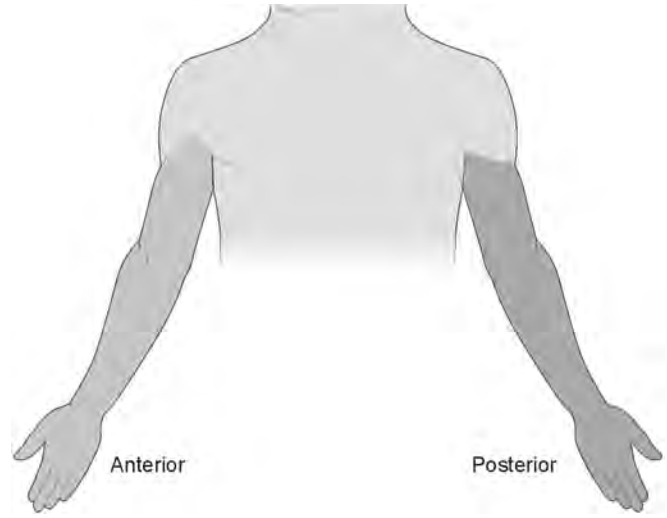
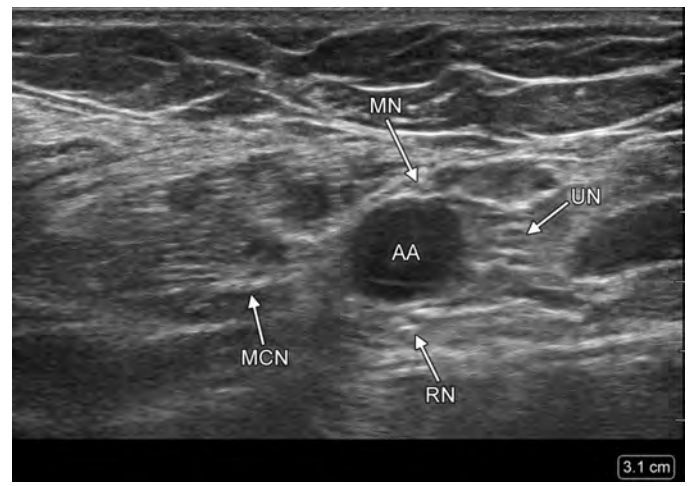


FIG. 26: Distribution of axillary block.



(AA: axillary artery; UN: ulnar nerve; RN: radial nerve; MN: median nerve; MCN: musculocutaneous nerve)

FIG. 27: Axillary block.

SUMMARY

Ultrasound-guided vascular access is a common but essential procedure that may be lifesaving. The use of ultrasound guidance improves procedural success, decreases the number of attempts, and decreases complications—particularly for central venous access. While the procedure may be performed using in-plane and out-of-plane techniques, both require practice and mastery in visualizing the needle tip to assure safety and success.

Pericardiocentesis can be a lifesaving procedure in patients presenting with hemodynamic instability due to pericardial tamponade. Ultrasound allows identification of the largest fluid collection to identify an optimal approach and permits real-time visualization of needle position. The use of point-of-care ultrasound is a gold standard to aid in the diagnosis of tamponade, improve procedural success, and minimize procedural complications.

Ultrasound-guided nerve blocks are an important tool for ED clinicians to provide effective pain management for acute injury or procedural anesthesia that can avoid the complications of systemic opioid administration. Knowledge of sensory distribution key nerves, sonographic anatomy of nerves and surrounding structures, and the dosing and complications of local anesthetic agents will enable the clinician to maximize procedural safety and success.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Cricothyrotomy

Sanjay Shah

INTRODUCTION

Cricothyrotomy also known as cricothyroidotomy is an emergency procedure that is used to secure an airway when routine methods, i.e., endotracheal intubation are failed or ineffective or contraindicated. Cricothyroidotomy is preferred over tracheostomy because it is easy to perform, is associated with less bleeding, and requires less time to perform. Cricothyroidotomy involves insertion of a needle or tube through the cricothyroid membrane into the trachea in an emergency situation to provide oxygen on a short-term basis until a definitive airway can be placed. Cricothyroidotomy can provide supplemental oxygenation temporarily so that one can get time to achieve definitive airway (intubation or tracheostomy) by expert.

APPLIED ANATOMY

Specific knowledge of anatomy of larynx is required for safe and successful performance of cricothyroidotomy. Ignorance of anatomy may lead to failure or complication. Identifying the cricothyroid membrane as shown in **Figure 1** or median cricothyroid ligament (situated between cricoid and thyroid cartilage) and its dissection is the main components of various type of cricothyroidotomy such as needle cricothyroidotomy, percutaneous cricothyroidotomy, or surgical cricothyroidotomy. Emergency physician must be aware about the anatomy related to cricothyroidotomy to avoid dreaded complication such as acute endolaryngeal hemorrhage. Cricothyroidotomy can be a lifesaving procedure in emergency department in case of difficult intubation. Various indications for performing the cricothyroidotomy are described further.

INDICATIONS

Cricothyroidotomy is indicated upon failure to obtain an airway with traditional methods in the following situations—various methods are described for performing the cricothyroidotomy and instruments are arranged according to the method used (**Box 1**).

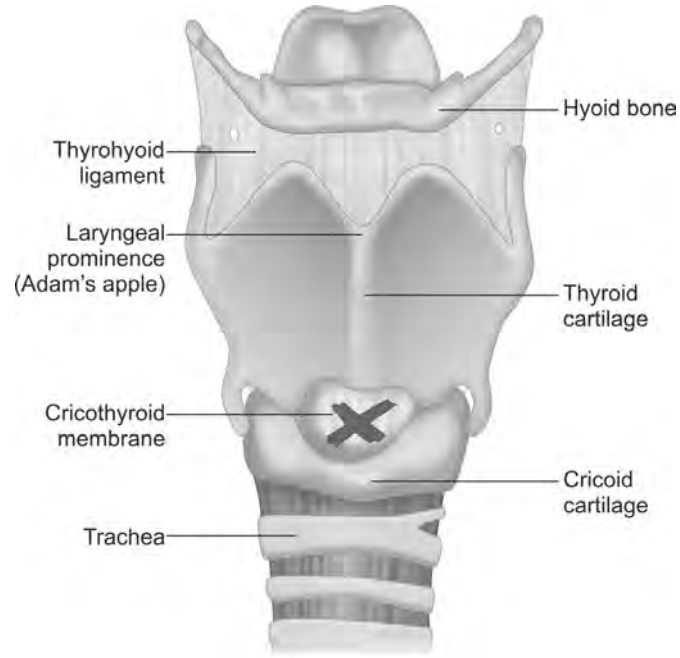


FIG. 1: Applied anatomy of larynx.

BOX 1: Requirements of instruments.

Antiseptic preparation: Antiseptic preparation solution lidocaine sterile drape/gown/gloves syringe (10 mL) bag-valve mask

For surgical cricothyroidotomy: No. 11 scalpel blade, trousseau dilator, tracheal hook, small size (4.5–6) tracheostomy tube, or endotracheal tube

For needle cricothyrotomy: Intravenous (IV) cannula catheter (14 gauge or larger), pediatric endotracheal tube or modified IV extension set for transtracheal jet insufflations (3-mm endotracheal tube adapter with a Y-connector)

For percutaneous cricothyrotomy: "Percutaneous cricothyroidotomy kit" for using the Seldinger technique, includes a finder needle with a dilator and a guidewire

- Trauma causing oral, pharyngeal, or nasal hemorrhage
- Facial muscle spasms or laryngospasm
- Uncontrollable emesis
- Upper airway stenosis or congenital deformities
- Clenched teeth
- Tumors, cancer, or another disease process or trauma causing mass effect

Airway obstruction indications include the following:

- Oropharyngeal edema
- Foreign body obstruction

The following are relative indications for cricothyroidotomy:

- Cervical spine immobilization secondary to injury
- Maxillofacial injuries

Cricothyroidotomy is contraindicated in younger patients with age of the patient <12 years, as the cricothyroid membrane is quite narrow resulting in an increased risk of permanent laryngeal injury. Other contraindications include obstruction distal to cricoid membrane, infection or lesion at site of incision, lack of expertise, history of neck surgery, hematoma, trauma/burns, and obesity which may make localization of landmark difficult.

POSITION OF THE PATIENT

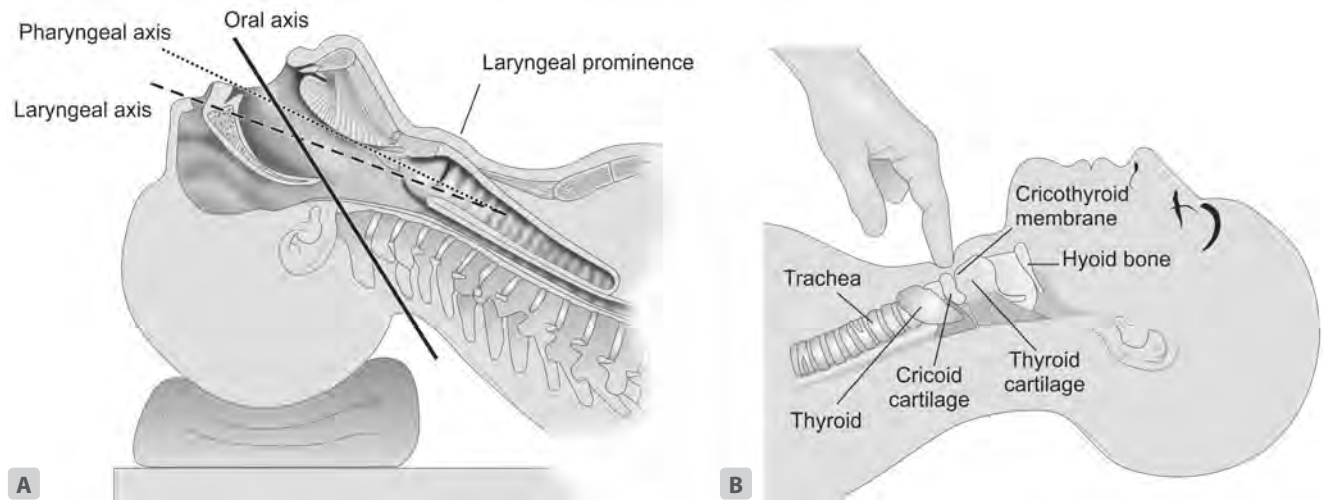
The patient should be placed supine with the neck in the neutral position. Position the patient in such a way that external anatomy or laryngeal prominence is exposed and palpate the cricothyroid membrane (**Figs. 2A** and **B**)

NEEDLE CRICOTHYROTOMY

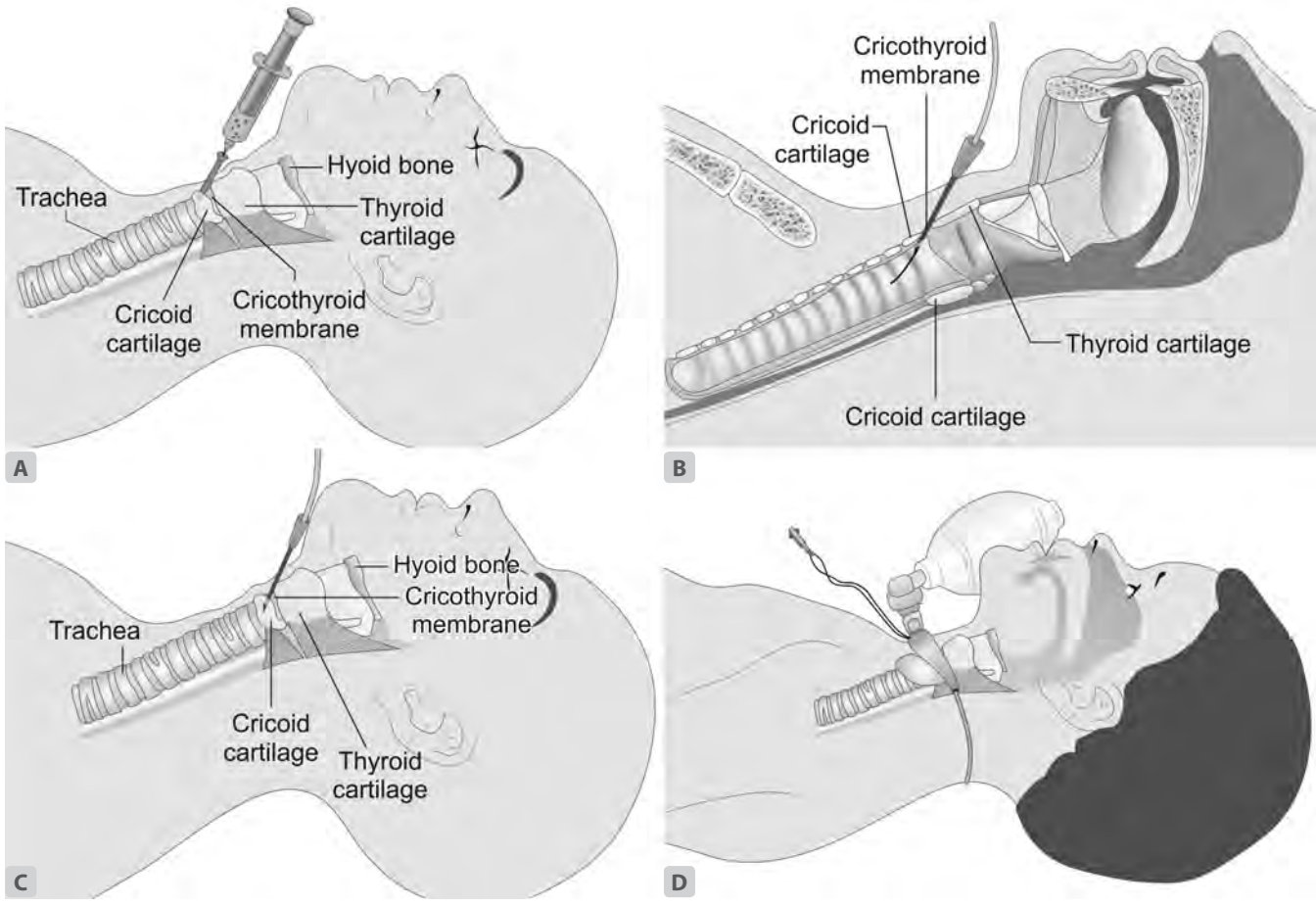
Under all aseptic precautions, proper painting and cleaning with antiseptic solution done over anterior aspect of neck with cervical spine immobilization. Thyroid and cricoid cartilage are palpated and stabilized using thumb and third finger of nondominant hand and cricothyroid membrane palpated with index finger. With the dominant hand, IV cannula catheter attached to the syringe filled with normal saline is inserted at a 45° angle in the caudal direction into the cricothyroid membrane (**Fig. 3A**). With continuous negative pressure applied to the syringe, the needle is advanced. As the needle pierces the cricothyroid membrane and enters the trachea, a distinct pop can be felt. In addition, air bubbles will appear in the syringe with saline (**Fig. 3B**). Catheter is advanced and the needle is pulled out (**Fig. 3C**). Catheter is attached with jet ventilation device, and ventilated at 40–50 lb psi or 15 L/min. If this device is unavailable, attach the barrel of a 3-mL syringe to the catheter, and place an endotracheal tube adapter. An Ambu bag can then be attached to deliver oxygen for ventilation (**Fig. 3D**). Placement is confirmed through observation of chest rise, auscultation, and assessment of end-tidal CO_2.

PERCUTANEOUS CRICOTHYROIDOTOMY (SELDINGER TECHNIQUE)

This is performed by using "cricothyroidotomy kit" (**Figs. 4A** and **B**) available commercially and by using a Seldinger technique. A finder needle attached to a syringe is substituted for the IV cannula catheter and steps of needle cricothyroidotomy are followed. Syringe is removed from the needle and the guidewire is advanced through the needle. The needle is removed once the guidewire is in place. A small stab incision is made using the scalpel in the skin close to the guidewire. Airway catheter along with dilator is inserted over the wire. The dilator and the guidewire both are removed once the airway tube is placed in the trachea. Placement is confirmed through observation of chest rise, auscultation, and assessment of end-tidal CO_2. The tube is secured in place with appropriate tape. The cannula is then connected to high-flow oxygen at 15 L/min (50–60 psi) with a Y-connector. Intermittent insufflation, 1 second on for inspiration and 4 seconds off for exhalation, should be done by placing the thumb over it. In this fashion, patient may be adequately ventilated for 30–45 minutes using this technique. Because of the inadequate exhalation, CO_2 slowly accumulates and thus limits the use of this technique for longer time, especially in head injury patients. Significant barotrauma can occur and may convert simple pneumothorax into tension pneumothorax. Therefore, careful and frequent monitoring must be done till definitive airway achieved either by intubation or tracheostomy.



FIGS. 2A AND B: (A) Positioning the patient to expose the laryngeal prominence; (B) Palpate laryngeal membrane.



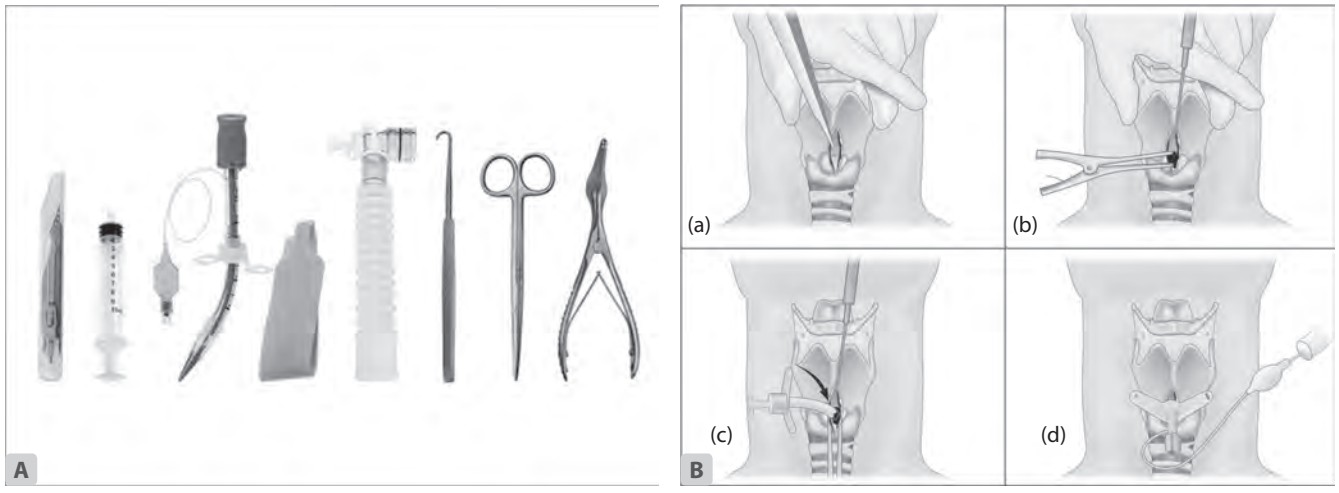
FIGS. 3A TO D: (A) Syringe attached with IV cannula is advanced; (B) Air bubble is seen in syringe; (C) Needle is pulled out and catheter is advanced; and (D) Attached with jet ventilation/Ambu.

FIGS. 4A AND B: Percutaneous cricothyroidotomy by "cricothyroidotomy kit."
Courtesy: Dr Amit D Nabar.

SURGICAL CRICOTHYROIDOTOMY

Requirements of instrument for surgical cricothyroidotomy are as per **Figure 5**.

Follow "step 2" from needle cricothyroidotomy. With the dominant hand, midline vertical incision is made, approximately 3 cm long and skin deep, over the cricothyroid membrane. The cricothyroid membrane is palpated through the incision, using the index finger of the nondominant hand. A horizontal stab incision is made through the membrane. A distinct pop will be felt as the scalpel pierces the membrane and enters the trachea. The tracheal hook is inserted by an



FIGS. 5A AND B: (A) Instruments for surgical cricothyroidotomy; (B) Steps of surgical cricothyroidotomy.

assistant at the superior end of the incision and the skin and membrane retracted cephalad. Using the Trousseau dilator, incision is dilated vertically. With the dominant hand, the tracheostomy tube is inserted between the two blades of the dilator, directing it initially to one side of the patient. Once the tube is through the membrane, it is rotated 90° and inserted caudally. The obturator is removed, and the inner cannula inserted and locked into place. The balloon is inflated with 5–10 mL of air. The tube attached to a catheter mount piece and attached to ventilatory support. Placement is confirmed through observation of chest rise, auscultation, and assessment of end-tidal CO_2. The tracheal hook is removed and the tube is secured in place.

COMPLICATIONS

Bleeding and misplacement of the tube are the most common complication related to cricothyroidotomy in emergency department, acute complications are incorrect placement of tube, subcutaneous emphysema, barotrauma, prolonged procedure time, and injury to surrounding structure. Complications are summarized in **Table 1**.

TABLE 1: Complications of cricothyroidotomy.

Early complications	*Late complications*
• Bleeding • Incorrect placement, resulting in possible creation of a false passage through tissue • Subcutaneous emphysema • Obstruction • Esophageal or mediastinal perforation • Aspiration • Vocal cord injury • Pneumothorax • Laryngeal injury • Posterior tracheal wall perforation • Thyroid perforation • Hypercarbia (needle cricothyroidotomy)	• Dysphonia • Infections • Hematoma • Persistent stoma • Scarring • Glottic or subglottic stenosis • Laryngeal stenosis • Tracheoesophageal fistula • Tracheomalacia

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57 CHAPTER

Tracheostomy Related Emergencies

Devendra Richhariya, Bhawana Sharma

INTRODUCTION

Tracheostomies are associated with complication in about 40–50% cases but majority of these complications are minor and in only 1% of tracheostomy patients, catastrophic complication occurs. That's why important for the emergency physician to recognize the signs and symptoms of tracheostomy-related emergencies and provide initial stabilization and, potentially, life-saving interventions. Tracheostomy is performed in upper airway obstruction, control of secretions, possibilities for long-term airway protection and or long-term ventilation, severe obstructive sleep apnea, and head and neck surgery. Percutaneous dilatational approach or open surgical approach are used to place tracheostomies, opening is created into the trachea through the anterior neck where the tracheal mucosa and brought into continuity with the skin, tracheostomies are placed between the second and third tracheal rings. Higher incisions increase the risk of laryngeal injury and lower incisions increase the risk of decannulation and vessel injury. Both two techniques have similar complications rate.

Tracheostomy-related complications can be divided in to three categories. (1) First intraoperative complications, including hemorrhage, air embolism, and damage to the trachea, (2) second intermediate (early postoperative) complications include hemorrhage, tube decannulation, extratracheal air (subcutaneous emphysema, pneumothorax, and pneumomediastinum), and infection and third Late (3) postoperative complications include hemorrhage, tracheal stenosis, tube decannulation, and fistula formation.

For the emergency management purpose, tracheostomy complications can be grouped into emergent life-threatening complications and urgent complications. Emergent life-threatening complications include tube decannulation, tube obstruction, and hemorrhage. Urgent subacute complications include tracheoesophageal fistula (TEF) formation, tracheal stenosis, infection, and tracheocutaneous fistula formation. Comorbid conditions must be considered when making management decisions.

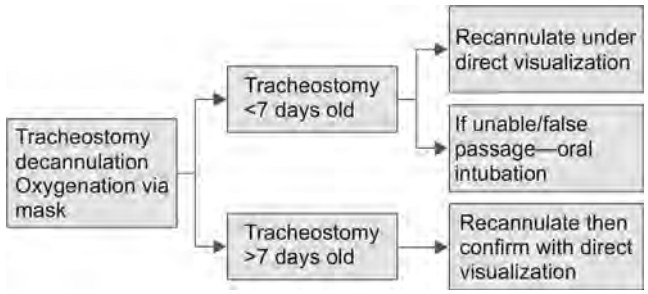
EMERGENT LIFE-THREATENING COMPLICATIONS

Tracheostomy Decannulation

Following tracheostomy placement, tracheostomy tube decannulation can occur at any time. The incidence of tracheostomy displacement varies between 0.35% and 15%. Often decannulations may be handled by the patient or caregiver without any further clinical care, so the incidence may be higher than reported. Lack of mature stoma formation and a narrower tracheocutaneous tract, within the first week of placement, decannulations are most concerning because this increases the risk of airway loss. Accidental decannulation of tracheostomy risk increases in conditions where altered mental status, traumatic brain injury, copious secretions, recent tracheostomy change, increased neck thickness, and pediatric age. Decannulation is reported more in percutaneously placed tracheostomies rather than those placed using an open surgical approach.

Emergency department (ED) management of displaced tracheostomy: When a patient presents to the ED with a displaced tracheostomy tube, two major information must be obtained through history taking. First, time of the tracheostomy placement, and second, time of decannulation of tracheostomy. On examination, possibilities of two variety of presentation, patient may present with the completely displaced tracheostomy from the stoma or partially displaced with the tracheostomy tip present in the soft tissue of the neck.

Action: Replacement of tube is indicated without delay is indicated when decannulation occurs, Stoma (opening) may significantly become narrow in few hours' time even if it is a mature stoma, delayed recannulation makes procedure more challenging and necessitating the use of a smaller tracheostomy tube during replacement. If history of placement of tracheostomy tube is <7 days, replacement of a dislodged tracheostomy is attempted only under direct



FLOWCHART 1: Management of tracheostomy decannulation.

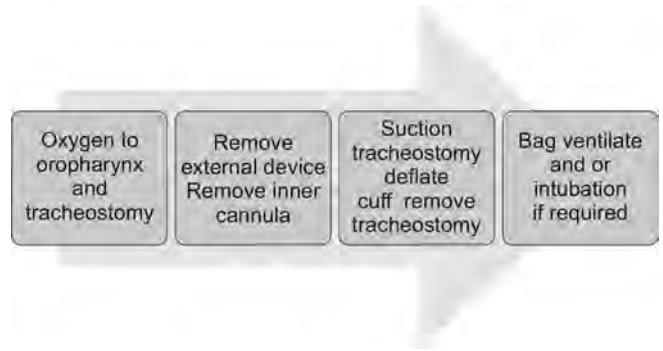


FIG. 1: Management of tracheostomy occlusion.

visualization of fiberoptic endoscopy because risk of creating a false passage into the soft tissue of the neck is very high. If fiberoptic visualization is unavailable or procedure is unsuccessful, oral intubation may be necessary to secure the airway and ventilate the patient (**Flowchart 1**). If history of tracheostomies placement is >7 days, if dislodgement occurs, a new tracheostomy tube is inserted through the stoma and confirmed by fiberoptic visualization. If any resistance is met while inserting the tube, a smaller tracheostomy tube should be selected and insertion reattempted. During unsuccessful procedure of recannulation, and patient fails to oxygenate or ventilate, bag-valve ventilation and oral intubation may be necessary.

Following recannulation, low-volume, gentle bag-valve ventilation can be used to assist ventilation. If subcutaneous emphysema develops, tracheostomy placement must be evaluated through direct visualization due to possible false passage with placement of the tracheostomy tube into the paratracheal soft tissue of the neck. If proper placement is confirmed, the trachea must be subsequently evaluated for injury. Continuous capnometry is used to monitor ventilation during and after recannulation.

Tracheostomy Obstruction

Dried secretions, mucous plugs, clotted blood, partial tube displacement, impingement by the posterior tracheal wall, granulation tissue build up, or displacement of the tracheostomy into a false lumen is the common causes for obstruction of the lumen of a tracheostomy tube. Other risk factors for obstruction include small tracheostomy tube size, single cannula tracheostomy tube, and poor tracheostomy care. Pediatric patients are more at risk for tracheostomy related death. Stepwise approach is required for management of tracheotomy obstruction (**Fig. 1**). An initial simple step is to remove any obstructing material from the external end of the tracheostomy lumen, such as a speaking valve, obturator, decannulation cap, bandages, or humidifying devices. Inner cannula is removed from the double-cannula tracheostomy and suctioning is performed when obstruction is suspected and will relieve most obstructions. Complete obstruction is ruled out if a suction catheter can be passed through the entire length of the tracheostomy till trachea. If a suction catheter cannot be passed, a complete obstruction of the tracheostomy tube is present. Stiff instruments, such as gum-elastic bougies should not be used to assess the patency because they can create a false passage. To improve ventilation and oxygenation patient's assisted with positive pressure ventilation, if necessary. The cuff should also be deflated so that airflow enters from surrounding of tracheostomy tube because flow through the tracheostomy tube lumen is obstructed.

If a new tracheostomy is placed, the balloon is inflated to provide effective positive pressure ventilation. If even after all these measures, patient continues to be distressed from airway obstruction, the tracheostomy tube should be removed and provides high-flow oxygen via both face and tracheostomy stoma and monitored by capnometry, and not necessary to reinsert the tube urgently. The patient with tracheostomy stoma has two airway openings (tracheostomy and oronasopharynx). If the patient is ventilated via the mouth, the tracheal stoma must be occluded with gauze (**Fig. 2A**). If the patient is ventilated via the tracheal stoma, the oral, and nasal pharynx must be occluded. A pediatric face mask or laryngeal-mask airway can be placed over the stoma to generate airway positive pressure when ventilating (**Fig. 2B**). Intubation should be attempted if oxygenation is not maintained by bag-valve ventilation. Endotracheal tube must be advanced beyond the stoma to generate positive pressure in the lower airway after the balloon is inflated. Fiberoptic scope or bougie-guided intubation of the stoma can be attempted if the tracheostomy is more than a week old. A smaller tracheostomy tube or endotracheal tube can be placed directly into the stoma, if oral intubation is anticipated to be difficult. Once the obstruction is partially or completely relieved, the patient's ventilation should be monitored with continuous capnometry and pulse oximetry and assisted with positive pressure ventilation as per clinical situation.

Hemorrhage

Minor to life-threatening tracheostomy bleeding complicates up to 5% of tracheostomies. Bleeding within the first 48 hours after placement is usually related to operative issues, including inadvertent vein puncture, suctioning, and infection. Beyond 48 hours, development of a tracheoinnominate artery fistula (TIAF), most critical and feared hemorrhagic complication. TIAF is a direct connection between the native trachea and the innominate artery branch of the aorta. The innominate artery crosses anterior to the trachea, typically at the level of the ninth tracheal ring; however, there is significant anatomic variation and the innominate artery may cross the trachea superior enough to be anterior to a tracheostomy tube.

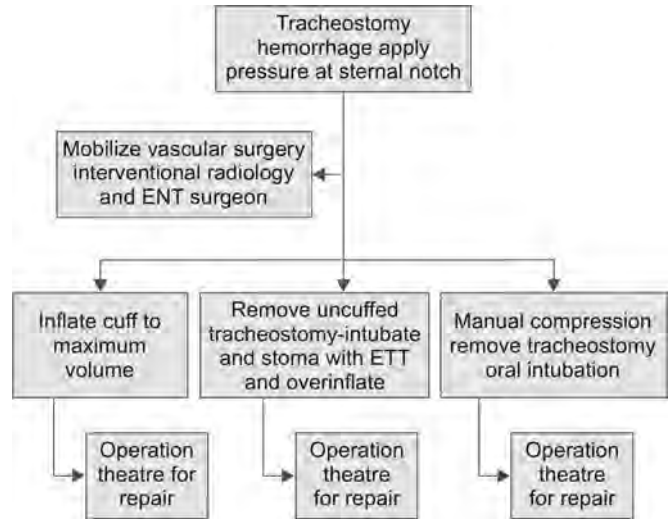
The incidence of TIAF is approximately 0.7% of patients with tracheostomy and the mortality is >90%. Around >70% of TIAF bleeds occurs within 3 weeks of tracheostomy placement but may occur at any time in the form of hemoptysis, or blood seen

FIGS. 2A AND B: (A) Occluding the tracheostomy opening to facilitate bag valve mask (BVM); (B) ventilating through opening with pediatric BVM.

with tracheal suctioning therefore, any hemorrhage occurring within 3 weeks of tracheostomy placement, must be considered a TIAF bleed until proven otherwise. Diagnostic options helpful in evaluation include bronchoscopy, computed tomography or traditional angiography, or local exploration. Risk factors for TIAF include a cuffed tracheostomy tube, low tracheostomy placement, high cuff pressure, high riding innominate artery, excessive neck movement, and tracheostomy infection.

Tracheoinnominate artery fistula should be suspected if catastrophic tracheostomy bleeding occurs and immediate resuscitative measures should be applied to minimize the bleeding and till operative repair is arranged (**Flowchart 2**). External compression of the innominate artery by applying pressure posteriorly at the sternal notch, and internal compression through over inflation of the tracheostomy balloon with up to 50 mL of air is the initial intervention. These interventions are successful in minimizing the bleeding in 85% of the time.

If these measures have failed to control the bleeding, the tracheostomy tube should be removed and endotracheal tube should be placed whose cuff is overinflated with up to 50 mL of air. If this also proves to be unsuccessful, an oral endotracheal tube can be advanced beyond the stoma to secure the airway with the addition of a finger inserted into the tracheostomy for digital compression of the innominate artery anteriorly against the manubrium. Digital compression must be maintained until definitive repair is undertaken. These measures are applied in an attempt to decrease the amount of blood loss while getting the patient to the operating room or interventional radiology suite for definitive management.


Tracheostomy hemorrhage apply pressure at sternal notch
Mobilize vascular surgery interventional radiology and ENT surgeon
Inflate cuff to maximum volume
Remove uncuffed tracheostomy-intubate and stoma with ETT and overinflate
Manual compression remove tracheostomy oral intubation
Operation theatre for repair
Operation theatre for repair
Operation theatre for repair

FLOWCHART 2: Management of tracheostomy hemorrhage.

URGENT COMPLICATIONS

Tracheoesophageal Fistula

A TEF is a communication between the posterior wall of the trachea and the anterior wall of the esophagus. Tracheostomy balloon causes prolonged pressure on the posterior membranous wall of the trachea results in ischemic necrosis, tissue breakdown, and subsequent fistula formation. Risk factors include high airway pressures, prolonged presence of a cuffed tracheostomy tube, high cuff pressures, excessive tracheostomy movement, steroid use, type 1 diabetes mellitus chronic hypoxia, poor nutritional status, hypotension, anemia, sepsis, the presence of a nasogastric tube, and gastroesophageal reflux disease (GERD).

Manifestations of TEFs are persistent tracheal air leaks, abdominal distention, pulmonary aspiration injury, cough with swallowing, copious bronchopulmonary secretions, and respiratory distress. In patients with tracheostomy, the TEF is generally located 1–2 cm distal to the tracheal stoma at the level of the balloon and can be large, measuring 4–5 cm. Diagnosis is made by bronchoscopy or, if not available, esophagogram.

Emergency department management includes discontinuation of oral feeding, and elevation of the patient's head to 45 and stop contamination of the airway through tracheal suctioning. Drain the gastric contents of the stomach through gastric tube if present, and it should be removed to prevent pressure necrosis and worsening of the fistula. Any other complications, such as pneumonia, should be treated. Long-term conservative management includes placing of the

tracheostomy balloon to a more distal position and nutrition via jejunostomy tube, minimally invasive treatment includes tracheal and esophageal stents, or surgery.

Tracheal Stenosis

Most patients experiencing some degree of tracheal narrowing after prolonged intubation or tracheostomy, only 3–12% of cases of tracheal stenosis require any intervention and very few requiring urgent intervention. Various risk factors are identified related to tracheal stenosis, one of them is formation of granulation tissue and fibrosis of peristomal and tracheal tissues. Trauma during procedure itself or ischemia from balloon over inflation leads to tracheal inflammation and ulceration. Other risk factors include surgical site infection, GERD, obesity, and hypotension. Tracheal stenosis frequently occurs at the site of the stoma, the level of the tracheostomy tube tip, the site of the balloon, or in a suprastomal position. Stenosis will not cause symptoms until the diameter of the tracheal lumen is reduced by >50%. Early symptoms include difficulty clearing secretions, cough, and exertional dyspnea. Dyspnea at rest and stridor are associated with a tracheal diameter of 5 mm. Tracheal stenosis can occur while a patient is still mechanically ventilated or years after decannulation, but most will present within 2 months of decannulation. Stenosis can make tube exchanges difficult due to narrowing of the space and bleeding risk. Early stenosis with exposed granulation tissue without overlying epithelium can bleed easily with minor trauma. Stenosis can be treated with dilation, excision with end-to-end anastomosis, or laser excision of granulation or fibrous tissues.

Infection

Patients are at risk of surgical site infection because of rich environment of blood and secretions at the surgical site place. Bacterial colonization of the skin and aerodigestive tract gives rise to common early infections such as cellulitis and tracheitis. Strict wound care with frequent dressing changes is the cornerstone of preventing infection after tracheostomy.

These infections are minor and more commonly observed after open tracheostomy but severe infections, including mediastinitis and necrotizing fasciitis, are possible. Presentations of serious infections osteomyelitis and septic arthritis of the sternoclavicular joint present late.

The presence of a cuffed tracheostomy tube disrupts swallowing, and increases the risk of aspiration while overinflated tube cuff can compress the esophagus, leading to aspiration. This aspiration is often asymptomatic or silent and therefore unrecognized by patients and caregivers. Aspiration of infected secretions can result in pneumonia or lung abscesses. These infections are most commonly attributed to *Staphylococcus aureus*, *Pseudomonas*, and mixed flora. Pneumonias and severe skin and soft tissue infections should be treated aggressively. Despite the frequency of infectious complications, the role of perioperative antibiotics in tracheostomy remains controversial.

Cutaneous Fistula

After decannulation, most stomas close in approximately 6 weeks. Persistent epithelialization of the stoma track can result in fistula formation. If the stoma persists after 3–6 months, a tracheocutaneous fistula is diagnosed. Persistent tracheocutaneous fistulas can lead to skin irritation and infection due to draining secretions, weak cough, and aspiration leading to recurrent pneumonias, poor phonation, poor cosmesis, and submersion intolerance. The most notable risk factor is prolonged tracheostomy tube placement with one small series noting tracheostomy placement for at least a year in all observed cases. Other risk factors include steroid use, advanced age, and malnutrition. Management options include tract cauterization or excision with healing by secondary intention or surgical closure.

MYIASIS (MAGGOTS) OF TRACHEOSTOMY WOUND

Myiasis is caused by dipterous larvae (maggots) a parasitic infestation of live human tissues (vertebrate animal) or cavities. Myiasis is the disease in which dipterous larvae invade organs and tissue, make them necrotic and then leave the necrotic tissue for viable tissue, causing extension of the lesion by local tissue destruction.

- *Causative agents*: Myiasis is caused by dipterous larvae which can be classified into two groups, (1) obligate parasites, specifically producers of myiasis, can develop only on live hosts and (2) facultative parasites, their larvae feed primarily on cadavers or vegetables, but can sporadically infest human or animal tissues.
- *Risk factors*: Human myiasis is extremely rare in western countries but Maggot infestation in tracheostomy wound is quite rare even in tropical country such as India. Myiasis is common in natural orifices such as ear, nose, and oral cavity, but myiasis of tracheostomy wound site is a very rare entity. Most important risk factors for the development of myiasis of tracheostomy wound are poor hygiene. Underdeveloped countries where malnutrition and unsanitary condition are common in people are more vulnerable to disease such as myiasis. Myiasis is also frequent in elderly and abandoned individuals, and mental institutions presenting poor hygiene habits.
- *Pathogenesis*: The eggs are deposited by the female flies over the unbroken suppurating lesions or open wounds. Depending on the number of viable eggs that are actually deposited by the female fly, the same number of larvae hatches and grows in any lesion. Upon hatching, the maggots with their sharp mouth hooks penetrate deep into tissue and cause necrosis of the tissue. With the mechanism of the progressive necrosis, larvae invade the deeper tissue until a cavernous lesion is formed, while the larvae aggregate and remain active. The cavernous lesion is characterized by tense and edematous surrounding tissue with pungent odor. The vital tissues can be damaged by larvae and they can cause life-threatening hemorrhage. The severity of the lesion depends on the time interval from the onset of infection and the diagnosis of the lesion. This is very important to diagnose and identify the condition in early stage with a smaller number of larvae, crucial for limited tissue damage. But if the lesion is presented at later stage or delayed, it will result in greater number of larvae with extensive tissue necrosis.
- *Treatment*: Mechanical removal of the larvae is the traditional treatment of myiasis. Antilarval measures include use of turpentine oil or mixture of turpentine oil and chloroform followed by removal of the larvae. But

also use of topical and systemic antibiotic as coadjuvants in the treatment improves the favorability of prognosis in severe cases. Clearing the maggots with ether meticulously, tracheostomy care and treatment of underlying disease is very vital. To classify the generic group, it is also important to send the larvae for culture. Keep in mind that with proper care, the condition can be controlled and cured. Special care at home as well as at hospital is required for tracheostomy wound site. Patient should be educated about proper tracheostomy care, regular cleaning habits and keeping the area covered are helpful in preventing of this problem.

Emergency physician should be aware of proper knowledge of the surrounding airway and disease process which is essential to treat such a case. Regular sterile dressing, proper nutrition, and through understanding of the importance of wound management by the patient and patient party helpful in preventing this condition.

Stepwise Approach for Tracheostomy Wound Myiasis

- *Step 1*: The wound site should be cleaned carefully using 10% povidone-iodine solution. Flushing is not done in uncuffed tracheostomy tube could not be changed to cuff due to chance of aspiration of infiltrating maggots surrounding the tracheostomy tube.
- *Step 2*: Normal saline soaked sterile gauge piece is wrapped around the tracheostomy tube to prevent maggot movement toward trachea thus reducing chance of maggot aspiration.
- *Step 3*: Careful apply the turpentine oil. The maggots will crawl toward the skin (the turpentine oil creates an anaerobic atmosphere for larvae forcing them to crawl out).
- *Step 4*: The maggots should be removed using nontoothed forceps carefully. The maggots should place in bowl containing ether solution.
- *Step 5*: The tracheostomy wound is then covered with povidone iodine-soaked gauge piece. The patient should be admitted, regular dressing is done maintaining the above mentioned five steps.
- *Step 6*: The patient should be discharged with counseling regarding importance of proper and regular tracheostomy tube care.

Prevention

Myiasis can be prevented by practicing good personal hygiene, primary care of wound, controlling fly population, and maintenance of sanitation of the surroundings. Apart from these, patient's relatives should be educated about the postoperative care, by teaching them the dressing and wound care and the importance of it, so that such manifestation of larvae could be prevented. Any symptoms relating to infestation should be reported to the hospital as the earliest, so that the lesion can be treated with minimal tissue damage rather than extensive necrosis when presenting at later stage.

SUMMARY

The emergency provider must be prepared to deal with both catastrophic and urgent tracheostomy-related emergencies. Life-threatening complications, including accidental decannulation, obstruction, and hemorrhage, are rare but require immediate action. Having a predetermined, stepwise approach to these complications will help guide management when such patients arrive in the ED. Subacute complications, such as TEF formation, tracheal stenosis, infection, and cutaneous fistula formation, may occur at any time, ranging from the postoperative period to years after a tracheostomy was placed or even following decannulation. The emergency provider must maintain a high index of suspicion for a tracheostomy-related complication when a patient with a present or prior tracheostomy presents with fever, dyspnea, or hemoptysis.

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CHAPTER

Chest Pain Evaluation in Emergency Department

Devendra Richhariya

INTRODUCTION

Acute chest pain is one of the most common reasons for emergency hospital visits accounting for approximately 8 million visits per annum in the United States. The main difficulty arises in differentiating the acute coronary syndrome (ACS) patients and other life-threatening causes of chest pain with other nonlife-threatening noncardiovascular causes of chest pain. It has been seen that the mortality rates increase by two-fold in acute myocardial infarction patients which were discharged prematurely from the hospital as compared to those admitted. Also, in patients with low risk of complications the cost of further investigations and hospital admission needs to be weighed apart from the small risk associated with the diagnostic procedures.

Recent advances in the medical field have improved the accuracy and efficiency in the evaluation of patients with chest pain. Development of new cardiac biomarkers (acute MI), radionuclide studies for low-risk patients, multislice CT scan for coronary artery disease (CAD), pulmonary embolism, and aortic dissection has improved the management of these patients. Also, the setting of chest pain units and pain pathways for evaluating the low-risk patients helps in the better outcome of the patients.

CAUSES OF CHEST PAIN

The causes of chest pain vary from life-threatening conditions needing urgent medical care to those that are relatively benign and nonlife-threatening (**Table 1**). Studies have shown that approximately one-third to one-half of patients have musculoskeletal chest pain, 10–20% have a gastrointestinal cause, 10% have stable angina, 5% have respiratory conditions, and approximately 2–4% have acute myocardial ischemia (including myocardial infarction).

Cardiac Causes

Myocardial Ischemia

Angina pectoris is defined as chest pain attributable to myocardial ischemia. Symptoms in chronic stable angina include heaviness, tightness, or constriction in the center or left side of the chest which gets precipitated on exertion and relieved by rest. Chest pain due myocardial ischemia can also be experienced in other locations also as shown in **Figure 1**. Other associated symptoms include provocation with emotional stress or cold and radiating to the neck, jaw, and shoulder. Sometimes patient does not present with classical angina but angina like symptoms such as dyspnea, nausea and vomiting, diaphoresis, presyncope, or palpitations. These set of patients are mostly women, diabetics and elderly population. Differentiating features of cardiac (ischemic) and noncardiac (nonischemic) pain are summarized in **Table 2**.

Patients presenting with ACS (myocardial infarction and unstable angina) have anginal symptoms at rest, or new onset angina that is more frequent, prolonged in duration and occurs with less exertion. These patients should be referred

TABLE 1: Common, life-threatening and nonlife-threatening causes of chest pain.

Common causes of chest pain	*Life-threatening causes*	*Nonlife-threatening causes*
• *Cardiac*: Coronary artery disease aortic valve disease, mitral valve disease, pericarditis, and pulmonary hypertension aortic stenosis • *Vascular*: Aortic dissection aortic aneurysm • *Pulmonary*: Pulmonary embolism, pneumothorax, and pneumonia pleuritis • *Musculoskeletal*: Costochondritis arthritis and muscular spasm • *Gastrointestinal*: Peptic ulcer disease, bowel diseases, cholecystitis pancreatitis, hiatus hernia	• *Acute coronary syndromes* • *Pulmonary embolism* • *Aortic dissection* • *Myocarditis* (most common cause of sudden death in the young) • *Tension pneumothorax* • *Acute chest syndrome* (in sickle cell disease) • *Pericarditis* • *Boerhaave's syndrome* (perforated esophagus)	• *Gastrointestinal*: Biliary colic, gastroesophageal reflux, peptic ulcer disease • *Pulmonary*: Pneumonia, pleurisy chest wall syndromes • *Musculoskeletal pain*: Costochondritis, thoracic radiculopathy • *Psychiatric*: Anxiety Shingles

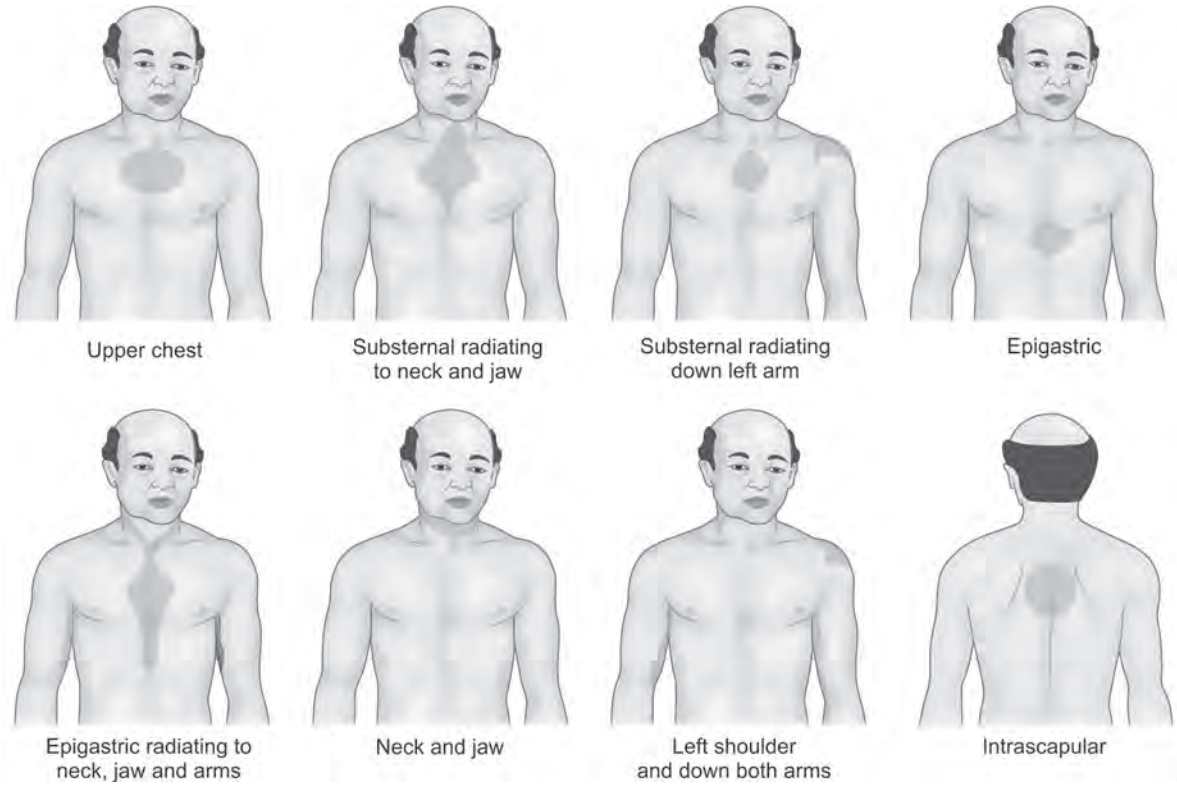


FIG. 1: Various locations of the pain induced by myocardial ischemia.

TABLE 2: Differentiating features of cardiac and noncardiac pain.

Cardiac (myocardial ischemia—coronary occlusion)	***Noncardiac chest pain***
• *Pain*: Severe, sudden onset, substernal, crushing, tightness, radiate to shoulder neck, back jaw, and arm may not relieve by nitroglycerin • *Associated features*: Dyspnea syncope tachycardia diaphoresis, extreme weakness nausea vomiting	• *Pain*: peripherally, localized, nonradiating, sharp, or stabbing may be provoked by posture respiration and palpitation • *Associated features*: Respiratory gastrointestinal or psychological features

to an emergency department and managed on a priority basis. Coronary heart disease is the most common cause of myocardial ischemia. Other less common causes include coronary dissection and vasospastic angina (Prinzmetal's angina).

Nonischemic Cardiac Causes of Chest Pain

- *Aortic dissection*: This condition is rare but a true surgical emergency needing immediate care. Typical symptoms include acute onset of chest and back pain that is severe, sharp, and tearing in nature radiating anywhere to the chest or into the abdomen.
- *Heart failure*: Patients with heart failure may present with chest discomfort, usually associated with dyspnea, orthopnea, cough, and peripheral edema.
- *Pericarditis*: Acute pericarditis refers to inflammation of the pericardium due to variety of causes. Patients often complain of pleuritic chest pain increasing on deep inspiration and relieved by sitting up and leaning forward. It is diagnosed based on history, physical examination, and electrocardiogram (ECG) findings. Etiologies include infections, drugs, autoimmune disorders, and malignancy.
- *Stress cardiomyopathy*: Stress (takotsubo) cardiomyopathy or apical ballooning syndrome occurs in the setting of physical or emotional stress or critical illness. Its clinical presentation is similar to that of acute myocardial infarction and needs to be suspected in patients with no traditional risk factors for CAD and classical echo findings.
- *Mitral valve disease*: Patients with mitral stenosis uncommonly experience chest pain or heaviness. This is most often due to pulmonary arterial hypertension and right ventricular hypertrophy seen in these patients. Patients with mitral valve prolapse may also experience chest pain, is usually mild, but often troubling.

Pulmonary Causes

Life-threatening pulmonary causes of chest pain include pulmonary embolism and tension pneumothorax.

- *Pulmonary embolism*: The most common symptoms of pulmonary embolism include dyspnea, pleuritic chest pain, cough, and sometimes hemoptysis. Often patients may have symptoms of deep venous thrombosis. Most common sign is sinus tachycardia. A high index of suspicion should be kept in mind while considering this diagnosis as it can be life-threatening if left undiagnosed. So past history of major surgery, malignancy, prolonged hospitalization, and immobilization should be enquired into.

- *Pneumothorax*: Patients with spontaneous pneumothorax present with sudden onset of pleuritic chest pain and dyspnea. A diagnosis of tension pneumothorax is considered if the patient is hemodynamically unstable. Primary spontaneous pneumothorax is usually seen in young, tall, and thin individuals with no underlying lung disease. A secondary spontaneous pneumothorax occurs as a complication of underlying lung disease [e.g., chronic obstructive pulmonary disease (COPD)].
- *Pneumonia*: Patients may have chest pain, often pleuritic but associated with fever and productive cough.
- *Malignancy*: Patients may complain of chest pain, typically on the same side as the primary tumor. Other symptoms include cough, hemoptysis, dyspnea, and weight loss.
- *Pulmonary hypertension*: Patients with pulmonary hypertension may have chest pain on exertion in addition to exertional dyspnea and syncope.

Gastrointestinal

- *Esophageal rupture/perforation*: Spontaneous rupture of esophagus (Boerhaave's syndrome) may results from a sudden increase in intra esophageal pressure usually seen after vomiting.
- *Gastroesophageal reflux disease (GERD)*: It is the most common clinical condition mimicking angina pectoris. Sometimes patients may describe it as squeezing or burning pain, radiating to the back, neck, jaw, or arms. Pain can last for minutes to hours, and resolves spontaneously or with antacids. It may be seen after meals, during sleep.
- *Esophagitis*: Patients with esophagitis may present with sudden onset retrosternal chest pain. It may be associated with odynophagia. It can be due to candidiasis, cytomegalovirus (in HIV-AIDS), or radiation injury.
- *Others*: Hiatus hernias may cause chest pain in addition to symptoms of reflux. Esophageal motility disorders/esophageal spasm generally manifests with dysphagia, but sometimes patients may complain of chest pain.

Musculoskeletal

Commonly seen in patients who present to the primary care physician with chest pain.

- *Isolated musculoskeletal chest pain syndrome*: Patients usually have local or regional chest wall tenderness without any other symptom. The most common causes are costochondritis and lower rib pain syndromes.
- *Rib pain*: Rib fractures are associated with pleuritic chest pain that is localized and reproducible with palpation. Patients often describe an associated injury/trauma, though some may occur without trauma. Other systemic disorders such as osteoporosis, metastasis, and infarction from sickle cell anemia can also cause acute rib pain.

Psychiatric

Chest pain is a common complaint in a wide variety of psychiatric disorders such as panic attack, depression, and somatization disorder. So a good clinical history and atypical symptoms in young individuals should raise a suspicion of underlying psychiatric illness. However, patients with underlying psychiatric illness may have coexisting CAD; hence a sound clinical judgment is needed.

Others

- *Substance abuse*: Cocaine abuse is commonly associated with myocardial ischemia. Other cardiac complications which can be seen include aortic dissection, coronary artery aneurysm, myocarditis and cardiomyopathy, and arrhythmias. Methamphetamine intoxication mimics cocaine and can cause similar cardiac complications.
- *Herpes zoster*: Sometimes chest pain may be the presenting symptom of herpes zoster, preceding the rash but is localized to a particular dermatome. Postherpetic neuralgia may also present with chest pain.
- *Domestic violence*: Patients may complain of chest pain or have chest pain in the setting of psychiatric conditions after suffering from intimate partner violence. In a community-based population, chest pain was one of the many physical symptoms associated with domestic violence.

EVALUATION

A detailed clinical history, physical examination, and relevant blood tests help in determining the probable cause of chest pain and the urgency of management. Stepwise approach is adopted to evaluate the chest pain in emergency (**Fig. 2**). History and physical examination are important part of chest pain evaluation and summarized in **Box 1**. Unstable patients or patients with high suspicion of ACS or ECG suggestive of ST elevation myocardial infarction (STEMI) should be treated with reperfusion therapy and chest pain with inconclusive ECG should be evaluated with serial ECG cardiac enzyme low molecular weight heparin and later disposition should be planned on the basis of risk stratification (**Flowchart 1**). Other life-threatening condition (e.g., aortic dissection, pulmonary embolism, and Boerhaave's syndrome) should be referred to the emergency department and managed on a priority basis.

DIAGNOSTIC APPROACH

The following is a diagnostic approach toward patients presenting with chest pain in the emergency department with priority for life-threatening conditions. Various screening and early diagnostic tools should be adopted in order to manage life-threatening conditions as early as possible (**Table 3**). Patients with life-threatening causes of chest pain should be

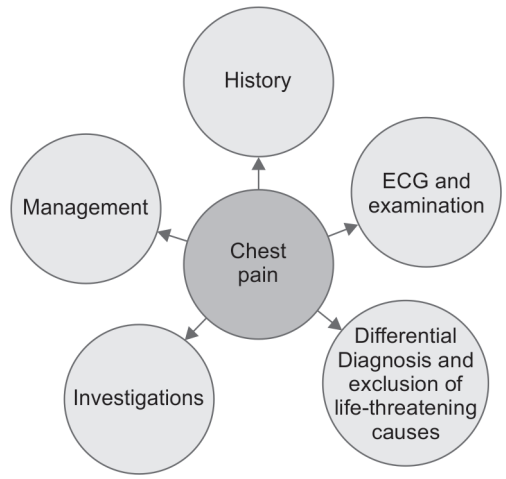


FIG. 2: Stepwise approach for evaluation of chest pain.

BOX 1: History and physical examination in chest pain evaluation.

***History*:**

- Patient presenting with chest pain should be evaluated with a detailed description of the pain and other associated symptoms should be noted
- *Description of chest pain*: It often helps in differentiating cardiac from noncardiac chest pain. Symptoms associated with a relatively high risk of myocardial infarction include radiation to an upper extremity, associated with diaphoresis or nausea and vomiting. However, no symptom alone or in combination helps in identifying patients in whom the diagnosis can be excluded safely
- *Quality*: Chest pain can be pleuritic, positional, sharp or dull, ripping or tearing, or tender on palpation. It is also important to enquire whether, the quality of the pain is similar to a previous episode if any. In a known case of CAD, pain similar to previous episodes is related to myocardial ischemia
  - A pleuritic chest pain gets worse on deep respiration. Causes include pericarditis, pulmonary embolism, pneumothorax, pleuritis, and pneumonia
  - Positional pain which improves on sitting and leaning forward suggests pericarditis
  - Ripping or tearing pain point toward aortic dissection
- *Location and radiation*: Ischemic pain is often diffuse and poorly localized. Well-localized pain associated with finger tenderness is more likely to be musculoskeletal in nature. Ischemic pain often radiates to the neck, throat, lower jaw, teeth, upper extremity, or shoulder
- *Temporal factors*: Acute onset of chest pain suggests pneumothorax, aortic dissection, esophageal rupture/perforation, or pulmonary embolism. However, the onset of ischemic pain is more gradual (over a period of few minutes) and gradually increasing in intensity over time
- Chest discomfort that lasts only for seconds or is constant over weeks is unlikely to be ischemic in origin. Myocardial ischemic pain usually lasts not >20–30 min, though it may be prolonged in the setting of a myocardial infarction
- *Exacerbating factors*: Chest discomfort on exertion is a classic symptom of angina. Sometimes esophageal pain can also present in a similar pattern. Other factors that may provoke ischemic pain include cold, emotional stress, meals, or sexual intercourse. Discomfort occurring with eating is suggestive of gastrointestinal etiology. Pain worsened on swallowing is likely to be esophageal in origin
- *Relieving factors*: Pain that subsides with cessation of activity strongly suggests an ischemic origin. Pericarditis pain typically improves with sitting up and leaning forward. Pain palliated by antacids or food is likely to be gastroesophageal in origin. However, pain which responds to sublingual nitroglycerin is usually associated with cardiac etiology but may be due to esophageal spasm as well
- *Other associated symptoms* may help in distinguishing the various etiologies of chest pain. However, sometimes even these symptoms may not reliably distinguish between cardiac and gastrointestinal origins of chest pain
- *Presyncope* can be seen in patients with myocardial ischemia. However, it is also associated with other pathologies such as aortic dissection, a hemodynamically significant pulmonary embolus, or critical aortic stenosis

Continued

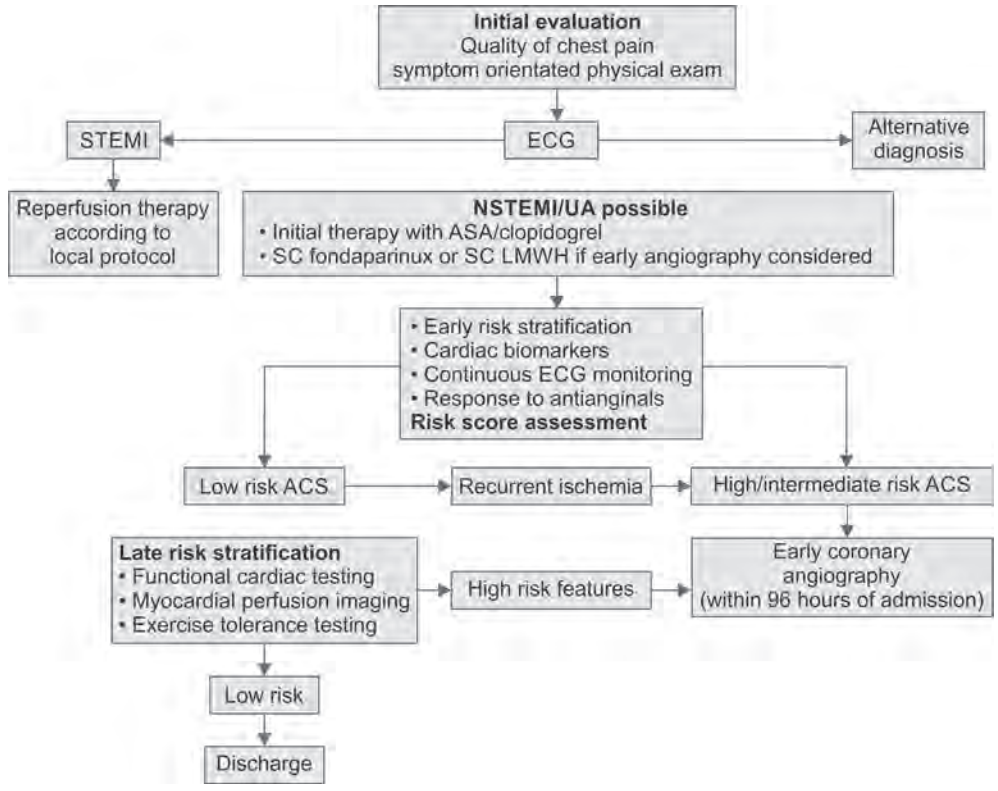
Continued

- *Palpitations* are often the complaint in patients with ischemia due to ventricular ectopic or atrial fibrillation
- Exertional dyspnea may be considered as anginal equivalent but it is also associated with other cardiac (e.g., aortic stenosis and atrial fibrillation) and pulmonary (e.g., asthma or chronic obstructive lung disease and pulmonary hypertension) causes of chest pain
- *Cough* is associated with infection, neoplasm, pulmonary embolism, and GERD
- *GERD* is associated with heartburn, regurgitation, and dysphagia. Belching, difficult, or painful swallowing is suggestive of esophageal disease, although belching and indigestion may also be seen in patients with myocardial ischemia. Nausea and vomiting are often seen in the setting of myocardial ischemia in addition to gastrointestinal problems
- *Musculoskeletal pain* in the neck, thoracic spine, or shoulder may cause referred pain to the chest. Chronic widespread musculoskeletal pain is associated with fibromyalgia
- *Presence of fever* leads to infective or autoimmune etiologies for chest pain. Fatigue, weight loss, and other constitutional symptoms raise concerns for malignancy or rheumatologic etiologies
- *Psychiatric symptoms* associated with pain may be due to panic disorder. Patients with depressed mood, decreased appetite, or sleep disturbances may have underlying depression
- *Other relevant medical history*: Diabetes, hypertension, smoking, and dyslipidemia are traditional risk factors for CHD. Prolonged immobilization, recent surgery, and trauma all increases the probability of pulmonary embolism. Hence knowledge about such risk factors provides important information regarding likelihood of a particular disease

***Physical examination*:**

- *Vital signs*: Presence of hemodynamic instability is an indication for immediate referral to the emergency department. Presence of hypoxemia points toward pulmonary or cardiac etiologies of chest pain whereas fever raises suspicion for infectious or autoimmune disease. In patients suspected of aortic dissection, blood pressure should be checked in both the arms and lower limbs
- *Cardiac examination*: A complete examination should be performed to evaluate for rate, rhythm, murmurs, and extraheart sounds. In pericarditis, one should examine in both supine and sitting and leaning forward position. This assesses for a pericardial rub which may only be present in the sitting position
- *Pulmonary examination:* It should be done to evaluate for symmetrical breath sounds, wheezing, crackles, and any evidence of consolidation
- *Musculoskeletal examination*: Chest pain reproducible with palpation may indicate musculoskeletal pain. Hyperesthesia associated with a rash is often due to herpes zoster. The presence of subcutaneous emphysema suggests Boerhaave's syndrome or pneumothorax
- *Abdominal exam*: A careful examination of the abdomen is required to assess for any referred pain, with attention to the right upper quadrant, epigastrium, and the abdominal aorta

(CAD: coronary artery disease; CHD: coronary artery disease; GERD: gastroesophageal reflux disease)



(ACS: acute coronary syndrome; ECG: electrocardiogram; SC: subcutaneous; STEMI: ST elevation myocardial infarction)

FLOWCHART 1: Evaluation and management of chest pain in ED.

TABLE 3: Screening and early diagnostic tools for acute coronary syndrome.

Pretest probability		*Early diagnostic tools for acute coronary syndrome*	
Demographic risk (CAD risk factors)	***Incident risk (typical Symptoms)***	***ECG***	***Cardiac enzyme***
• Diabetes hypertension • Hyperlipidemia smoking • Family history of CAD in a first degree relative: ○ Age >45 years for men ○ Age >55 years for women ○ Male Gender	• Chest pain, pressure, or discomfort • Arm pain, neck/jaw pain • Atypical symptoms shortness of breath • Fatigue • Nausea • Vomiting • Dizziness • Upper abdominal pain	• ST segment elevations that meet STEMI criteria • New ST depressions • New T-wave inversion in a coronary distribution • ST and T-wave abnormalities in a nonspecific (noncoronary) distribution • Normal ECG	• Elevated troponin Normal troponin but an elevated CK-MB ratio • Normal troponin and normal CK-MB ratio elevated CK-MB with a normal CK-MB ratio only

(CAD: coronary artery disease; CKMB: creatine kinase-MB; ECG: electrocardiogram; STEMI: ST elevation myocardial infarction)

referred immediately to the emergency department. These include patients with:

- Hemodynamic instability
- Sudden onset of chest pain and/or suspected life-threatening etiology such as pulmonary embolism, aortic dissection, esophageal rupture, and tension pneumothorax.
- Suspected ACS based on history (angina at rest, prolonged, or progressive) or ECG changes. Appropriate initial interventions should also be started such as 325 mg of aspirin tablet, sublingual nitroglycerin, and intravenous morphine.

ELECTROCARDIOGRAM

An ECG should be obtained for all the patients with new onset of chest pain or any pain that is different from previous episodes of noncardiac pain. ECG is very helpful in the evaluation of patients with suspected myocardial ischemia as well as in making a diagnosis of many other etiologies. Patients with ECG findings suggestive of ACS should be referred to the emergency room for further evaluation and management. Those patients with a history suggestive of ACS but a normal ECG should have serial ECGs done and monitored in the

emergency department. A normal ECG helps in ruling out ACS but findings must be interpreted in the context of the clinical history and physical examination. Sometimes ECG also helps in making a diagnosis of nonischemic chest pain such as acute pericarditis (diffuse ST elevation with PR depression), pulmonary embolism (sinus tachycardia, RBBB, RAD, and S1Q3T3 pattern). So, in an emergency department, an ECG should be obtained in all the patients presenting with chest pain.

OTHER STUDIES

Laboratory tests and other studies such as chest radiograph and cardiac enzymes are determined on initial evaluation and vary depending upon the need. Many patients will not need any additional tests for their chest pain evaluation. When there is a possibility of ACS, cardiac enzymes (CK-MB, Trop-I) should be tested. Chest X-ray if pneumonia, tension pneumothorax is the possibility. Perform 2D echo to rule out cardiac tamponade and aortic dissection. Multislice CT for pulmonary embolism and aortic dissection can be considered.

SUMMARY

The most common cause of chest pain in primary care practice is musculoskeletal pain and gastrointestinal conditions. Initial evaluation of chest pain starts with a detailed clinical history and physical examination. It helps in assessing the probability of various causes of chest pain and the need for further testing. ECG will be required in many patients suspected of myocardial ischemia. Patients with hemodynamic instability or life-threatening pathology (e.g., pulmonary embolism, aortic dissection, esophageal rupture, tension pneumothorax, and ACS), should be referred to the emergency department and managed on a priority basis. Patients with suspected ACS due to classical history or ECG changes should be given 325 mg aspirin tablet to chew. Symptoms consistent with stable angina should be further evaluated for myocardial ischemia. The appropriate diagnostic test will depend on the most likely etiology. In patients with a negative work-up for myocardial ischemia or in whom clinical suspicion is low, further evaluation depends upon the most likely diagnosis that emerges from the initial evaluation.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Palpitation

Roberta Petrino, Aldo Tua

INTRODUCTION

The term palpitations are referred by the patient when he/she feels a sense of abnormality of the heart beating in terms of rate or regularity. The heart is defined as skipping, frisking, fluttering, racing, or jumping. Frequently, the abnormality is lasting for a prolonged period and thus causes anxiety or anguish.

ETIOLOGY

The causes of palpitations may be several and different. Any situation that can cause acceleration or deceleration of the heart beating, or a change in the regularity can determine the unpleasant feeling referred as palpitation. Causes of palpitations can be of cardiac or noncardiac etiology. About 40% of the causes are of cardiac origin, one-third is of psychiatric origin, while the remaining is of other or unknown origin. In **Table 1**, there are summarized the most common causes of palpitations. *Cardiac etiology* is generally due to an impairment of the conduction system that causes brady or tachyarrhythmias with the mechanisms such as altered automatism, reentry of a premature beat, and postpotential excitation due to cell membrane ion channels disturbances. *Psychiatric causes* of palpitations may be anxious state, panic attack, and conversion crisis. Palpitations in these cases normally are more frequent, last longer than for cardiac causes and may be accompanied by different symptoms. In any case, it is necessary to rule out any cardiac cause before accepting the diagnosis of a psychiatric disorder, thus a 12-lead electrocardiogram (ECG) is mandatory and eventual other investigations. Other etiologies include:

- *Physiological*: Exercise, pregnancy, excitement, and emotional trauma
- *Hyperkinetic circulatory state*: Fever, hyperthyroidism, anemia, and hypoglycemia
- Vasovagal syndrome
- *Drugs*: Aminophylline, atropine, antiarrhythmic, tricyclic antidepressants, and calcium channel blockers
- *Toxic*: Cocaine, alcohol, amphetamines, and tobacco
- Systemic mastocytosis
- Da Costa's syndrome or effort syndrome or neuro-circulatory asthenia

TABLE 1: Etiologies of palpitations.

Arrhythmic causes	*Nonarrhythmic cardiac causes*	*Noncardiac causes*
• Supraventricular tachycardia • Ventricular tachycardia • Atrial flutter • Atrial fibrillation • Supraventricular and ventricular extrasystoles • Sick sinus syndrome • Bradyarrhythmias • Brugada syndrome • Arrhythmogenic right ventricular dysplasia	• Mitral valve prolapses • Aortic stenosis or insufficiency • Pulmonary embolism • Atrial myxoma • Congenital heart disease • Arterial hypertension • Pericarditis • Myocarditis • Pacemaker malfunction	• Exercise • Anxiety, fear, stress, and panic attack • Emotional trauma • Fever • Hyperthyroidism • Hypoglycemia • Anemia • Pregnancy • Poisoning and drug abuse with cocaine, amphetamines, and other drugs • Alcohol and caffeine abuse

PATHOPHYSIOLOGY

- *Palpitation intermittent*: Normally due to extrasystole (**Fig. 1**). The patient feels the beat after the extrasystole because the major end-diastolic filling after the pause and the increased strength of contraction.
- Palpitations that appear only after exercise or excitement or emotional stress—normally, the heart rate is not faster than 120 bpm and regular. Palpitation is due to catecholaminergic stimulus and transitory hyperdynamic cardiovascular state.
- *Palpitation continuous and regular*: Generally due *to supraventricular tachycardia (SVT) or atrial flutter or ventricular tachycardia* (**Figs. 2** to **4**). The pathogenesis of the former is a reentry mechanism, around the atrioventricular node or through an atrioventricular accessory pathway. Atrial flutter is normally occurring in patient with a cardiac scar or cardiomyopathy and

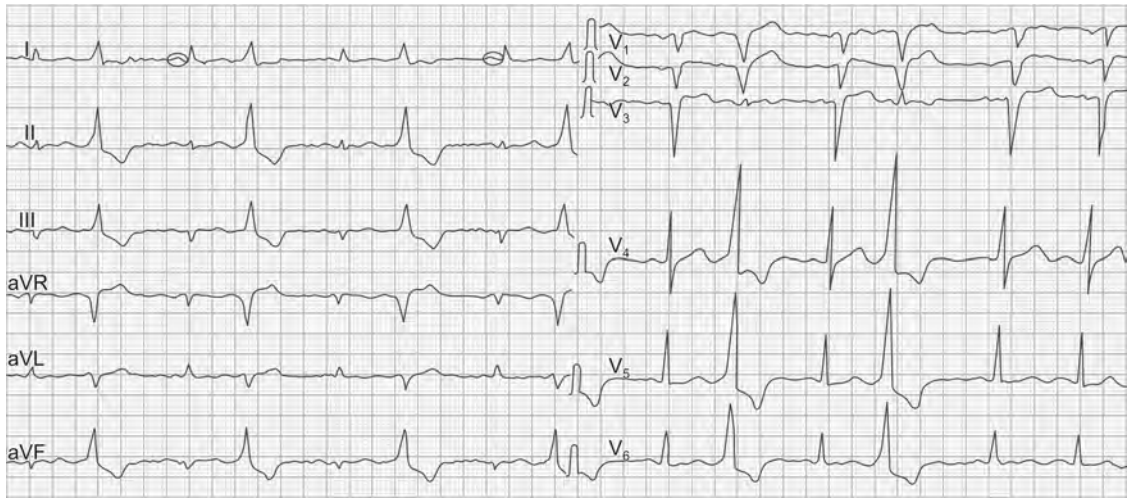


FIG. 1: 12-lead ECG showing ventricular extrasystole bigeminies.

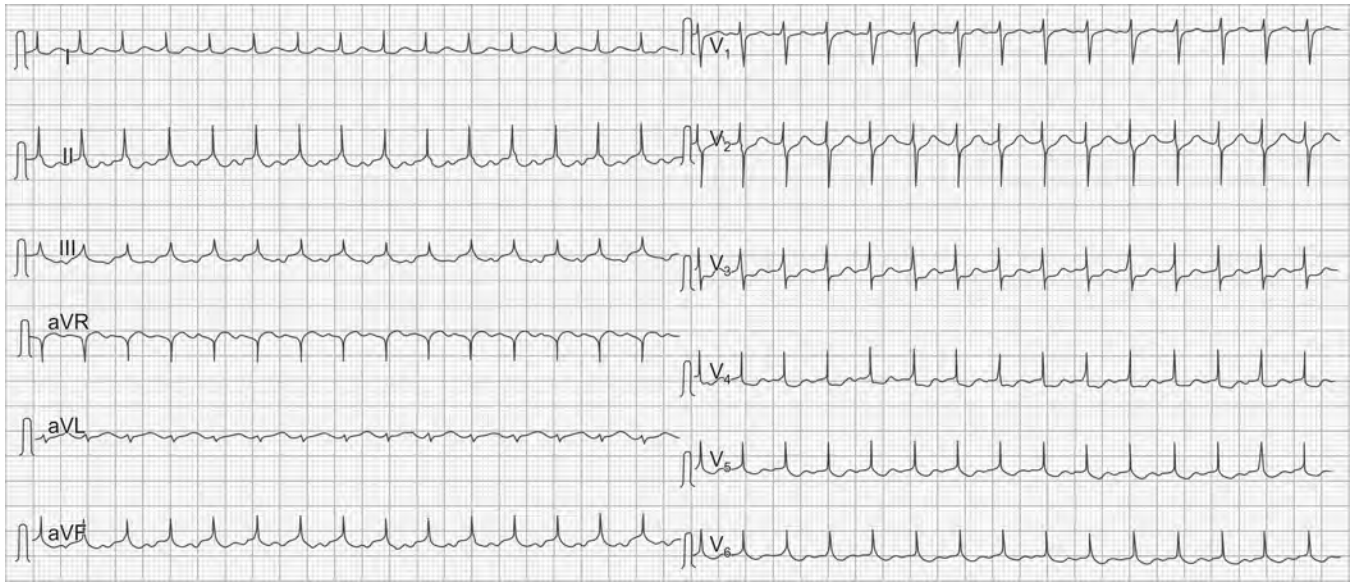


FIG. 2: 12-leads ECG showing a supraventricular tachycardia.

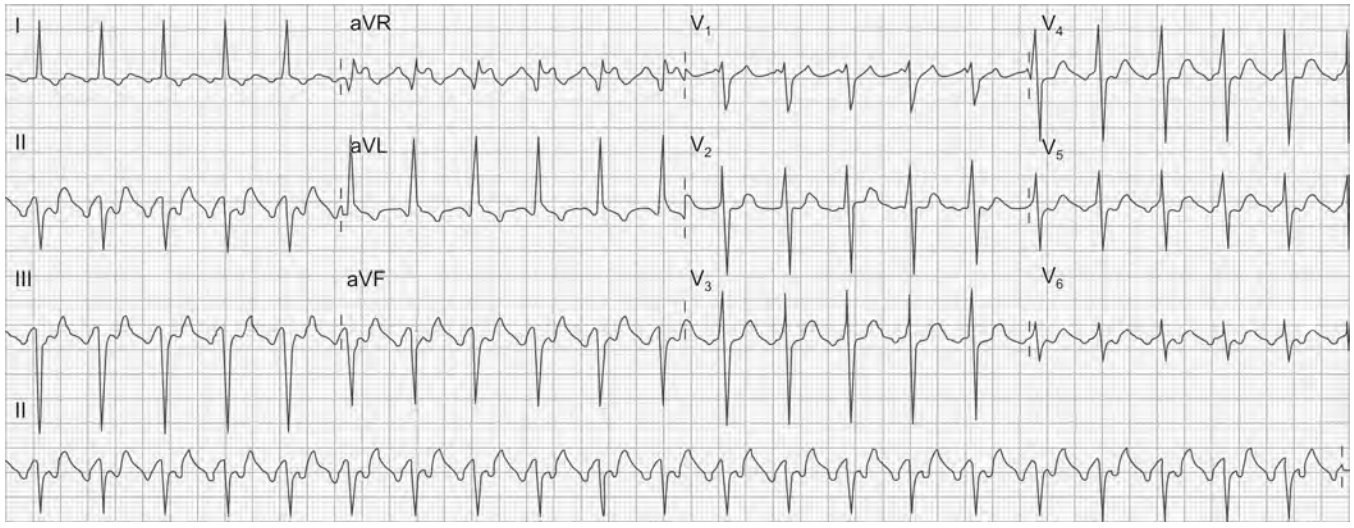
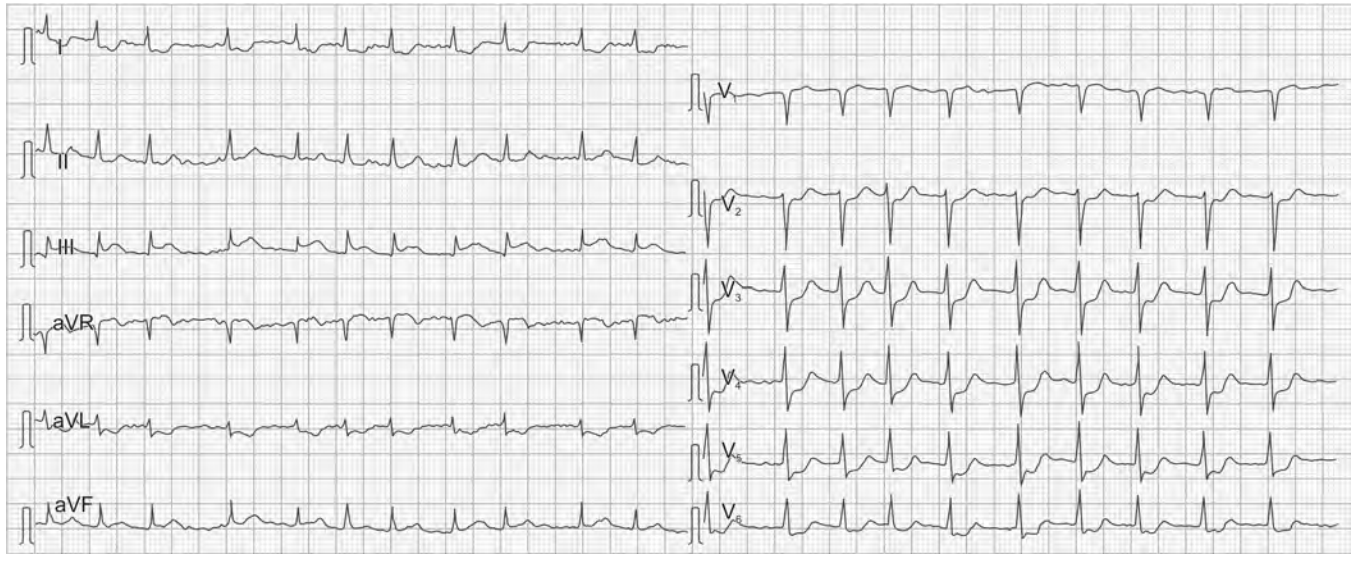


FIG. 3: 12-lead ECG showing an atrial flutter with conduction 2:1.

FIG. 4: 12-lead ECG showing a ventricular tachycardia.



(ECG: electrocardiogram; STEMI: ST segment elevation myocardial infarction)

FIG. 5: 12-leads ECG showing an atrial fibrillation and an inferior STEMI.

is sustained by reentry mechanism around the scar or around anatomic or functional atrial circuits. Ventricular tachycardia is the most threatening as it may evolve toward pulseless tachycardia or ventricular fibrillation is normally due to ischemia, dilative cardiomyopathy, hypokalemia, or other arrhythmogenic congenital or acquired diseases.

- *Palpitation continuous irregular*: It may be due to *atrial fibrillation* (**Fig. 5**), but also to atrial flutter with variable ventricular conduction, multifocal atrial tachycardia (MAT) or frequent extrasystoles. Pathogenesis of atrial fibrillation is several mini reentry mechanisms due generally to atrial walls distension and dilation. Very important to keep in mind the need for anticoagulation to prevent thrombus formation in the atria due to the absence of an efficacious atrial systole. MAT may be seen in chronic respiratory failure.
- Palpitation is associated with:
  - *Chest pain*: Possible myocardial infarction with arrhythmia
  - *Syncope*: Low cardiac output with arrhythmia and hypoglycemia
  - *Dyspnea*: Heart failure and chronic obstructive pulmonary disease (COPD) exacerbation
  - *Sweating*: Vasovagal syndrome, anxiety, and hypoglycemia

- *Polyuria*: SVT
- *Diarrhea*: Thyrotoxicosis

- *Positional palpitation*: It may be due to the presence of an intracardiac (atrial myxoma) or mediastinal mass that in certain positions triggers the arrhythmia.

CLINICAL PRESENTATION

As already described above, palpitation may be continuous or intermittent, may start and stop abruptly, and may be associated with other symptoms such as chest pain, dyspnea, fever, sweating, syncope, polyuria, anxiety, or agitation. Very often when the patient comes to the ED palpitation is extinguished and is necessary to make a hypothesis according to the patient history and the associated symptoms. Whenever possible, it is important to ask the patient to tap on the table the rhythm and frequency of the palpitation. In **Table 2**, there is the correlation of the description of the palpitation and the possible cause. The patient may be in shock or hemodynamically unstable or may present palpitation only in orthostatic or lying position. Very often the patients are young and otherwise healthy so easily labeled as "anxious."

RED FLAGS

When palpitation is recurrent, persistent, and is provoked by *exertion*, or accompanied by light—*headedness, syncope, chest pain, and dyspnea,* a careful workup is mandatory and if the diagnosis is not evident at the beginning a period of observation and monitoring is necessary. Preceding episodes of syncope can be associated with long QT syndrome, idiopathic or acquired, that may develop torsade des pointes. A syncope may also happen with the onset of an atrioventricular advanced block or a ventricular tachycardia. The onset of chest pain and palpitation is always alarming as it can be due to a ventricular tachycardia or another arrhythmic complication of a coronary syndrome.

TABLE 2: Description of palpitation and possible cause.

Description	*Suggestion*
Beat skipping and thumps	Extrasystole
Worsen at rest	Extrasystole
Fast and regular	Supraventricular or ventricular tachycardia
Sudden onset	Supraventricular or ventricular tachycardia
Ends with vagal maneuvers	Reentry supraventricular tachycardia
Fast and irregular	Atrial fibrillation or flutter with varying block
Nonfast and irregular	II-degree AV block or extrasystole
Hard and regular	Awareness of sinus rhythm (hypertension, anxiety, and cocaine)
Dizziness, heart failure, syncope, and shock	Ventricular tachycardia

EVALUATION

History

The patient should be asked about the onset of palpitation, the duration, and the associated symptoms. The rate of heartbeat and regularity is an important information, like the onset with a syncope, or other symptoms, and whether the patient was in activity or at rest. In particular, palpitation occurring during exertion or just after, it is a warning sign for possible cardiomyopathy or conduction disturbance. Doctors should enquiry about the interruption of the palpitation—if it is sudden or triggered by vagal maneuvers such as Valsalva or diving reflex, a paroxysmal SVT is likely.

The previous medical history in fundamental to disclose preexisting cardiac, respiratory, or metabolic diseases such as thyroid diseases, to:

A = Allergies: Investigate on known allergies and manifestations

M = Medications: Investigate on drugs taken by the patients in particular cardiovascular medications such as antiarrhythmics, diuretics, hypotensive, antithyroids or thyroid-stimulants, and drugs acting on the central nervous system.

P = Past medical history: To investigate on any past or chronic disease, with particular attention to cardiac diseases, previous arrhythmias, syncope, and cardiac arrest; history of drug and alcohol abuse. Family history of sudden cardiac arrest, genetic cardiac disease and psychiatric problem.

L = Last meal: To investigate on the kind of food or beverages taken in the previous hours or days.

E = Events: To investigate on the present symptoms and all the events that may be linked with them, in particular ask whether, palpitation is felt as alteration of the heart rate, of the heart rhythm or to a sensation of awareness of the heartbeat.

It is also important to know whether the patient is in a difficult or stressful period, is in sleep deprivation or with a fever.

Physical Examination

The patient should be evaluated according to ABCD approach.

- *Airway*: If the patient is able to speak fluently the airway is clear. Disclose a possible allergic-anaphylactic reaction that may cause glottis edema.
- *Breathing*: Take respiratory rate and oxygen saturation, look for signs of cardiac decompensation, or respiratory failure, the presence of rales, wheezes, and rhonchi on auscultation that may be the cause or the consequence of a tachyarrhythmia.
- *Circulation*: Blood pressure and heart rate give immediately the idea of a cardiac arrhythmia and of the stability of the patient. In this phase, it is essential to make a 12-lead ECG directly at the triage, because it permits immediately to find the cause of palpitations in a wide majority of cases, or at least to disclose life-threatening situation such as ventricular tachycardia or hemodynamically unstable tachyarrhythmia, myocardial infarction, or evident signs of electrolyte disorders, like hyperkalemia.
- *Disability*: Once excluded an obvious cardiac cause of palpitation, it is necessary to evaluate all the other signs

and symptoms that may lead to the diagnosis, like signs of hyperthyroidism, evidence of intoxication, psychosis, anxiety, panic attack, etc.

Interpretation of Findings

If at the first clinical evaluation, an unstable cardiac or respiratory disease is evident, it will be necessary to start immediately the proper treatment and monitoring. An eventual arrhythmia that may be related to palpitation may need to be treated with the condition (e.g., high-rate atrial fibrillation in pulmonary edema) or may be a consequence of the disease (e.g., MAT in COPD exacerbation with respiratory failure) and will resolve once the situation is getting better. When at the ECG, it is clear that the pure cause of palpitation is an acute arrhythmia; the best option is to treat it immediately as described later in the text. If the clinical examination excludes a cardiac or another medical problem, the probability of a psychiatric disorder is high, so a proper specialist consultation is recommended.

INVESTIGATIONS

As already reported, a 12-lead ECG is mandatory and needs to be available as soon as possible. Some laboratory tests are recommended, including blood cell count, to exclude anemia or leukocytosis, creatinine, electrolytes, arterial blood gas analysis, to evaluate respiratory failure, hypercarbia, metabolic acidosis, and carbon monoxide poisoning. If the ECG is negative, but the patient is describing episodes of syncope, dyspnea, or chest pain, a period of observation or monitoring in the ED is recommended, and very often is possible to scavenge a new arrhythmic episode or another cardiac problem like ischemia.

If the patient is discharged should be referred to the cardiologist to apply a Holter ECG recording or an implantable loop recording. An echocardiogram is recommended either before discharge or soon after. In **Table 3**, there are the ECG criteria for cardiologist urgent or deferred involvement.

TABLE 3: Indication for urgent o nonurgent expert opinion of a cardiologist according to the ECG finding.

ECG finding	*Acute onset*	*Unknown*
STEMI, coronary syndrome	Urgent	Urgent
Atrial fibrillation and atrial flutter	Urgent or deferred (if treated by the EP)	Nonurgent
Left ventricular hypertrophy and left bundle branch block	Urgent if acute cardiac decompensation	Nonurgent. Echocardiogram mandatory
Second degree atrioventricular block	Urgent for Mobitz II	Nonurgent for Mobitz I
Third degree atrioventricular block	Urgent	Urgent
Atrioventricular accessory pathway (Wolff–Parkinson–White pattern)	Urgent if associated with tachyarrhythmia	Nonurgent

(ECG: electrocardiogram; STEMI: ST segment elevation myocardial infarction)

TREATMENT

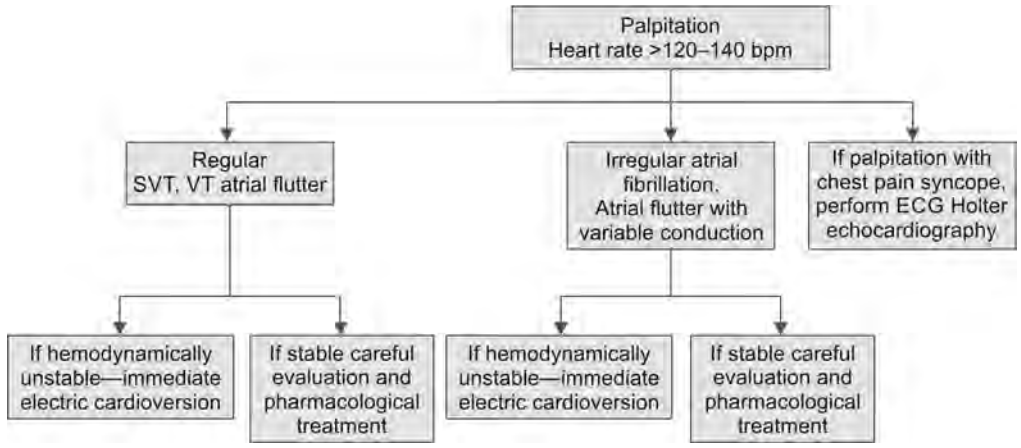
Arrhythmias

- *Extrasystoles* are normally not treated unless really disturbing the patient. In this case, a beta-blocker or some magnesium is indicated.
- *Atrial fibrillation:* According to the most recent guidelines, it is necessary to identify the time of onset because if it is <48 hours, it is possible to attempt a cardioversion, if not it is necessary to do a "rate control" approach and postpone the cardioversion after a period of anticoagulation. According to patient choice, it will be possible to do an electrical cardioversion that needs sedation, or a pharmacological cardioversion with flecainide, if the patient has not structural cardiac disease or amiodarone if there is a cardiac disease or decompensation. A hemodynamically unstable atrial fibrillation as any other unstable tachyarrhythmia requires an urgent electrical cardioversion. According to the CHA2DS1-VASc score for the risk of thrombotic stroke, an oral anticoagulation therapy should be initiated. The patient needs to be always referred to the cardiologist, in the ED or at discharge.
- *Supraventricular tachycardia*: Reentry SVT often is self-limited or may be interrupted by vagal maneuvers. If these are not efficacious, the drug of choice is adenosine, 6 mg IV flush that can be repeated at 12 mg. A period of asystole after the drug is possible but the very short half-life of adenosine makes it a very safe option. The third choice is a nondihydropyridine calcium channel blocker like verapamil, but it must be avoided in patients with a Wolff–Parkinson–White syndrome.
- *Ventricular tachycardia* is generally treated with electrical cardioversion or, in a stable situation, can be treated with amiodarone or lidocaine.
- *Arrhythmias due to electrolytes alterations or drug* poisoning need to be treated by treating the underlying cause.
- *Symptomatic bradycardias* require the use of transthoracic or transvenous cardiac pacing, and a washout of the drugs that may have provoked the bradyarrhythmia.
- *Any other structural cardiac disease or any noncardiac disease* will be treated properly or referred to a specialist evaluation.

In a majority of cases, palpitation does not need pharmacological treatment but only reassurance of the patient and can be resolved by lifestyle modification.

SUMMARY

Palpitation is a common symptom that leads the patient to the emergency department. It is generally described as the sense of abnormality of the heart beating in terms of rate or regularity. About 40% of the cases or of cardiac origin, 30% have a psychiatric cause and 30% of other medical causes. Any acute arrhythmia may cause palpitation, for this reason a 12-lead ECG is mandatory every time a patient refers palpitation at the triage. Approach to palpitation is summarized in **Flowchart 1**.


Palpitation
Heart rate >120–140 bpm
Regular
SVT, VT atrial flutter
Irregular atrial fibrillation, Atrial flutter with variable conduction
If palpitation with chest pain syncope, perform ECG Holter echocardiography
If hemodynamically unstable—immediate electric cardioversion
If stable careful evaluation and pharmacological treatment
If hemodynamically unstable—immediate electric cardioversion
If stable careful evaluation and pharmacological treatment

(ECG: electrocardiogram; SVT: supraventricular tachycardia)

FLOWCHART 1: Showing approach to the patient with palpitation.

At the first evaluation, it is necessary to exclude all the possible life-threatening conditions that may cause or present with palpitation such as unstable ventricular or supraventricular arrhythmia, cardiac ischemia, structural arrhythmogenic cardiac disease, poisoning, electrolyte disorders, or advanced AV block. If not evident immediately, a proper period of monitoring and observation is mandatory. Particular attention must be given when palpitation is provoked or followed by chest pain, dyspnea, lightheadedness, or syncope that may be the alarm sign of ischemia or a structural heart disease. A careful evaluation of previous medical history, with recording of all the drugs and structural cardiac diseases, is of utmost importance, as well as the habit to consume alcohol or illegal drugs. An acute arrhythmia or any other critical illness related to the symptom must be stabilized and addresses immediately, while in all the other cases it will be indicated a follow-up with some investigations such as Holter ECG, or loop recording to scavenge eventual arrhythmic episodes. It is important to recognize the noncardiac causes of palpitations, such as thyrotoxicosis and hypoglycemia, and when all the organic causes have been excluded to address the patients toward a psychiatric evaluation.

MULTIPLE CHOICE QUESTIONS

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60
CHAPTER

Syncope

Brajesh Kumar Mishra

INTRODUCTION

Syncope is a common, disabling, and often challenging symptom. It can cause fall and injury, and can be the warning sign before sudden cardiac death. Syncope is defined as transient loss of consciousness (TLOC) due to transient global cerebral hypoperfusion; it has three important features rapid onset, short duration, and complete recovery. Differentiation of syncope from other causes of TLOC such as seizure and "syncope mimics" (pseudo seizure, nonsyncopal TLOC, and psychological disorder) is very important for emergency physician while evaluating such type of patient.

EPIDEMIOLOGY

Transient loss of consciousness events of suspected syncope are highly prevalent in the general population. It affects about 50% of human being in their life time. First episode occurs generally around the age of 15 year, it is more common in female population, around age of 65 years. Syncope rises sharply as age increases. Syncope contributes to about 1% of total in hospital admission and 3% of emergency evaluation, although this is just tip of iceberg because <50% of patient of syncope visits emergency department (ED) or consults their doctor.

PATHOPHYSIOLOGY

Overall mechanism in syncope is transient cerebral hypoperfusion because of decreased cardiac output. Commonly, neutrally mediated syncope occurs when ventricular filling is decreased by venous pooling. It leads to a fall in cardiac output and BP activation of arterial baroreceptors, result rise in catecholamine levels, combined with reduced venous filling, and volume-depleted ventricle. Activation of "C fibers" receptors found in the atria, ventricles and pulmonary artery can result in "paradoxical" loss of peripheral sympathetic tone and an increase in vagal activity, which ultimately causes vasodilation and bradycardia leading to syncope or presyncope. Various risk factors are responsible for syncope are summarized in **Box 1**.

BOX 1: Important cardiac risk factors for syncope.

- Severe structural heart disease (low heart function, previous heart attack, and heart failure):
  - Clinical or ECG suggestive of arrhythmia
  - Syncope during physical exercise
  - Palpitations during syncope
  - Family history of sudden death
  - Non sustained VT
  - Bifascicular block or QRS >120 ms
  - Severe sinus bradycardia (<50 bpm) in the absence of medications or physical training
  - Preexcitation
  - Prolonged or very short QT interval
  - Brugada ECG pattern (right bundle branch block with ST elevation in leads V_1–V_3)
  - Arrhythmogenic right ventricular dysplasia ECG pattern (T wave inversion in leads V_1–V_3 with or without epsilon waves)
  - ECG suggestive of hypertrophic dilated cardiomyopathy
- Clinical evidence or suspicion of a pulmonary embolus (clinical setting, sinus tachycardia, and shortness of breath)
- Severe anemia

CLASSIFICATION

Syncope can be classified according to etiology or mechanism. Classification of syncope according to etiology modified by ESC guidelines versus classification according to mechanism modified by International Study on Syncope of Uncertain Etiology (ISSUE) classification is given in **Table 1**.

LIFE-THREATENING CAUSES OF SYNCOPE

Very important to identify the Life-threatening etiology such as acute coronary syndrome (ACS), aortic dissection, leaking abdominal aortic aneurysm (AAA), subarachnoid hemorrhage

TABLE 1: Etiological classification of syncope.	
Reflex syncope (neurally mediated)	• Vasovagal • Situational • Carotid sinus syncope • Atypical forms
Orthostatic hypotension	• Primary autonomic failure • Secondary autonomic failure • Drug-induced volume depletion
Cardiac Arrhythmia	• Bradycardia • Tachycardia (atrial fibrillation, ventricular tachycardia • Structural heart disease (aortic stenosis and atrial myxoma)

(SAH), ruptured ectopic pregnancy, and gastrointestinal (GI) bleed which may present as syncope in about 15% of cases—missed diagnosis in these conditions can lead to medicolegal action inpatients presenting as syncope. The physician evaluating a patient with TLOC should be alert for the possibility of this disease in addition to cardiovascular diagnosis of ominous significance.

- *Cardiac syncope*—cardiac causes which are associated with syncope include arrhythmia, ischemia, structural/valvular abnormalities (e.g., aortic stenosis), cardiac tamponade, and pacemaker malfunction. Brady and tachycardia are second the most common reason of syncope after reflex syncope.
- *Hemorrhage*—large blood loss because of acute severe bleed can manifest as syncope. Important potential causes include—trauma, GI bleed, leaking aortic aneurysm, ruptured ovarian cyst, ectopic pregnancy rupture, and ruptured spleen.
- *Massive pulmonary embolism (PE)*—hemodynamically significant PE is an uncommon but well-documented cause of syncope.
- *Subarachnoid hemorrhage*—patients presenting with syncope following a headache require evaluation for a possible SAH.

COMMON CAUSES OF SYNCOPE

Neurocardiogenic Syncope

Often referred to as vasovagal or vasodepressor syncope, neurocardiogenic syncope is the most commonly reason of syncope, accounting for 25–65% of cases. In this condition, the cardiovascular reflexes mechanism that controls the circulation become improper in response to a triggering factor, which results in vasodilation with or without bradycardia and a drop in BP leading to global cerebral hypoperfusion. Patients diagnosed with neurocardiogenic syncope have a benign course with no increase in mortality or morbidity. Three types of responses are seen: (1) A cardioinhibitory response which is characterized by asystole, (2) A vasodepressor response presents as fall in BP, and (3) A mixed response with features of both. Significant bradycardia and/or hypotension accompany the acute loss of consciousness. Potential triggers are numerous and often determination of the underlying cause is made in the outpatient setting. Most patients with neurocardiogenic syncope experience a prodrome, which may include dizziness or lightheadedness, a sense of warmth, pallor, nausea/vomiting, abdominal pain, and diaphoresis, prior to their loss of consciousness. Examples include micturition or defecation syncope, situational syncope (e.g., while having blood drawn), or cough-mediated syncope.

Carotid Sinus Hypersensitivity

Carotid sinus hypersensitivity is a variant of neurocardiogenic syncope, resulting from pressure at the carotid sinus. External pressure to the neck can induce this reflex response. Common causes include shaving, a tight collar, and turning of the head.

Orthostasis

Orthostatic syncope comprises between 5% and 24% of syncope cases and can be defined by a fall in blood pressure of 20 mm Hg or more, or a reflex tachycardia of >20 bpm. Orthostasis is most often caused by a loss of intravascular volume, from any number of causes, or by failure or instability of the autonomic nervous system. Nevertheless, clinicians should remain cautious because orthostasis can occur with cardiac syncope. Syncope from orthostatic hypotension is a diagnosis of exclusion in the ED, reserved for low-risk patients who have symptoms consistent with the diagnosis. Orthostatic hypotension can be an isolated disease (Bradbury-Eggleston syndrome) or can be a part of systemic disease like Parkinsonism or Shy–Drager syndrome. Postural orthostatic tachycardia syndrome (POTS) is characterized by symptoms of orthostatic intolerance because of milder form of chronic autonomic incompetence. Orthostatic vital signs are neither sensitive nor specific in assessing volume status or diagnosing syncope. Many patients become symptomatic if their systolic blood pressure drops below 90 mm Hg, but a large portion of the population who meets the definition of orthostasis does not have syncope. Elders, pregnant women, and patients taking drugs with vasodilating effects are predisposed to develop symptomatic orthostasis.

Medications

The effects of medications account for 5–15% of syncopal events due to volume depletion or as a result in vasodilatation. Elderly patients are affected more due to the hypotensive effects of drugs because of renal sodium wasting, reduced baroreceptor sensitivity, decreased cerebral blood flow, and an impaired thirst mechanism that develops with aging. Medications often implicated include calcium channel blockers, beta-blockers, alpha-blockers, nitrates, antiarrhythmics, digoxin, diuretics (affecting volume status and electrolyte concentrations), erectile dysfunction medications, and medications affecting the QTc interval (e.g., antipsychotics and antiemetics). Alcohol can also cause symptomatic orthostasis by impairing vasoconstriction.

OTHER CAUSES OF SYNCOPE

Neurologic Syncope

True syncope is defined by an immediate, spontaneous return to baseline function following loss of consciousness, without new focal neurologic findings. Therefore, true neurologic causes leading to syncope are rare. Examples of neurologic syncope

include SAH, transient ischemic attack (TIA), subclavian steal syndrome, and migraine headache. Stroke and TIAs generally cause focal neurologic deficits that do not recover rapidly or completely.

Psychiatric Syncope

Anxiety and panic disorders can cause situational syncope. Emergency clinicians must be cautious when attributing syncope to psychiatric causes. Patients with hypoxia, inadequate cerebral perfusion, or other medical conditions may appear confused or anxious. Patients with psychiatric syncope are generally young, without cardiac disease, and complain of multiple episodes.

Metabolic

Metabolic causes of syncope include hypoxia, hypoglycemia, and hyperventilation. These comprise <5% of cases of syncope.

Rare Causes

Rare causes of syncope include atrial myxoma, Takayasu's arteritis, systemic mastocytosis, and carcinoid. Anaphylaxis can involve syncope and loss of consciousness, and both patients and witnesses sometimes overlook or forget the more subtle, earlier symptoms, such as flushing, itching, hives, cough, bronchospasm, or abdominal cramping. In addition, these less dramatic symptoms may have resolved by the time the patient is evaluated.

OBJECTIVES FOR EVALUATION

There are two main objectives for evaluation of a patient with syncope in ED:

1. To identify the syncope so that an effective specific treatment strategy can be given.
2. To assess the prognosis in view of death, severe adverse events, and syncope recurrence

During ED evaluation, the differential diagnosis of syncope is extensive, main focus remains on the treatment of underlying cause when this is obvious. However, the cause of syncope often remains unclear. First challenge during evaluation of syncope is differentiate it from seizure (**Table 2**). Epilepsy, stroke, and head trauma may present with TLOC and syncope like situations. Taking careful history alone can narrow down the diagnosis. History of previous seizure, head injury, tongue bite, the presence of a tonic-clonic activity, abnormal posturing, incontinence of bowel or bladder, missed antiepileptic medication, and postictal confusion gives clue about seizure. While syncope associated with sweating or nausea and rapid return of orientation upon awakening.

Evaluation

The utmost important parameters in evaluation of syncope are a careful history, physical examination, supine and upright BP, and a 12-lead electrocardiogram (ECG), followed by additional testing in selected patient subgroups, including carotid sinus massage, echocardiography, ECG monitoring, and tilt-table testing. A thorough history and clinical examination

TABLE 2: Differentiation of syncope caused by neurally mediated hypotension, arrhythmias, seizures, and psychogenic causes.

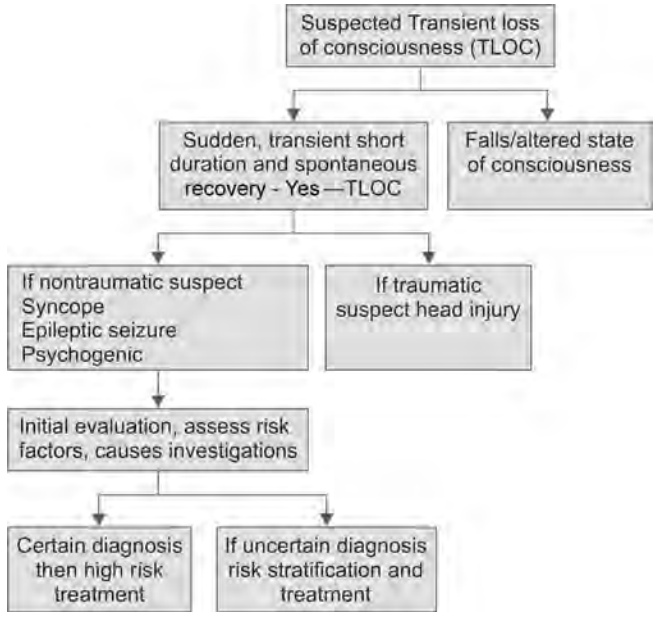
	Neurally mediated hypotension	***Arrhythmia***	***Seizures***	***Psychogenic***
Demographics and clinical settings	• Female > Male • Younger age (<55 years) • >2 episodes • Standing • Warm room • Emotional upset	• Male > Female • Older age groups • Fewer episodes (<3), during exertion or supine position • Family history of sudden death	• Younger age <45 years • Any setting	• Female > Male • Younger age • Occurs in the presence of gathering, often many episodes in a day, no identifiable trigger
Premonitory symptoms	Longer duration >5 sec with palpitation, blurred vision, nausea, warmth, diaphoresis, lightheadedness	• Shorter duration (<6 sec) • Palpitation less common	Sudden onset or brief aura	Usually absent
Observation during events	Pallor, diaphoresis, dilated pupil, slow pulse, low BP, incontinence may occur, brief clonic movement may occur	Blue not pale, Incontinence can occur, brief clonic movement can occur	Blue face, no pallor frothing from mouth prolonged syncope, tongue bite, eye deviation, Incontinence more likely, increase in heart rate and blood pressure	• Normal color • No diaphoresis • Eye closed • Normal heart rate and blood pressure • No incontinence, Prolonged duration
Residual symptoms	• Residual symptoms common • Prolonged fatigue common • Oriented	Residual symptoms uncommon unless prolonged unconsciousness, Oriented	Residual symptoms common, aching muscle, disoriented, fatigue headache, slow recovery	Residual symptoms uncommon Oriented

are by far the most important components of the evaluation of a patient with TLOC, which contribute to diagnosis in 25% of patients. During history, special attention should be given to age and sex, surrounding circumstances, position, premonitory symptoms, index event witness, recovery, past medical history, medication, and family history. Based on this initial evaluation, patients can be divided into those with established syncope and those with nonsyncopal transient LOC. Patients with syncope can be further classified into two groups: (1) Those with a certain diagnosis and clear treatment plan and (2) those with an uncertain diagnosis. For the latter, attention should be on risk stratification of patients. The patients which require hospitalization and/or an intensive timely outpatient cardiovascular evaluation should be identified. These patients may require exercise stress testing, cardiac catheterization, and electrophysiology (EP) testing. Conversely, patients who are presenting with only a single episode of syncope and are determined to be at low risk for a cardiovascular event or death may require no further evaluation. Patients who fall between these two extremes can undergo further testing selected on the basis of results of the initial evaluation. There are subtle features in history and investigation which can assist clinicians in identifying high risk patient with risk to life in comparison to low-risk patient who can be discharged safely. Approach to evaluation of syncope is summarized in **Flowchart 1**.

INVESTIGATION

Laboratory Test

Blood tests helpful in only <2% of cases of syncope. Routine laboratory blood tests are helpful in identifying anemia and electrolyte abnormalities. Acute drop in hemoglobin can suggest bleeding. Arterial blood gas (ABG) can reveal hypoxia suggestive of PE. Elevation of cardiac biomarkers may suggest ACS, PE, arrhythmia, and cardiac decompensation. Electrolyte imbalance contributing to TLOC can also be detected.


Suspected Transient loss of consciousness (TLOC)
Sudden, transient short duration and spontaneous recovery - Yes—TLOC
Falls/altered state of consciousness
If nontraumatic suspect
Syncope
Epileptic seizure
Psychogenic
If traumatic suspect head injury
Initial evaluation, assess risk factors, causes investigations
Certain diagnosis then high risk treatment
If uncertain diagnosis risk stratification and treatment

FLOWCHART 1: Approach to patients with transient loss of consciousness (TLOC) and syncope.

Electrocardiogram

The initial ECG can contribute to diagnosis in 5% of patients and suggests a probable diagnosis in another 5% of patients. ECG showing sinus bradycardia, sinus pauses, Mobitz type II atrioventricular (AV) block, high-grade AV block, or congenital heart block (CHB) suggests bradyarrhythmia as culprit. Right bundle branch block (RBBB), left bundle branch block (LBBB), and bifascicular block will require further evaluation. Extensive massive myocardial infarction can suggest ACS as a cause. PE may manifest as sinus tachycardia, RBBB, and S1Q3T3 pattern. RBBB in V_1–V_3 with ST elevation may suggest Brugada syndrome similarly Epsilon wave suggests arrhythmogenic right ventricular (RV) dysplasia. Preexcitation or Wolff-Parkinson-White (WPW) can also be detected with ECG. Abnormality of QT interval can lead to diagnosis of long or short QT interval. Ventricular tachycardia (VT) or nonsustained VT (NSVT) can also confirm diagnosis. ECG monitoring can also be done with Holter, telemetry, or loop recorder for better yield. Current guidelines recommend that an implantable event recorder should be tried when the mechanism of the syncope is unclear even after a complete evaluation.

Carotid Sinus Massage

This test is indicated in patient with syncope >40 year of age with unexplained reason; however, it is contraindicated in patient with history of recent stroke (within 3 month) or patient with carotid bruit. A pause of >3 seconds and fall in BP of >50 mm Hg is considered as criteria for hypersensitive carotid sinus syndrome.

Head-up Tilt Table Test

Tilt table test is done in patient with recurrent unexplained syncope when the cardiac evaluation and carotid sinus massage is noncontributory. This test demonstrates patient susceptibility for reflex syncope and helpful in initiating treatment in these undiagnosed cases. It also helps in differentiating all the three types of neurogenic syncope: (1) Cardioinhibitory; (2) Vasodepressor and; (3) Mixed response. It also helps in differentiation of orthostatic (immediate blood pressure falls and no bradycardia) vasovagal (delayed blood pressure fall and bradycardia) and reflex syncope, as well as psychogenic, pseudo seizure, and reflex syncope.

Ambulatory Blood Pressure

Monitoring is an important test to diagnose syncope in elderly population because of recurrent hypotension because of autonomic failure.

Echocardiography

It is an important inexpensive noninvasive test. It confirms the cardiac diagnosis when there is suspicion of structural heart disease—left ventricular (LV) or RV dysfunction, valvular heart disease, pericardial effusion, cardiac tumor, myxomas, outflow tract obstruction, or hypertrophic cardiomyopathy (HCM). Yield of the test increases if there is history suggestive of cardiac diagnosis or abnormal ECG. The yield may go up to 27–40%.

Coronary Angiography or CT Angiography and EP Study

It is helpful in suspected ischemia or ischemia-related arrhythmia. Electrophysiological study is helpful in establishing a diagnosis of sick sinus syndrome, carotid sinus hypersensitivity, heart block, SVT, and VT. EP testing should be performed in patients when the initial evaluation suggests an arrhythmia as a cause of the syncope. Dedicated syncope unit has shown better overall diagnosis and management of syncope patient. Initial evaluation gives a diagnosis in 21%, further workup reveals a diagnosis in 61% but in 18% diagnosis still remains uncertain.

TREATMENT

Treatment of a patient with syncope has three aims:

1. Prolong survival
2. Prevent traumatic injuries
3. Prevent recurrences

The syncope treatment is based on the etiology and mechanism of the syncope. Current guidelines recommend that patients with syncope be hospitalized when there is known or suspected cardiac diagnosis, ECG suggestive of arrhythmic syncope, syncope with severe injury or during exercise, patients with a history of sudden unexplained death in family.

Nonpharmacological General Measures

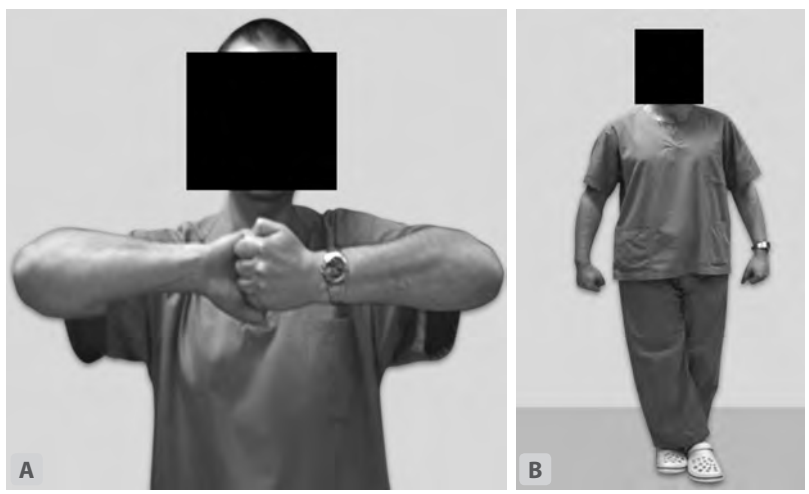
Single episodes of reflex syncope do not require any treatment, patients should be educated about common precipitating factors such as dehydration, prolonged standing, alcohol, and medications such as diuretics and vasodilators. Patients should also be taught to sit or lie down at the beginning of symptoms and to initiate physical counter pressure maneuvers (**Fig. 1**). One recent study reported that a standard education protocol decreased traumatic injuries and recurrences of syncope significantly· expansion of volume by salt supplementation is also commonly recommended. Intake of approximately 500 mL of water immediately increases orthostatic tolerance to tilt in healthy subjects and may be of value as prophylaxis for syncope in blood donors. Orthostatic hypotension patient may be benefited by various nonpharmacological measures such as tilt table training, increased salt intake, physical counter pressure maneuvers, abdominal binder and compression stocking, midodrine, and fludrocortisone are another alternative in these scenarios.

Pharmacological Treatment

If syncope is refractory to nonpharmacological measures then drugs such as alpha agonist midodrine, droxidopa, and pyridostigmine can be considered for frequent hypotensive episodes. Drugs with less proven efficacy such as β-blockers and fludrocortisone are also in use for reflex syncope. Despite the widespread use of agents such as midodrine and fludrocortisone, these drugs proven ineffective in many prospective randomized clinical trials. Even though β-blockers metoprolol, propranolol, and nadolol were previously considered by many to be first-line therapy, recent studies have reported contrary (not better than placebo).

Role of Pacemakers

Role of pacemakers in patients with neurally mediated syncope is debatable. Although the 2008 guidelines for device-based therapy state that pacemaker implantation has a IIb indication for the treatment of patients with highly symptomatic, neurally mediated syncope associated with bradycardia documented spontaneously, or at the time of tilt-table testing. Management of syncope because of specific clinical entity requires the appropriate treatment for specific diagnosis, as for example a patient with syncope related to AV conduction block would require a pacemaker in most situations. However, a patient with syncope secondary to heart block on the background of an inferior wall myocardial infarction will not usually require a permanent pacemaker because the heart block usually resolves spontaneously after revascularization. Similarly, heart block resulting from neurally mediated syncope does not generally require pacemaker implantation. Management of a patient of WPW syndrome presenting with syncope typically involves catheter ablation. Management of a patient with syncope due to VT or in the setting of ischemic or nonischemic cardiomyopathy would probably include implantation of an implantable defibrillator. However, ICD implantation may not be required for patients with VT/VF occurring within 48 hours of an acute myocardial infarction. For other types of syncope, treatment may involve cessation of likely culprit drugs,



FIGS. 1A AND B: Counter-pressure maneuvers: (A) Arm tensing; (B) Leg crossing.

increased salt intake, education and counseling of the patient. In the case of syncope because of neurological or GI disease, respective super specialty must be involved.

RISK STRATIFICATION FOR SYNCOPE IN EMERGENCY DEPARTMENT

In emergency department, risk stratification evaluation of patients presenting with syncope is an important step in management. There are several predictors and scoring system used for risk stratification of syncope patient as, for example, OESIL Study, STePS study, San Francisco rule, Rose rule EGSYS Score, etc. The EGSYS Score: During follow-up at a mean of 20 months, patients with an EGSYS score ≥ 3 predict higher mortality than patients with score <3 (**Box 2**).

FUTURE PERSPECTIVE

Syncope will be an important clinical problem in coming years because of increasing life expectancy and more frequent occurrence of cardiac disease in this subset. Over the next 5 years, additional studies will confirm the clinical and economic value of syncope evaluation units. This will lead to more widespread use of syncope evaluation units, much like chest pain emergency rooms which are now routinely used to evaluate patients with chest pain. Clinical genetic testing is now available on a routine clinical basis for many of the inherited cardiac conditions that may be accompanied by syncope, including long-QT syndrome, arrhythmogenic right ventricular dysplasia (ARVD), and HCM. Therefore, it also seems likely that genetic testing will grow in diagnostic importance in the evaluation of patients with syncope.

BOX 2: The EGSYS score long-term predictor.

- Palpitation preceding syncope (4 points)
- Heart disease and abnormal ECG (3 points)
- Syncope during effort (3 points)
- Syncope during supine (2 points)
- Precipitating and predisposing factor — (minus 1 point)
- A prodrome of nausea and vomiting— (minus 1 point)

Note: Score ≥3 predict higher mortality.

SUMMARY

The evaluation and management of syncope in emergency department are very challenging. First, "syncope" is only one of many causes of TLOC. Second, symptoms are variable, and the patient is usually asymptomatic at the time of evaluation. Third, events are often unwitnessed; or even when witnessed; questions about reliability exist. Finally, there is often an urgent need to carry out diagnostic procedures. Initial risk stratification in emergency department is more likely to give a correct diagnosis. Before prescribing investigation, it is important to spend enough time on history. Despite the difficulties, a thorough evaluation of the cause of syncope is necessary in all patients. The emergency physician must carefully consider whether detected abnormalities are compatible with the clinical circumstances. The goal in every case should be to determine the cause with sufficient confidence to provide a reliable assessment of prognosis and treatment options.

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CHAPTER

Interpretation of ECG

Kartikeya Bhargava

INTRODUCTION

The electrocardiogram (ECG) is often the first investigation in any patient presenting with symptoms related to cardiovascular disease. Rather, it is seen as an extension of a good history and physical examination in view of its almost universal availability. Emergency physicians are usually the first ones and often the only ones to analyze the ECG performed in a patient presenting in an emergency department. Hence, it is imperative that they should have proficiency in reading and analysis of ECGs so as to arrive at a diagnosis rapidly and take appropriate clinical decisions regarding treatment. The present chapter is not supposed to be a comprehensive review of ECG diagnosis, rather it tries to summarize ECG findings to assist interpretation in a typical patient presenting in the emergency department with symptoms of cardiovascular disorders such as chest or epigastric pain, palpitations, syncope or presyncope, breathlessness, etc. The findings on ECG in certain systemic or noncardiac conditions that can assist in the clinical diagnosis and therapy are also mentioned. *The various groups of cardiovascular conditions in which ECG is of diagnostic value* are listed in **Box 1**.

A systematic approach to read and analyze the ECG is essential to arrive at an accurate diagnosis and the steps (not necessarily in the order given) that can be used in this approach are mentioned in **Box 2**. However, it is important to realize that in an emergency, especially if the patient is hemodynamically unstable, a rapid diagnosis may be needed based on the most significant finding correlated with patient's symptoms and a stepwise approach can be deferred to a later time.

The following sections discuss various ECG patterns grouped according to the ECG findings that may be seen in patients presenting in the emergency department. The description of each finding and its clinical correlation with the cardiovascular disorder is not comprehensively presented but can be found elsewhere in this book.

CARDIAC ARRHYTHMIAS

One of the most common uses of ECG is a diagnosis of an abnormal rhythm. The arrhythmias include disorders with abnormally fast rhythm (tachyarrhythmia) or abnormally slow rhythm (bradyarrhythmia). Sometimes, though an abnormal rhythm may not be present at the time of presentation, but an abnormal finding during sinus rhythm ECG may point to a specific rhythm disorder during the time of symptoms. For example, presence of ventricular preexcitation during sinus rhythm may suggest episodes of supraventricular tachycardia (SVT) in a patient with palpitations. Similarly, presence of left bundle branch block (LBBB) in a patient with history of syncope may suggest intermittent complete atrioventricular (AV) block.

TACHYARRHYTHMIAS

Any rhythm with a rate >100/min qualifies to be called as tachycardia. These can be classified based on the QRS duration and regularity of the ventricular rhythm as shown in **Flowchart 1**. The patients with tachyarrhythmias usually present with complaints of palpitations, presyncope or syncope, breathlessness, and/or chest discomfort. Though, the details regarding the diagnosis of these are beyond the scope of this chapter, a few comments are outlined below for the aid of emergency physician:

BOX 1: Cardiovascular conditions where ECG is likely to be useful.

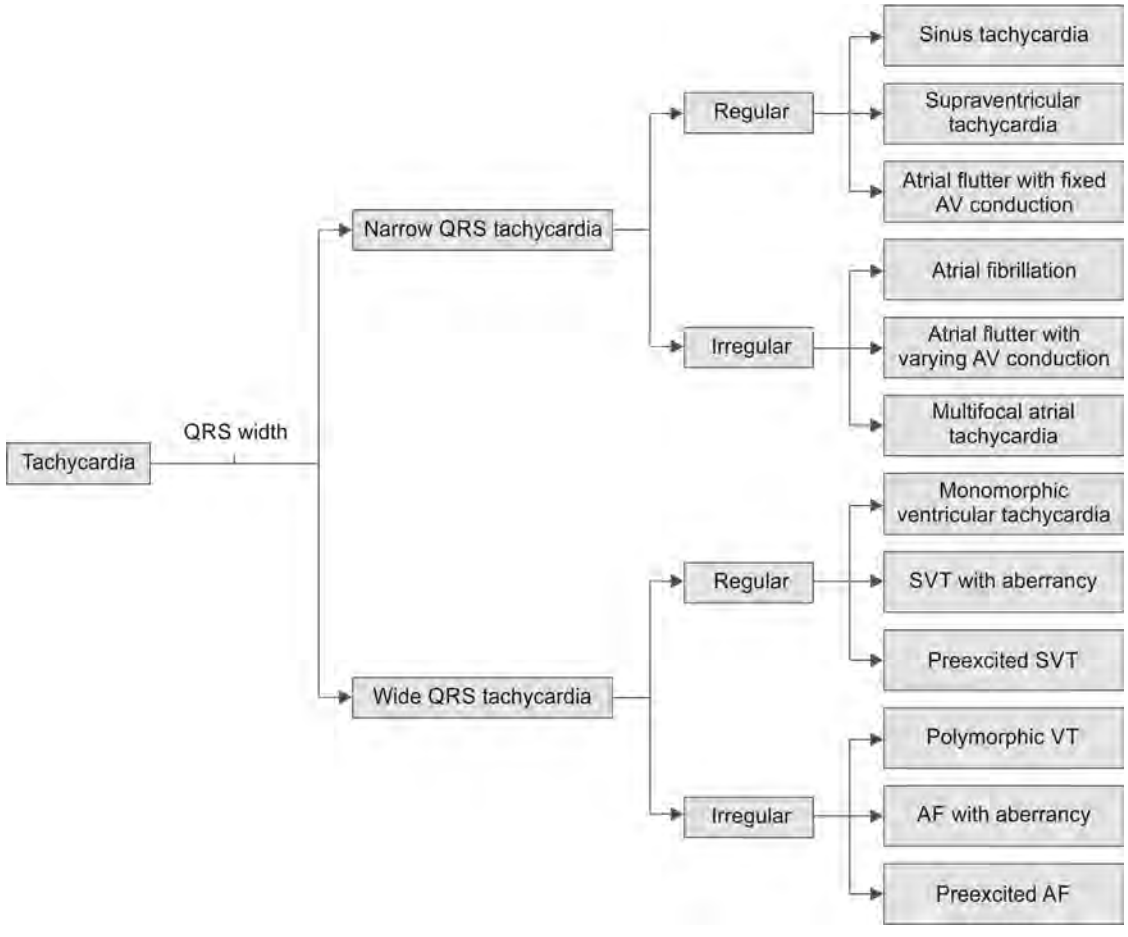
- *Arrhythmias*: Bradycardia-tachycardia, WPW syndrome, Long QT syndrome, and others
- *Acute coronary syndrome*: STEMI, NSTEMI, and noncoronary causes of ST elevation
- *Miscellaneous nonarrhythmic cardiac emergencies*: Aortic dissection, acute pulmonary embolism, and acute pericarditis
- *ECG in systemic conditions presenting in emergency*: Electrolyte imbalance—hypokalemia, hyperkalemia, hypocalcaemia, hypercalcemia, hemorrhagic stroke, pericardial effusion, myxedema cor pulmonale due to COAD, drug effects and toxicities

(ECG: electrocardiogram; COAD: chronic obstructive airway disease; STEMI: ST elevation myocardial infarction; WPW: Wolff–Parkinson–White)

BOX 2: Steps in systematic analysis of ECG.

- *Rate and rhythm*: Rate is estimated by 1,500/small square between two consecutive R wave. If distance between R-R and P-P is same then rhythm is regular
- Relationship between *P waves and QRS complexes, PR interval*: Every P wave is followed by QRS complex, PR interval extends from end of the P wave to beginning of the QRS complex (PR duration 0.12-0.20 second)
- *QRS duration, morphology and amplitude*: Presence of bundle branch block (BBB) or intraventricular conduction defect (IVCD), and ventricular preexcitation; pathological Q waves; left or right ventricular enlargement or hypertrophy, fragmentation, and notches
- *ST segment and T wave abnormalities*: ST segment elevation or depression; early repolarization pattern; T wave inversion, flattening, tall and pointed patterns, etc.
- *QRS axis* in the frontal plane and fascicular blocks
- *P wave morphology*: Site of atrial origin, left or right atrial enlargement/hypertrophy patterns
- *Intervals:* PR interval, QT interval, PP, and RR intervals
- *Miscellaneous*: Paced ECG interpretation, disease specific diagnostic patterns—acute pulmonary embolism, arrhythmogenic right ventricular dysplasia (ARVD), electrolyte imbalance, etc.
- *Correlate with patient signs and symptoms*

- *Sinus tachycardia* is identified by gradual onset (history), normal or reduced PR interval, and a P wave morphology suggestive of sinus node origin (negative in lead aVR, positive in leads I, II, III, aVF, and biphasic in lead V1). It is usually secondary to some other underlying cause that can be physiological (anxiety, fever, and pregnancy) or pathological (pulmonary embolism, myocardial ischemia, etc.).
- *Paroxysmal SVT (PSVT)* starts abruptly and presents with symptoms of palpitations. It shows regular RR intervals with rate varying from 140 to 220 beats/min. The various subtypes of PSVT (**Figs. 1** to **3**) can also be inferred from the ECG based on the location of the P waves in the cardiac cycle, however, since the acute treatment of different sub forms of the PSVTs is more or less same, their identification is not of paramount importance in the emergency. The QRS complexes during SVT are usually narrow, however, preexisting BBB or transient aberrant conduction can result in wide QRS complexes during SVT. The clue lies in the fact that the QRS morphology is typical of either right or left BBB in SVT with aberrancy.
- *Atrial flutter* can be recognized by rapid atrial rate (220–350 beats/min, usually 300 beats/min) with P waves of single morphology occurring in a saw-tooth pattern without any isoelectric line between them. The ventricular rate and rhythm depend on the AV conduction pattern and can be rapid or controlled and regular or irregular.



FLOWCHART 1: Classification of tachyarrhythmias.

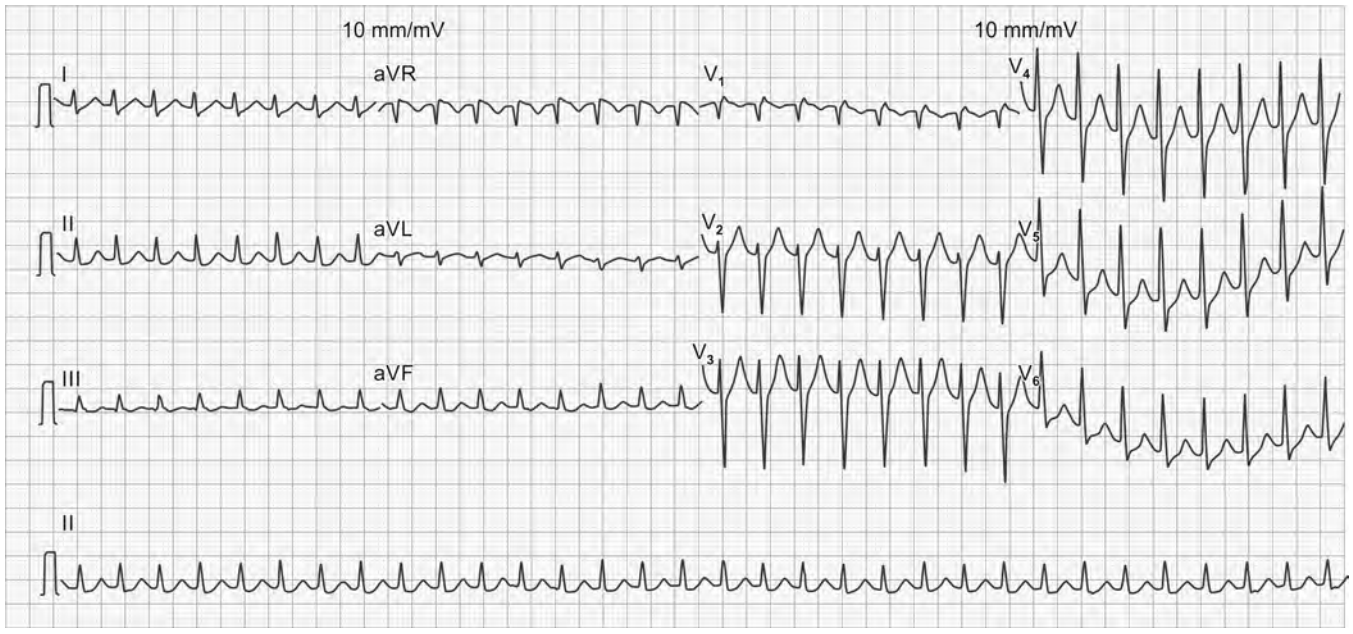


FIG. 1: Paroxysmal supraventricular tachycardia (PSVT) due to atrioventricular nodal reentrant tachycardia (AVNRT). A regular narrow QRS tachycardia with QRS morphology that is normal is diagnostic of PSVT. Note the lead V_1 shows a small positive deflection similar to r′ after the S waves that suggest presence of P waves occurring just at the end of the QRS complex. These P waves may also be visible as small negative deflections in leads II, III, and aVF immediately at the end of QRS. This location of P waves during PSVT indicates a diagnosis of AVNRT—the most common mechanism of PSVT.

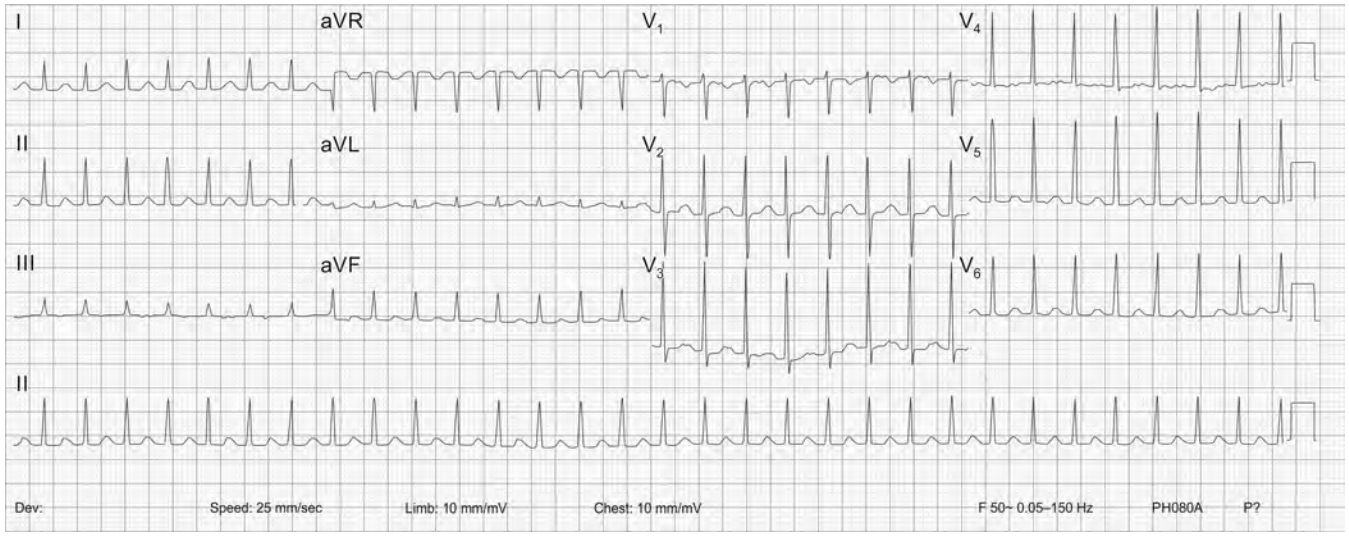


FIG. 2: Paroxysmal supraventricular tachycardia (PSVT) due to atrioventricular reciprocating tachycardia (AVRT). Another example of regular narrow QRS tachycardia where the P waves are seen in the ST segment. The most common mechanism of this pattern is AVRT wherein the reentrant circuit involves antegrade conduction over the normal AV node—His-Purkinje system and retrograde conduction over an accessory pathway. A similar pattern of ECG can also occur in a focal atrial tachycardia, however, that is much less common.

- *Atrial fibrillation* presents with rapid irregular ventricular rhythm with P waves that is either not visible or exist as small, nonuniform undulations (fibrillatory waves). The QRS complexes are usually narrow but can be wide if there is aberrant intraventricular conduction (transient BBB), preexisting BBB (**Fig. 4**) or ventricular preexcitation. The clue to recognition of atrial fibrillation is markedly irregular RR intervals.
- *Monomorphic ventricular tachycardia (MMVT)* presents as a regular wide QRS tachycardia. It is the most common cause of wide QRS tachycardia in clinical setting and its diagnosis is even more likely if the patient has structural heart disease or prior myocardial infarction (MI) (**Figs. 5** to **7**). The ECG pointers to a diagnosis of MMVT as against the other differential diagnosis of SVT with aberrancy include AV dissociation, fusion and capture beats, wider QRS [(>140 ms with right bundle branch block (RBBB) type and >160 ms with LBBB type)], precordial concordance (**Fig. 5**), and northwest axis of the QRS in the frontal plane. Though, many algorithms exist to help in differentiation of MMVT

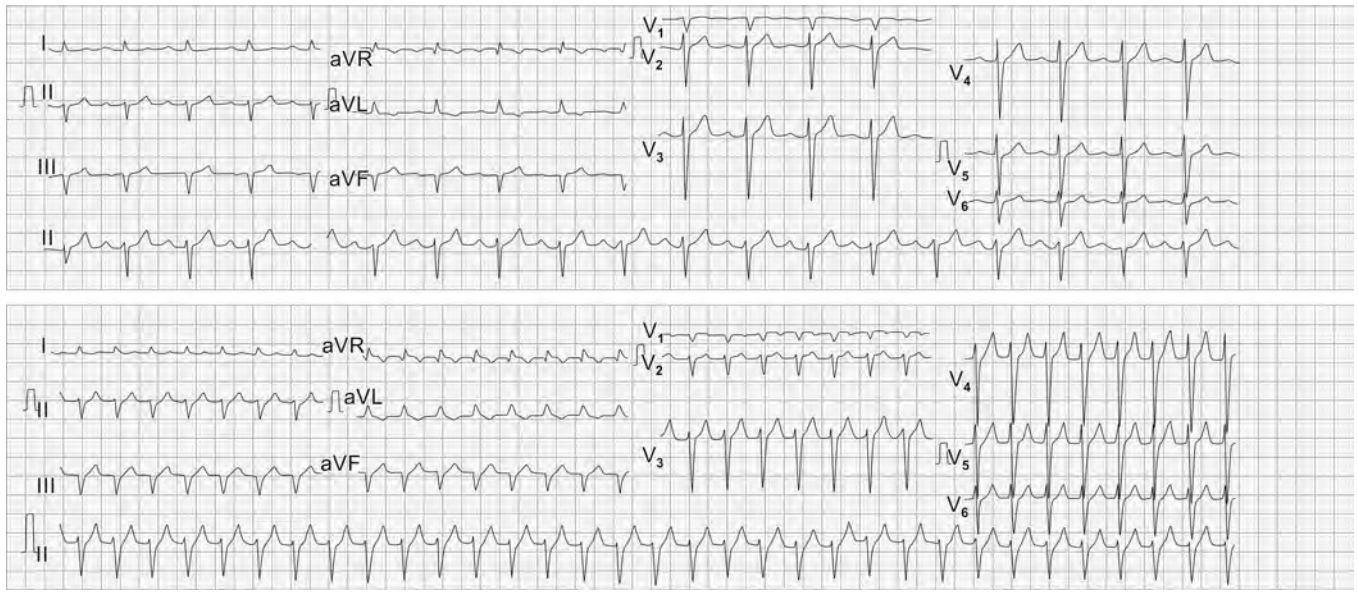


FIG. 3: ECGs of sinus rhythm (top panel) and paroxysmal supraventricular tachycardia (PSVT) (bottom panel) showing identical QRS morphology. Note that in both panels, the 12-lead ECG is displayed at half voltage (5 mm/mV) resulting in small QRS amplitude. The rhythm strips in both panels display lead II at standard 10-mm/mV voltage. The sinus rhythm ECG was recorded immediately after termination of PSVT with injection of metoprolol that also explains prolonged PR interval during sinus rhythm. The P waves are not visible during the regular narrow QRS PSVT suggesting atrioventricular nodal reentrant tachycardia (AVNRT) as the likely diagnosis.

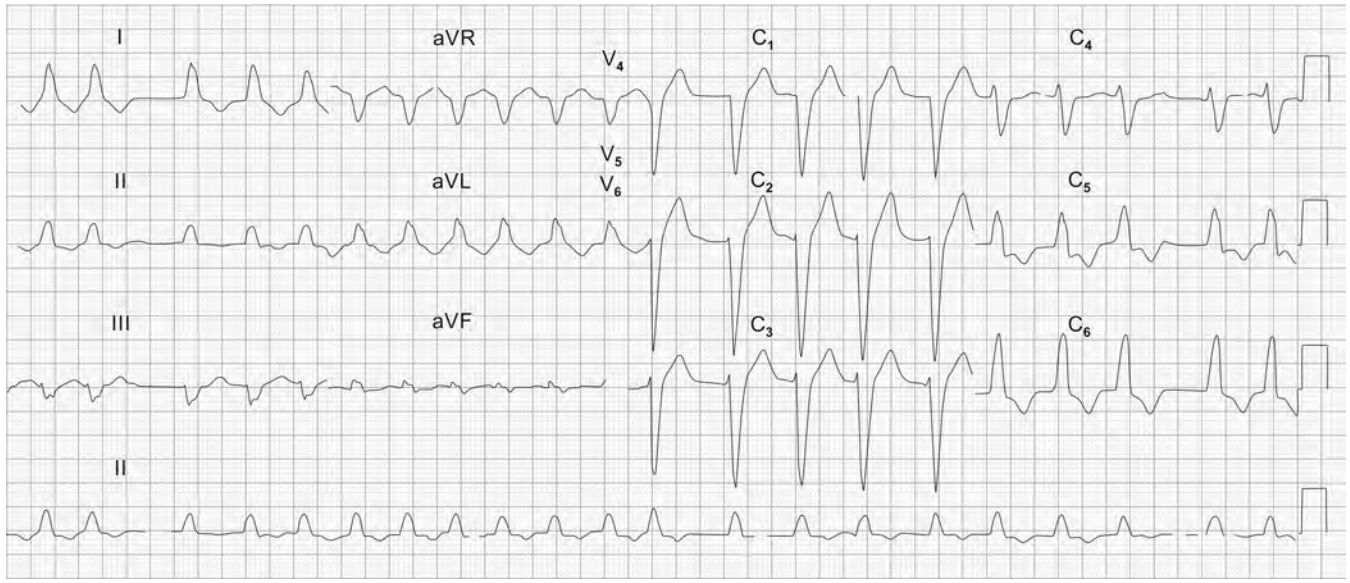


FIG. 4: Atrial fibrillation with aberrant conduction. Irregular wide QRS complex tachycardia with predominantly negative QRS complexes in lead V_1 [left bundle branch block (LBBB) type] with no identifiable P waves indicating a diagnosis of atrial fibrillation. The typical LBBB morphology of the QRS suggests aberrant intraventricular conduction rather than ventricular tachycardia. Also, marked irregularity of RR intervals clinches the diagnosis of AF.

from SVT with aberrancy; the history of prior infarction, QRS morphology not resembling typical LBBB or RBBB, and QRS morphology different from baseline indicate a diagnosis of ventricular tachycardia.

- *Preexcited SVT*—any SVT can present as a wide QRS complex tachycardia in patients with ventricular preexcitation or Wolff–Parkinson–White (WPW) syndrome. The QRS morphology does not resemble that during sinus rhythm or typical BBB but suggests the location of commonly found accessory pathways. The sinus rhythm ECG (of prior times or recorded after termination of SVT) shows typical preexcitation pattern with short PR interval, delta waves, and wide QRS complexes.
- *Polymorphic ventricular tachycardia (VT)* presents as an irregular tachycardia with wide QRS complexes with marked variation in the morphology of the QRS complexes from beat to beat. If the tachycardia is sustained, the patient is usually hemodynamically unstable. It can exist in the presence of normal QT interval, but is more common with QT interval prolongation, when it is known as *Torsades*

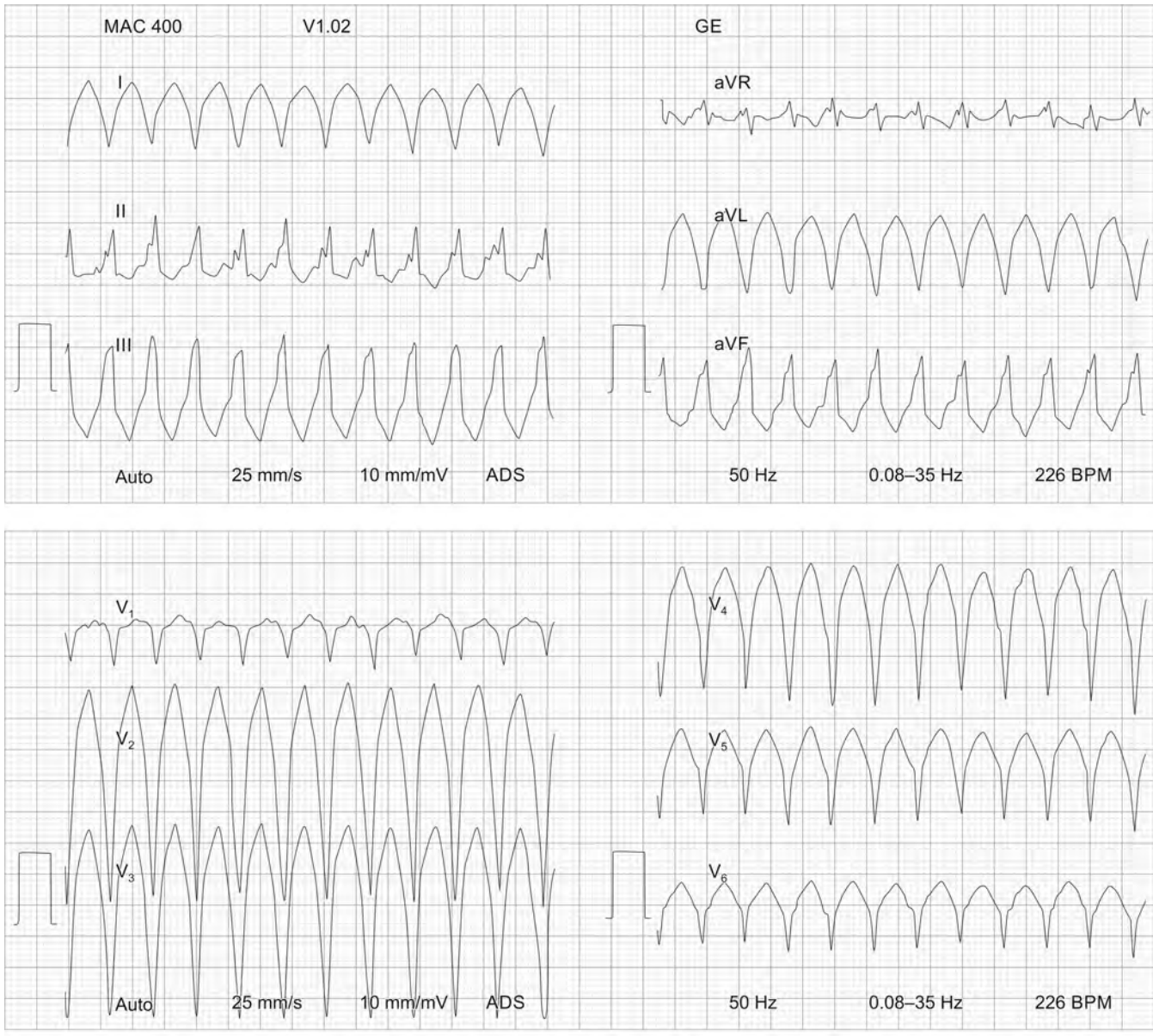


FIG. 5: Ventricular tachycardia (VT) in a patient with prior myocardial infarction (MI). A regular wide QRS tachycardia with predominantly negative QRS complexes in V_1 [left bundle branch block (LBBB) type] is displayed. The clues to the diagnosis of VT include history of prior MI, atrioventricular dissociation (best seen in V1), negative concordance of QRS in the precordial leads, axis-morphology discordant pattern (LBBB morphology with right axis deviation of QRS in the frontal plane) and QRS morphology not resembling typical LBBB.

de pointes due to appearance on the ECG as if the QRS complexes are twisting around a point or line.

BRADYARRHYTHMIA

The normal heart rate in an adult person at rest varies from 60 to 100 beats/min. Any rhythm where the heart rate is <60 beats/min is known as bradyarrhythmia. *AV block of second or higher degree even with a ventricular rate > 60 beats/min is classified as bradyarrhythmia*. These rhythm disorders can occur due to either sinus node dysfunction (disorder or impulse formation or conduction) or AV block (disorder of impulse conduction). The patients with bradyarrhythmia usually present with complaints of syncope or presyncope, weakness or fatigue, and/or breathlessness on exertion. Though**,** *commonly these rhythm disorders occur as a result of degenerative diseases of the electrical system*, at times *reversible causes such as drugs, electrolyte imbalance, or acute myocardial ischemia or infarction* (**Fig. 8**) may be the causative mechanism:

- Sinus node dysfunction can present as sinus pauses, sinus arrest with junctional or ventricular escape beats and rhythm, sinus bradycardia, or sinoatrial exit block (**Fig. 9**). Other ECG manifestations that may be found in patients with so called sick sinus syndrome include AV block, BBB, atrial fibrillation, and episodes of bradycardia alternating with tachycardia (tachybrady syndrome).
- Atrioventricular block presents as delay in conduction (prolonged PR interval, first degree AV block) or block

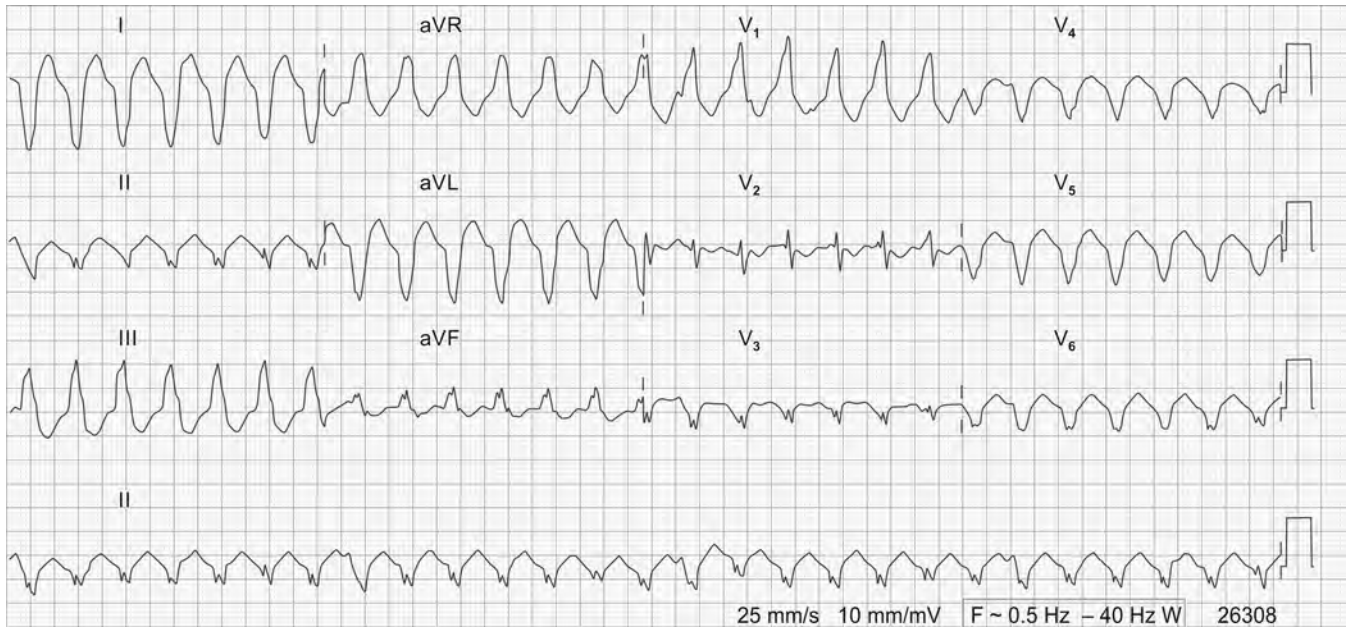


FIG. 6: Ventricular tachycardia (VT) in a patient with idiopathic dilated cardiomyopathy. A regular wide QRS tachycardia with predominantly positive QRS in lead V_1 [right bundle branch block (RBBB) type] is shown. The clues to the diagnosis of VT include atrioventricular dissociation (best seen in rhythm strip of lead II), markedly wide QRS complexes, Q waves in lead V_6 and QRS morphology not resembling typical RBBB among many others. Note that the QRS looks deceptively narrow in lead V_2 and an erroneous diagnosis of supraventricular tachycardia can be made if this lead is chosen as the only monitoring lead and a 12-lead ECG is not recorded.

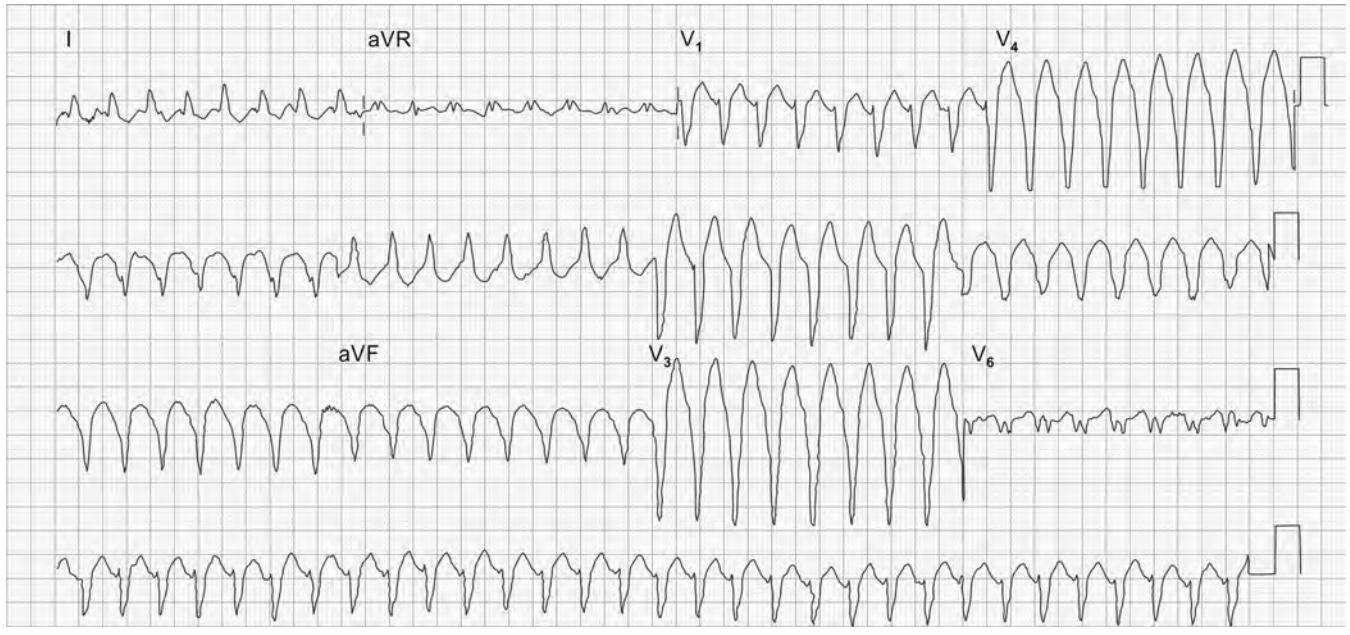


FIG. 7: Ventricular tachycardia (VT) in a patient with arrhythmogenic right ventricular dysplasia (ARVD). A regular wide QRS tachycardia with left bundle branch block (LBBB) type pattern and left axis of the QRS in the frontal plane is shown. The presence of AV dissociation (seen best in rhythm strip of lead V1) and negative precordial concordance clinches the diagnosis of VT. Note that during LBBB type VTs, left axis deviation of QRS complex is suggestive of ARVD as the underlying diagnosis, whereas a right axis deviation is more common with idiopathic outflow tract VTs.

of some (second degree, **Fig. 10**) or all (third degree or complete AV block, **Fig. 11**) atrial impulses to the ventricles. The need for temporary and permanent pacemaker implantation depends on the presence and severity of symptoms, presence of reversible causes, ventricular rate, QRS width, and underlying heart disease.

ST-T CHANGES

ST Segment Deviation

ST segment is the deflection from the end of QRS complex to the onset of T wave and is normally isoelectric. Deviation

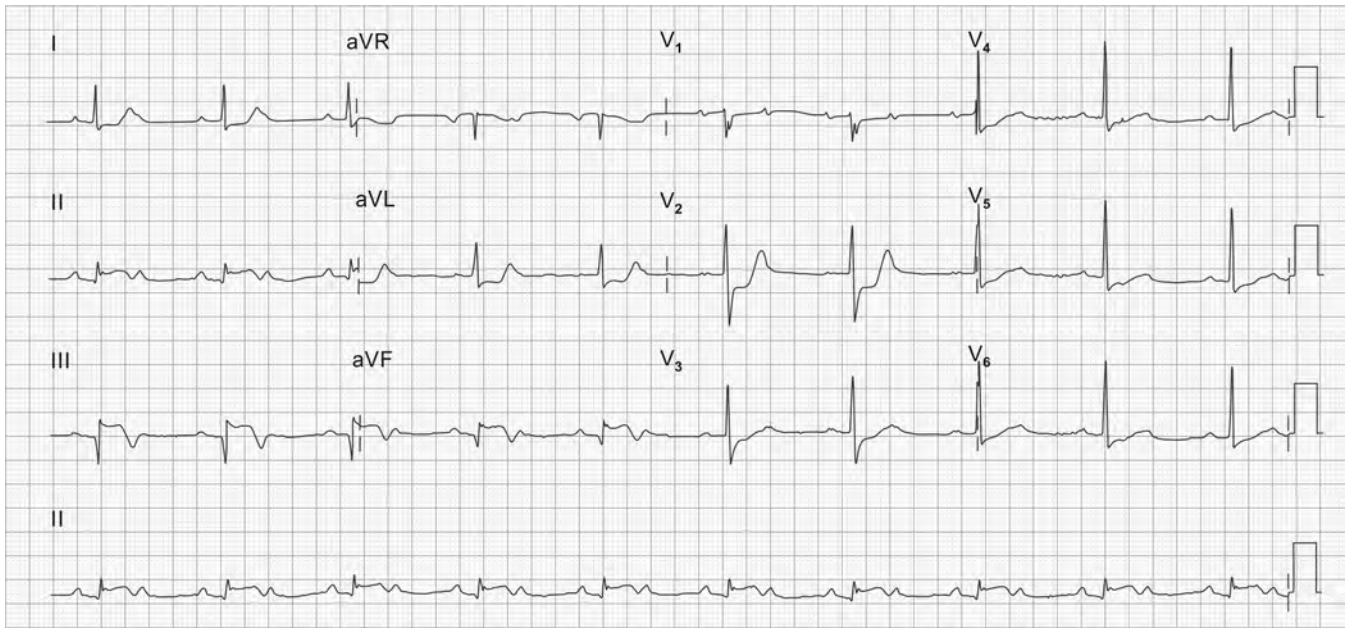


FIG. 8: Acute inferior-posterior myocardial infarction (MI). Sinus rhythm with 2–1 atrioventricular block with narrow QRS complexes in the conducted beats is seen. The leads II, III, and aVF show ST segment elevation with prominent Q waves indicating acute evolving inferior wall MI. Notice that large R wave in lead V_2 with marked ST depression suggests presence of concomitant posterior wall MI. ST segment elevation that is greater in lead III than in lead II indicate involvement of the right coronary artery and presence of AV block suggests a proximal location of the culprit lesion.

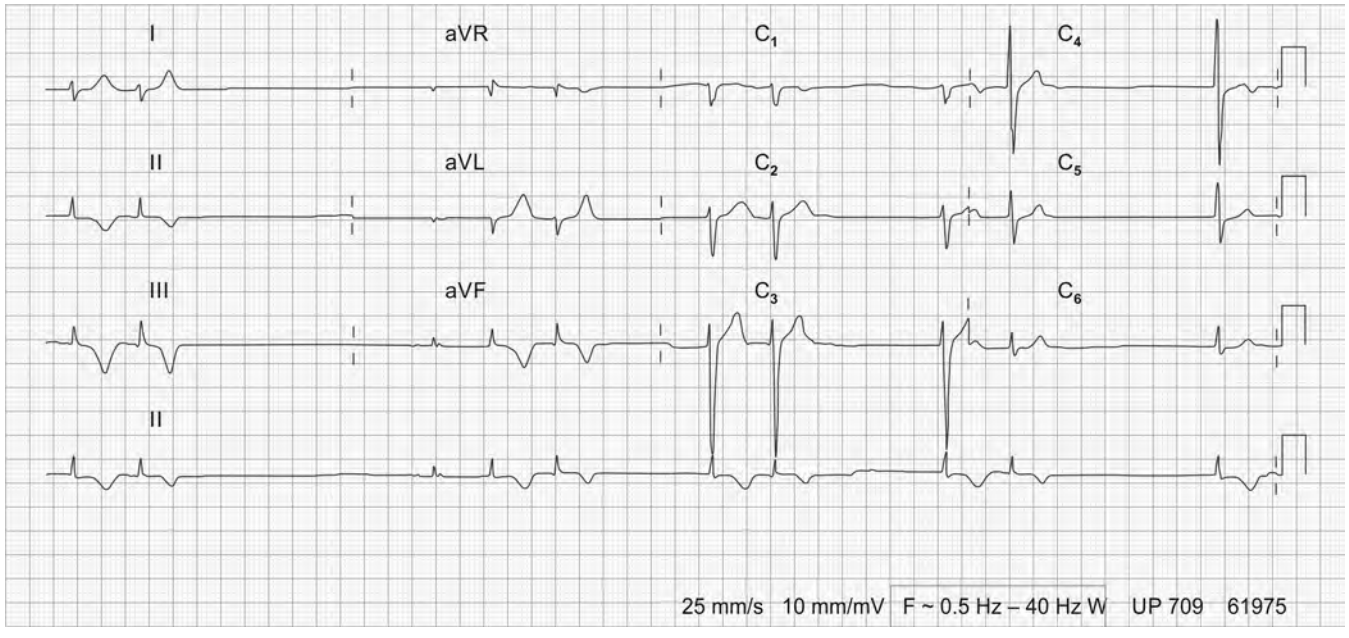


FIG. 9: Sinus node dysfunction. An ECG showing sinus pauses and junctional escape beats and rhythm in a patient with sinus node dysfunction is displayed. Also, note that marked T wave inversion in inferior leads that could be either due to underlying heart disease (for example, myocardial ischemia) or due to cardiac memory as a result of prior persistent ventricular escape rhythm. Also present in this tracing is possibly left posterior fascicular block (right axis deviation of QRS; qR pattern in leads II, III, and aVF; and rS pattern in leads I and aVL).

of the ST segment upward (ST elevation) or downward (ST depression) in various ECG leads is an important sign of many heart diseases the most important of which is coronary artery disease. In fact, presence or absence of ST segment elevation is a means of classifying acute MI into ST elevation MI (STEMI) or non-ST elevation MI. Few important points are provided below in reference to ST segment deviation and its utility in the emergency:

- The ECG leads can be grouped according to the location of the ventricles that they overlie. These are known as contiguous leads and include:
  - *Inferior wall*—Leads II, III, and aVF
  - *Anterior wall*—Leads V_1 to V_6
  - *Antero-lateral wall*—V_4 to V_6, I, and aVL
  - *Antero-septal wall* —V_1 to V_3, aVR

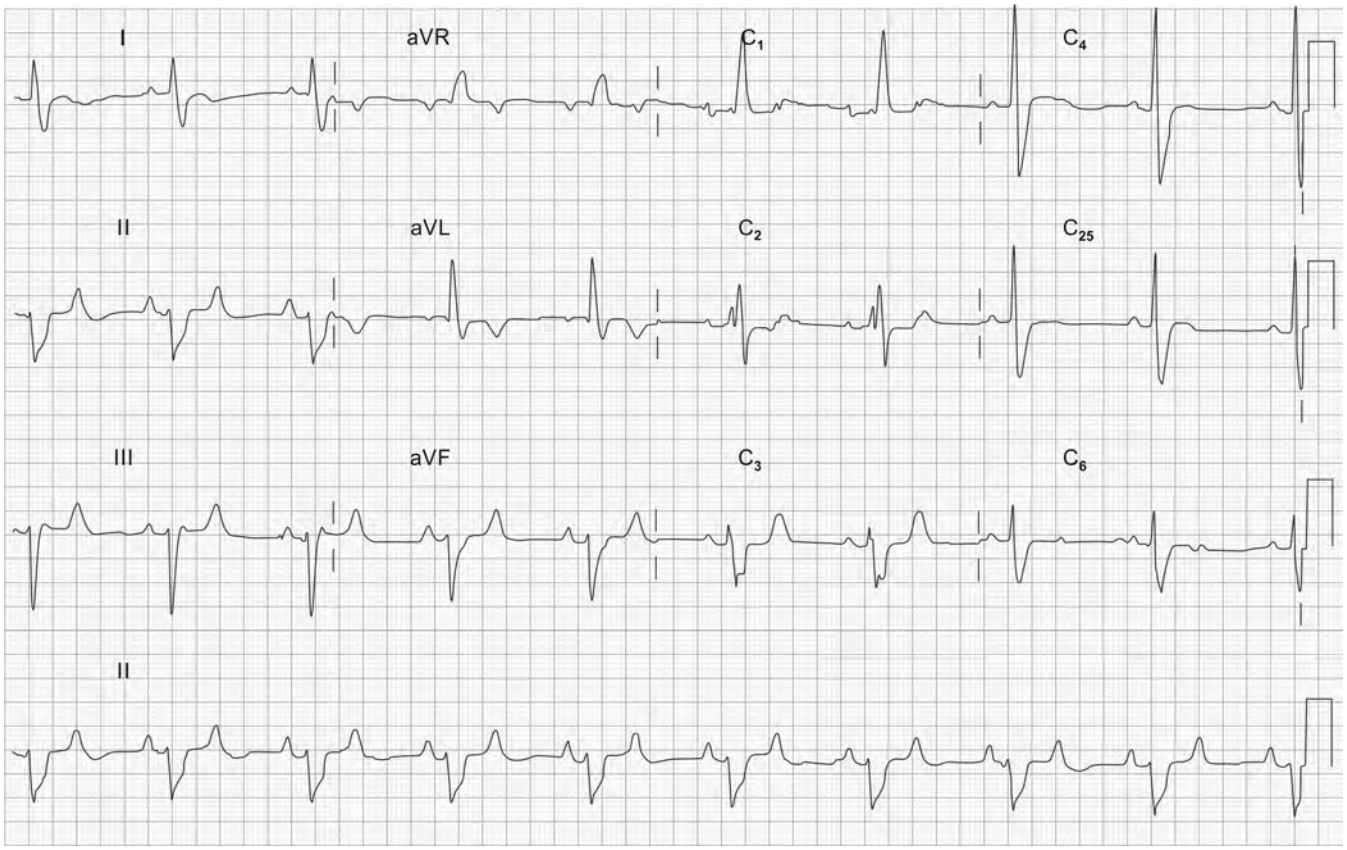


FIG. 10: *Two to one AV block*. Sinus tachycardia with 2 to 1 AV block with RBBB and LAFB in the conducted beats is seen. Notice that there are two P waves for each QRS complex, and the PR intervals of the conducted beats are constant as are PP and RR intervals. A wide QRS complex in the conducted beat (RBBB in this case) suggests infra-Hisian location of the AV block and need for permanent pacemaker implantation even in the absence of bradycardia-related symptoms.

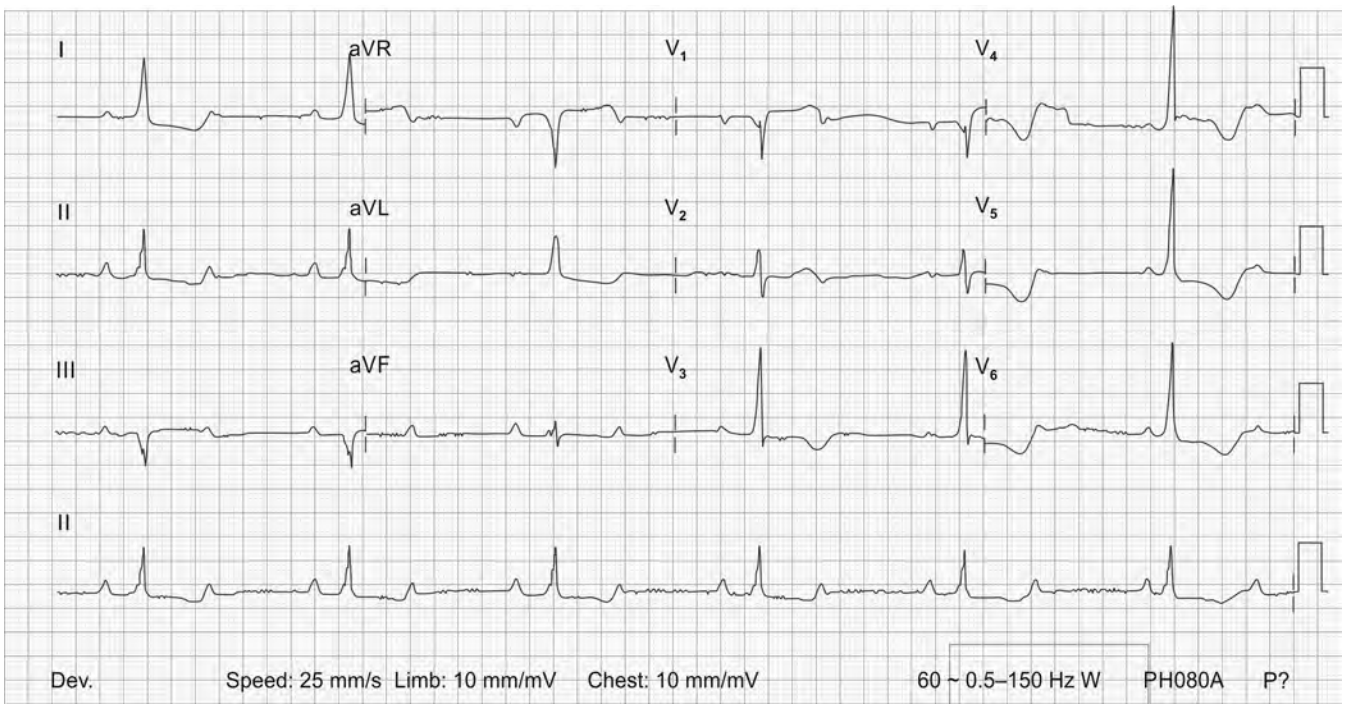


FIG. 11: *Complete AV block*. Sinus rhythm with complete AV block and a slower wide QRS (ventricular) escape rhythm is seen. Note that the P waves occur at a much faster rate, and have no association with the QRS complexes (AV dissociation). The clue to the presence of AV dissociation is varying apparent PR intervals in the presence of constant RR and PP intervals.

- *Right ventricle*—right-sided precordial leads V_1 to V_6
- *Posterior wall*—Leads V_7 to V_9.

- ST elevation of 1 mm (0.1 mV) or greater in two or more contiguous leads in a patient with chest discomfort is indicative of STEMI (**Figs. 8** and **12**). A prompt recognition of STEMI suggests the need of emergency reperfusion therapy in the form of either primary angioplasty or thrombolysis.
- ST elevation and depression both are suggestive of myocardial ischemia. ST elevation has localizing value but ST depression does not. Hence, ST elevation in leads II, III, and aVF indicates acute inferior wall MI. ST depression in these leads may indicate myocardial ischemia but not necessarily in inferior wall of the left ventricle.
- Serial changes in ECGs taken over time have more importance than fixed changes.
- The ECG not only has value in diagnosis of MI but also helps in localization of infarct, culprit artery localization, estimation of infarct size, timing of infarction, risk stratification, and prognostication.
- Various other causes of ST elevation apart from STEMI exist and should be considered if diagnosis of MI is doubtful. These are listed in **Box 3**.
- ST segment depression indicates myocardial ischemia especially if it is >1 mm, present in two or more contiguous leads, of horizontal or down-sloping (rather than upsloping) nature or if associated with marked T wave changes.
- ST segment depression of <1 mm especially if present in the absence of typical chest discomfort is commonly nonspecific and is seen in a variety of clinical conditions.

T Wave Changes

The T wave represents part of the recovery period of the ventricles (repolarization). The T wave is normally upright in leads I, II, and V_4 to V_6; inverted in aVR; usually upright in aVF and can be variable in III, aVL, and V_1. The T wave changes can often be nonspecific and should always be interpreted along with the ST segment abnormalities and clinical setting. The common T wave abnormalities are described in **Box 4**.

BOX 3: Noninfarction causes of ST segment elevation.

- Acute pericarditis
- Coronary artery spasm
- Left ventricular aneurysm
- Left bundle branch block
- Left ventricular hypertrophy
- Early repolarization syndrome
- Hypertrophic cardiomyopathy
- Acute pulmonary embolism

BOX 4: T wave abnormalities.

- T wave inversion associated with ST segment deviation and/or abnormal Q waves—myocardial ischemia or infarction, digitalis effect, or toxicity (**Fig. 13**)
- Diffuse deep T wave inversion (usually nonspecific and seen in variety of conditions)—myocardial ischemia, evolving MI, apical or hypertrophic cardiomyopathy, cardiac memory, electrolyte imbalance, and cerebrovascular accidents
- Asymmetric T inversion in lateral precordial leads—left ventricular hypertrophy
- Asymmetric T inversion in right precordial leads—right ventricular hypertrophy and acute pulmonary embolism
- Peaked T waves in precordial leads—hyperkalemia
- Peaked T waves in V_1 and V_2 with positive QRS complexes—*posterior wall MI*

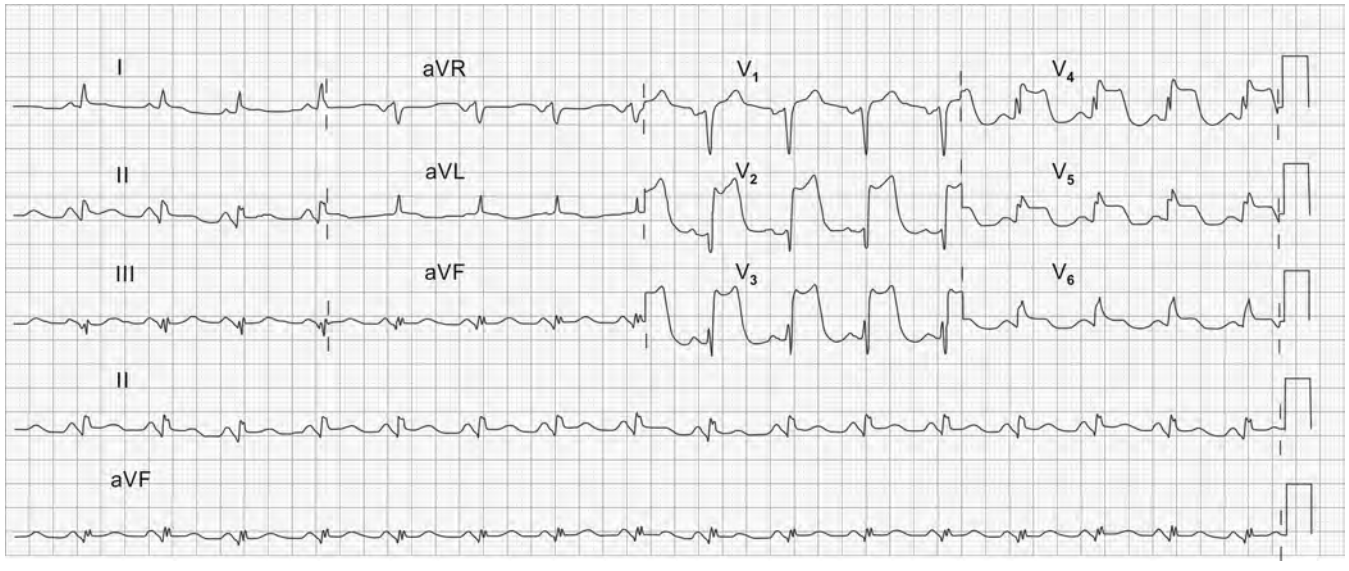


FIG. 12: *Acute anterior wall myocardial infarction (MI)*. Marked ST elevation is seen in precordial leads V_2 to V_6 indicating acute anterior wall MI and involved of left anterior descending (LAD) coronary artery. Notice, that the inferior leads also show ST segment elevation. This pattern suggests that the site of culprit lesion in the LAD artery is distal to the origin of the septal and diagonal branches. Hence, ECG not only helps in diagnosis but indicates the culprit vessel and localizes the site of lesion.

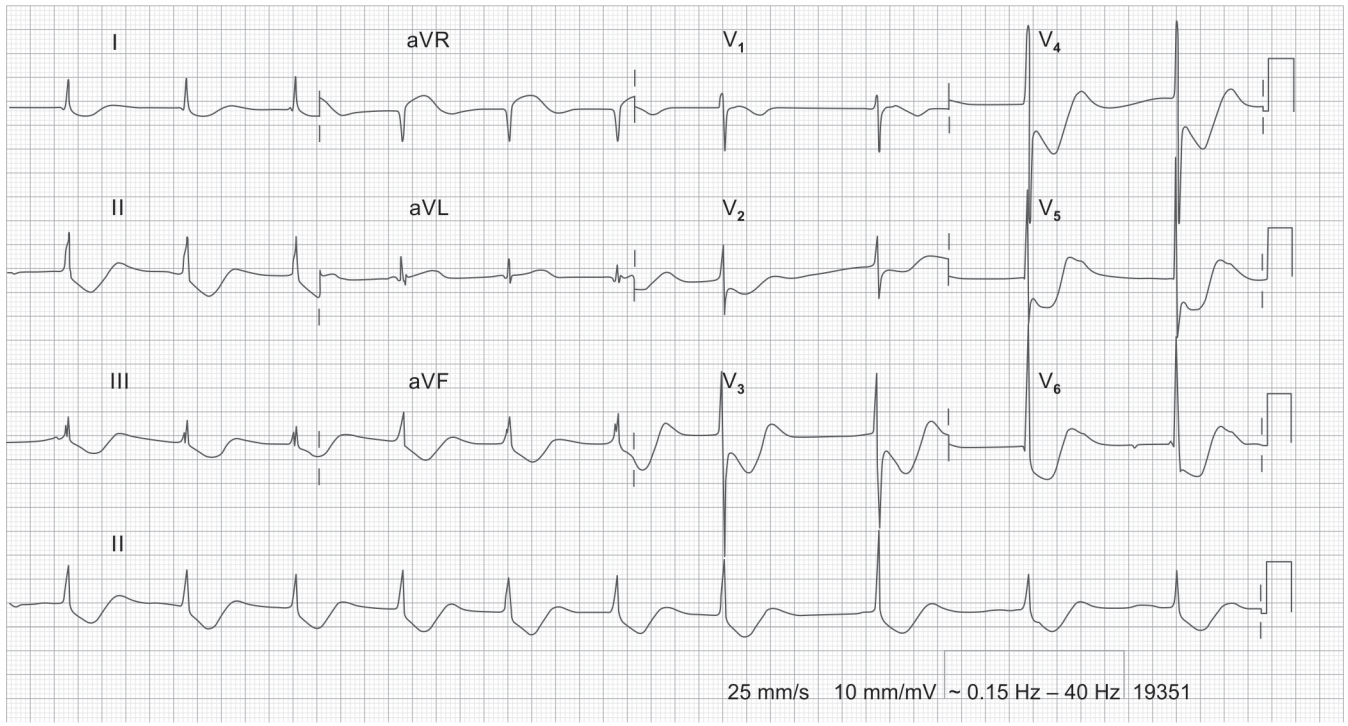


FIG. 13: *Digitalis toxicity. This is an ECG of a patient with permanent AF and digitalis toxicity*. The P waves are absent and the ventricular rhythm is irregular with narrow QRS complexes. Importantly there is marked ST segment depression with T wave inversion in most leads. Note, that the J point (end of QRS) is also markedly depressed in leads V_3 to V_6 that differentiates it from digitalis *effect* wherein the ST depression and T wave inversion are present without J point depression. Note is also made of large amplitude R waves in V_5 and V_6 due to underlying left ventricular hypertrophy.

QRS MORPHOLOGY AMPLITUDE DURATION AND AXIS PATTERN

The normal coordinated simultaneous activation of both right and left ventricle is responsible for *normal QRS complex that is narrow (QRS duration < 100 ms), has normal axis in the frontal plane, and has normal amplitude in various leads (in absence of normal left and right ventricular thickness)*.

Delay or block in conduction of left or the right bundle branches results in sequential activation of the ventricles with resultant right or left BBB pattern. The block in conduction of the left anterior and posterior fascicles (*see* **Fig. 9**) does not result in QRS widening but causes change in the QRS axis in the frontal plane. The diagnostic criteria for left and right BBB and fascicular blocks are summarized in **Box 5**. A diagnosis of BBB especially LBBB (**Fig. 14**) or bifascicular block in a patient presenting with history of syncope or presyncope may suggest intermittent complete AV block as the cause and requirement of additional evaluation and possible pacemaker implantation. All physicians should have an imprint of typical LBBB and RBBB patterns inscribed in their minds for an accurate diagnosis of many arrhythmias.

Similarly, presence of an antegrade conducting accessory pathway *(WPW syndrome)* (**Fig. 15**) results in preexcitation of the ventricle in which it is inserted resulting in sequential activation of ventricles. The QRS complex in this situation of ventricular preexcitation occurs as a result of fusion of activation of ventricles by the accessory pathway and the

BOX 5: Diagnostic criteria for left and right BBB and fascicular blocks.

Left bundle branch block (LBBB):
- QRS duration > 120 ms
- Wide notched R waves in V_5, V_6, I, and aVL
- Small or absent initial r wave in right precordial leads V_1 and V_2 followed by deep S waves
- Absent septal Q waves in left-sided leads V_6 and lead I
- Prolonged intrinsicoid deflection (>60 ms) in V_5 and V_6

Right bundle branch block (RBBB):
- QRS duration > 120 ms
- Wide notched R waves (rsr′, rsR′, or rSR′ patterns in right precordial leads—V_1 and V_2
- Wide and deep S waves in left precordial leads—V_5 and V_6
- Bifascicular block—RBBB and LAFB/RBBB and LPFB

Left anterior fascicular block (LAFB):
- Left axis deviation (QRS axis in the frontal plane –45 to –90°)
- rS pattern in leads II, III, and aVF
- qR pattern in lead aVL
- QRS duration < 120 ms

Right anterior fascicular block (RAFB):
- Right axis deviation (QRS axis in frontal plane > 120°)
- qR pattern in leads II, III, and aVF
- rS pattern in leads I and aVL
- QRS duration < 120 ms

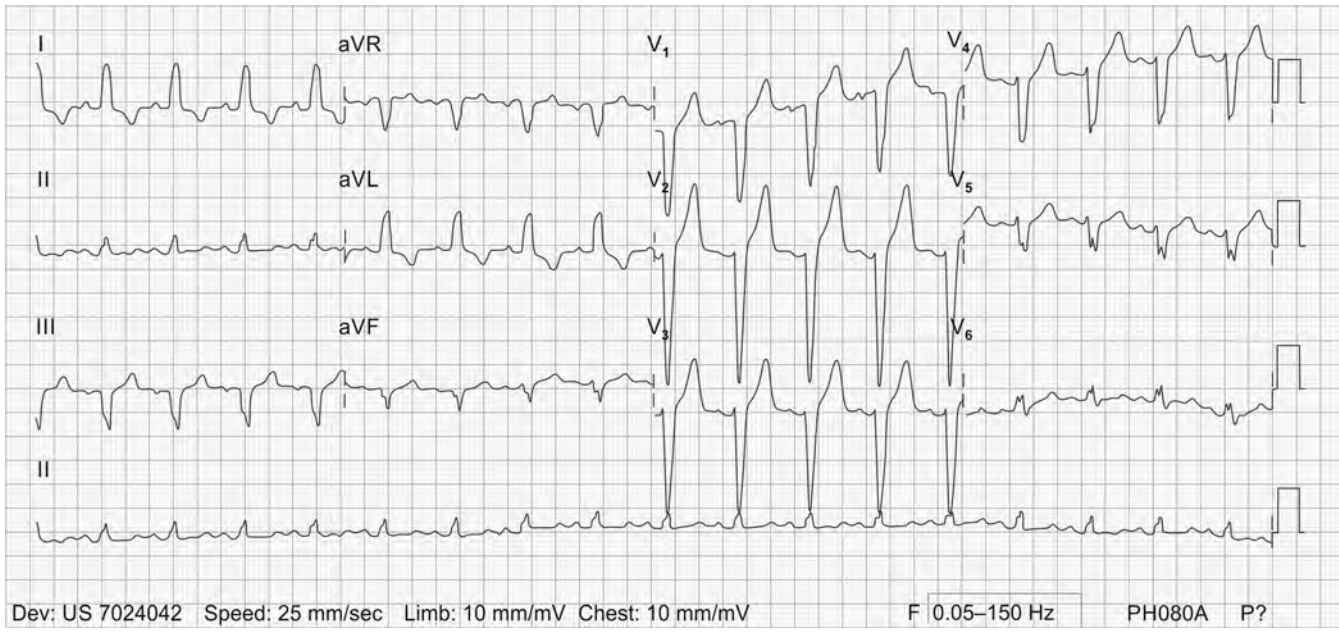


FIG. 14: *Left bundle branch block (LBBB)*. Sinus tachycardia is present with wide QRS complexes that have predominantly negative QRS in lead V_1, notching in V_4 to V_6, absent (very small) r in lead V_1 and absent q waves in leads V_6, I, and aVL. These are typical features of LBBB.

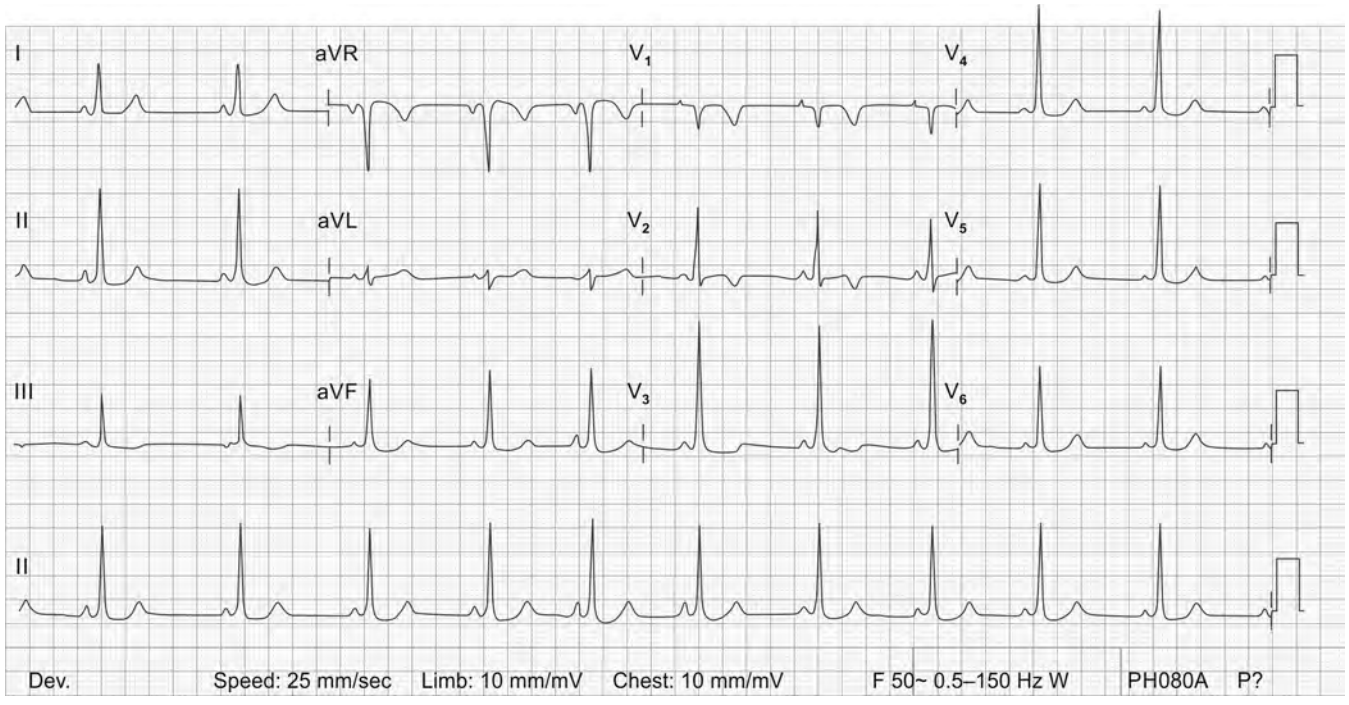


FIG. 15: *Wolff–Parkinson–White (WPW) syndrome*. Sinus rhythm with short PR interval, delta waves and wide QRS complexes are present indicating ventricular preexcitation due to an accessory pathway. The negative delta and QRS in lead V_1 suggest a right sided pathway. The presence of symptoms or documented arrhythmias related to accessory pathways in a patient with ventricular preexcitation makes a diagnosis of WPW syndrome. Note is made of marked irregularity in sinus rhythm that is as a result of sinus arrhythmia due to respiratory variation.

normal AV node—His-Purkinje system and is wide with an initial delta wave. Recognition of WPW syndrome or ventricular preexcitation during sinus rhythm in a patient with episodic palpitations may indicate PSVT as a cause of palpitation.

MISCELLANEOUS ECG FINDINGS IN EMERGENCY

Many other findings in the ECG may be present that may provide an important clue to the diagnosis in the emergency setting. These include:

- Wide QRS complexes with absent P waves—hyperkalemia (**Fig. 16**)
- Low voltage ECG—pericardial effusion, hypothyroidism, thick chest wall, obesity, emphysema, and incorrect standardization
- Electrical alternans—cardiac tamponade
- Prolonged QT interval—congenial long QT syndrome, drug- induced QT prolongation, hypocalcemia, and hypomagnesemia
- Osborn wave—abnormal wave seen at the end of QRS seen classically in hypothermia.

SUMMARY

The ECG plays an important role in the initial diagnostic evaluation of all patients presenting with symptoms related to cardiovascular disorders or at times systemic illnesses in the emergency. Emergency physicians cannot afford to miss the finding of ST segment elevation, the hallmark of diagnosis of acute MI as it may result in disastrous consequences. Studies have shown that emergency physicians are usually good and accurate at diagnosing MI from the ECG, but are not up to the mark in diagnosis of cardiac arrhythmias. A systemic nine-step approach to ECG interpretation as outlined below can be useful to arrive at a quick and accurate diagnosis in most patients presenting in the emergency in emergency department (**Box 6**).

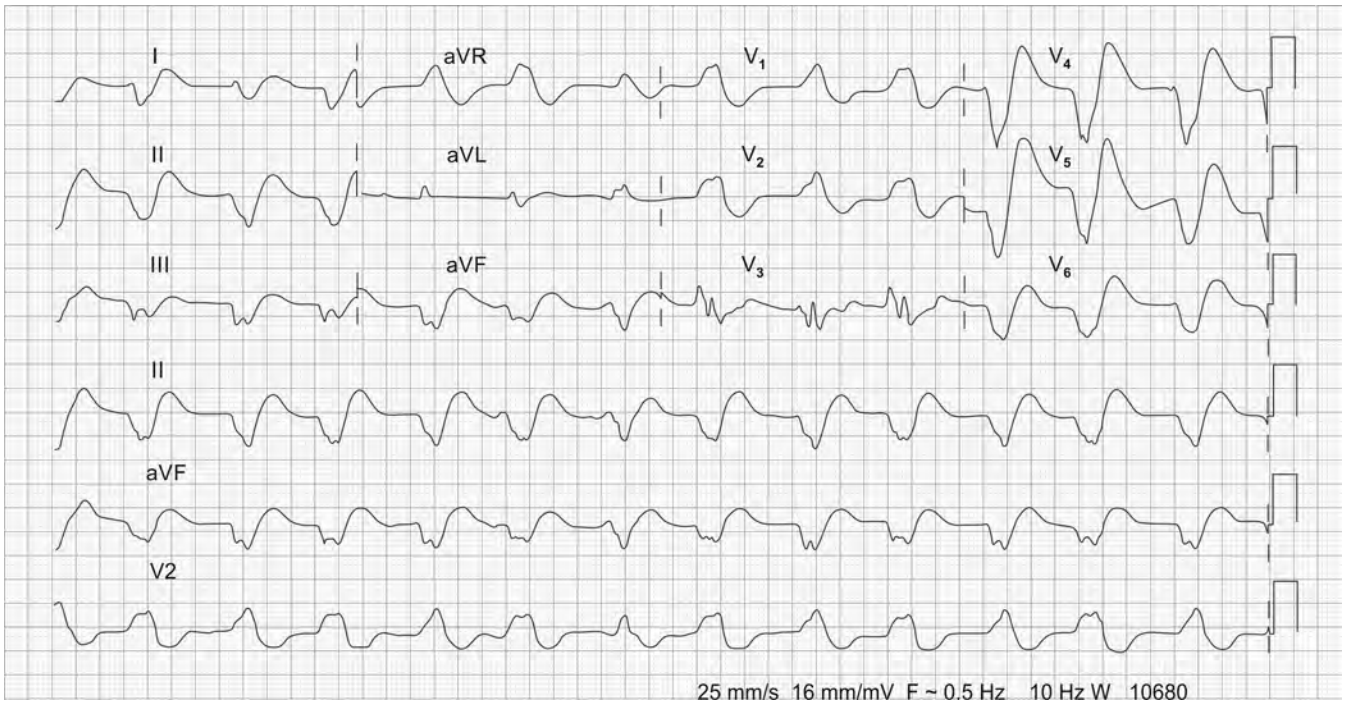


FIG. 16: *Hyperkalemia*. A regular rhythm with markedly wide and bizarre QRS complexes that are not preceded by P waves—sinoventricular rhythm. The T waves start immediately after the end of QRS complexes with almost absent ST segment. These are ECG features of severe hyperkalemia.

BOX 6: 9 Steps approach of ECG interpretation.

1. *Is the rhythm regular*? QRS segment of the ECG is observed to determine to ascertain depolarization within the ventricles is regular. Measure the distance between one R to another R. Check all other R-R distance, whether they are equal within a given amount of time, typically 6–10 seconds. If case of any irregularities is noted, check with the patient or previous ECG if these abnormalities are persisted. If so, look for symptoms associated with CHAPS—chest pain, hypotension, altered mental state, poor perfusion, or shortness of breath
2. *Calculate heart rate*: Check and count radial pulse also. Determine from the reading whether the patient is experiencing bradycardia, tachycardia, supraventricular tachycardia, or ventricular tachycardia with a pulse
3. *Diagnose the P waves*: Check presence of the upright P waves and followed by the QRS segment. Check the same on the monitor also. If these are within normal limits, chances are the electrical impulse, are generating from in the SA node, as it should
4. *Measure the P-R interval*: Normal P-R interval is 0.12—0.20 seconds. Calculation is done by counting the time between the P wave and the beginning of the QRS segment. Prolonged P-R interval suggestive of impulse conduction delay through the AV node
5. *Measure the QRS segment*. QRS segment of 0.04–0.10 seconds is considered normal duration. A prolonged QRS segment suggestive of a bundle branch block. Bundle branch blocks may be incidental findings, but associated with symptoms may indicate heart disease
6. *Check the T wave*: The upright T wave followed by the QRS segment is considered normal. Inverted T waves may indicate a myocardial ischemia, peaked tall and tented T waves suggestive of hyperkalemia, flat T waves may indicate hypokalemia, and a raised ST segment may suggest acute coronary syndrome
7. *Note any ectopic beats*: Accessory fibers outside the SA node that stimulate the heart to beat cause premature atrial contractions, premature junctional contractions, or premature ventricular contractions. Determine characteristics of the ectopic beats, the interval, shape, and whether they are single or in groups
8. *Determine the origin*: After calculating the all the above information, following point should be noted:
   - *Sinus*: Regular rhythm with 60–100 beats/min; P waves upright, round, and occurring before the QRS segment; normal P-R interval; normal QRS duration
   - *Atria*: Rhythm may or may not be regular; QRS segment is normal with abnormal P waves (premature, flat, notched, peaked, inverted, or hidden)
   - *Junctional*: Is the P wave junctional, inverted before, during or after the typical QRS segment?
   - *Ventricular*: If the rhythm originates below the SA node, the QRS segment will be wide and unusual with no P waves
   - *Paced rhythm*: Low voltage pacer spikes before the QRS should be reviewed
9. *Correctly identify the rhythm*: Correlate the information from the ECG and the patient's symptoms and vital signs. This will give a much better understanding about the management

MULTIPLE CHOICE QUESTIONS

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62
CHAPTER

Cardiac Biomarkers

Omar Ghazanfar, Israa M Salih, Saleh Fares

INTRODUCTION

Biomarkers are fundamental in establishing the diagnosis and managing cardiovascular diseases (CVD), the leading cause of morbidity and mortality in the world. The delicate nature and time sensitivity of CVD, in which minutes can hugely impact the outcome, have made biomarkers an area of continuous research and development. In the United States, cardiac biomarker testing occurs in nearly 30 million emergency department visits nationwide each year. The National Institutes of Health defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

Biomarkers are tools of screening, diagnosis, prognosis, and monitoring. Multiple molecules are classified as biomarkers and exist in the forms of enzymes, proteins, peptides, the newly added microRNAs, and many others. There are multiple markers for each disease process, the decision of what to use should be justified by indications, standard guidelines, and cost effectivity. Cardiac troponin and the B-type cardiac natriuretic peptides are the two best markers utilized in clinical settings; due to their major role in diagnosis and risk stratification in acute coronary syndromes (ACS) and heart failure. The myocardial infarction (MI) fourth universal consensus definition by the European Society of Cardiology (ESC) and American College of Cardiology (ACC) takes troponin as the key factor in case definition, owing to its high sensitivity and specificity for myocardial injury. History and physical exam remains the most important portion in clinical assessment and diagnosis, any laboratory test including biomarkers should not be taken out of context or as an independent parameter.

IDEAL CARDIAC BIOMARKER

As discussed above, biomarkers can have several roles and it is an ideal situation, if a single biomarker provides multiple information which are pivotal to the management in the emergency. An ideal cardiac biomarker is thus expected to have most of the attributes (**Box 1**) such as early detection in blood, highly specific for cardiac injury, be low cost, and have a sensitive assay to detect it. Clearly no such ideal cardiac biomarker exists and usually a multimarker strategy (discussed later) is practiced depending on the clinical scenario, for optimal outcomes. In the subsequent sections, we discuss the common cardiac emergencies along with the role of appropriate blood biomarkers.

BOX 1: Attributes of an ideal biomarker.

- Found in high concentration in heart and not in other tissue even in pathological state
- Should have low molecular weight so released early in blood, before myocardial necrosis
- Should peak early and remain elevated in for many days
- Level in blood should be proportional to severity of myocardial injuries
- There should be sensitive assay available to detect it and low cost and widely available

TROPONIN

Troponin is the biomarker of choice in the diagnosis of MI, as indicated in the fourth universal consensus definition of MI, and a detrimental factor in subcategorizing ACS. This protein is a component of the contractile apparatus found in skeletal and cardiac myocytes; it regulates the interaction between actin and myosin filaments. Cardiac troponin (cTn) is a three subunits complex: (1) Troponin T, (2) Troponin C, and (3) Troponin I. Troponin T and I isoforms are highly specific and sensitive for cardiac myocytes, and are indicators of cardiac damage. Whereas troponin C is found in both skeletal and cardiac muscles. The half-life of troponin T and troponin I in the blood is about 2 hours. Fluctuating readings might indicate reversible ischemia rather than necrosis, where a time-dependent fall over a longer period (4–10 days) would be expected because of gradual degradation of myofibrils and release of the troponin complex, which makes serial testing a requirement in some cases. The sensitivity of troponin is about 95%, and the specificity is about 80% when ACS is the primary suspected diagnosis, after excluding renal disease and sepsis which can give false positive results. Various

cardiac conditions other than ACS can cause elevated serum troponin which includes pericarditis, myocarditis, heart failure, and chest trauma. Troponin can also be increased in noncardiac conditions such as sepsis, renal disease, pulmonary embolism (PE), chronic obstructive pulmonary disease (COPD), strenuous exercise, and hypertension.

High-sensitivity cardiac troponin (hs-cTn T and I) has substituted the old cTn tests. It can detect troponin at concentrations 10- to 100-fold lower than the old assays, with higher sensitivity, precision, and NPV at an earlier point of time. Cardiac troponins are detected in the serum by the use of highly specific monoclonal antibodies. The European Society of Cardiology and American College of Cardiology consensus document recommends using laboratory cutoffs at the 99th centile of normal with 10% coefficient of variation. This will make serum cTnI values from 0.1 to 2 μg/L indicative of myocyte necrosis. American College of Emergency Physicians (ACEP) and American Heart Association (AHA) guidelines recommend the use of Troponin as level A class 1 in diagnosis of ACS. Cardiac troponin also has a prognostic value in mortality and adverse cardiac events.

CREATININE KINASE-MB

Creatinine kinase-MB (CK-MB) played a major role for decades in the diagnosis of acute MI (AMI) prior to troponin. CK-MB is not specific for myocardium and is also found in skeletal muscles. Noncardiac conditions can cause elevated levels, commonly seen with trauma, rhabdomyolysis, heavy exertion, and myopathy. It appears 4–6 hours after symptoms onset, peaks at 24 hours, and returns to normal in 48–72 hours. A trend rather than a single measurement is more helpful to aid in detection of MI. A more useful way to help differentiate rise due to myocardial pathology from other causes of increased CK-MB is the relative index; in which the ratio of the CK-MB to total CK is measured, a ratio > 5% is indicative of myocardial injury. CK-MB testing is still ordered in many hospitals and emergency departments; however, many efforts have been made to stop routine use.

MYOGLOBIN

Myoglobin is a heme protein exists in skeletal and cardiac muscles. Due to its sensitivity and early rise, it can be serviceable in early detection of MI. It typically rises 2–4 hours after onset of infarction, peaks at 6–12 hours, and returns to normal within 24–36 hours.

NATRIURETIC PEPTIDE

Natriuretic peptides are secreted by ventricles in response to pressure and stretch. These peptides are considered markers of hemodynamic stress, and are involved in diuresis, natriuresis, vasodilation, inhibition of renin and aldosterone, and in reduction of blood pressure. The half-life of B-type natriuretic peptide (BNP) is (≤20 min), and for N-terminal pro-B-type natriuretic peptide (NT-proBNP) half-life is (60–120 min). BNP levels of >100 pg/mL are diagnostic of heart failure with an accuracy of 85%. According to (PRIDE) study, NT-proBNP >900 pg/mL were highly sensitive and specific for the diagnosis of acute congestive heart failure ($p < 0.001$). An NT-proBNP level <300 pg/mL was optimal for ruling out acute congestive heart failure, with a negative predictive value of 99%. ACEP and AHA recommend both BNP and NT-pro BNP (level 1 class A) in acute setting and hospitalization, for supporting diagnosis of HF and establishing prognosis and disease severity.

OTHER MARKERS

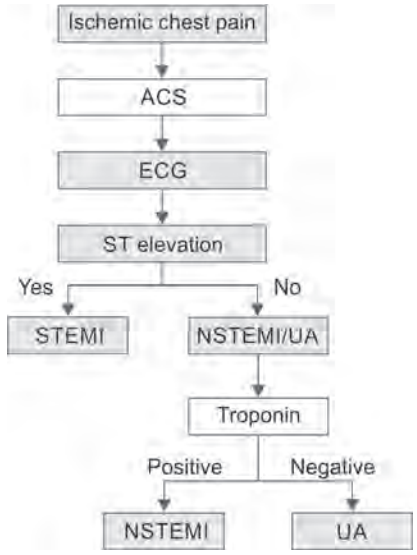
Along with troponin, CK-MB, and myoglobin, there are other molecules that can be classified as myocardial biomarkers. Those promising markers such as ischemia-modified albumin and heart-type fatty acid-binding protein might aid in the diagnosis of ACS but till now their role is limited. It is also important to mention that inflammatory markers play a considerate role in assessing ACS, for their described prognostic value. The famous among which are the high sensitivity CRP and homocysteine, the latter has been linked to direct vascular injury, and both are used in risk assessment. The soluble CD40 ligand (sCD40L) is another marker that is also linked to inflammation and plaque instability in ACS.

MULTIPLE MARKER APPROACH

In the emergency setting, it is often necessary to differentiate diverse clinical conditions, having similar clinical presentation but markedly different treatment and prognosis. There is thus a need to test for the possibility of multiple clinical conditions rapidly and accurately in order to diagnose and institute appropriate therapy at the earliest. It clearly implies that use of biomarkers one by one would be detrimental in this scenario. In view of this need, several biomarkers are used together according to the clinical scenario and several point-of-care kits incorporating these multiple markers have also been made available. For example, in a patient who presents with acute onset dyspnea where it is necessary to differentiate between acute PE and AMI, the use of D-dimer, along with troponin could be useful. Also, multiple biomarkers could be used to provide additional information related to prognosis and timing of the index event. For example, in a patient with ischemic chest duration of very short duration will require the use of troponin along with myoglobin while in a patient with typical electrocardiogram (ECG) changes but a history of ischemic chest discomforts 2–3 weeks before will require the use of troponin and CPK-MB in view of the temporal profile of these markers. The disadvantage of this approach is increased cost and sometimes leading to inappropriate management. Besides, these have not been recommended as a preferred strategy and exercising clinical judgment in choosing the appropriate biomarkers, in a given clinical situation is recommended.

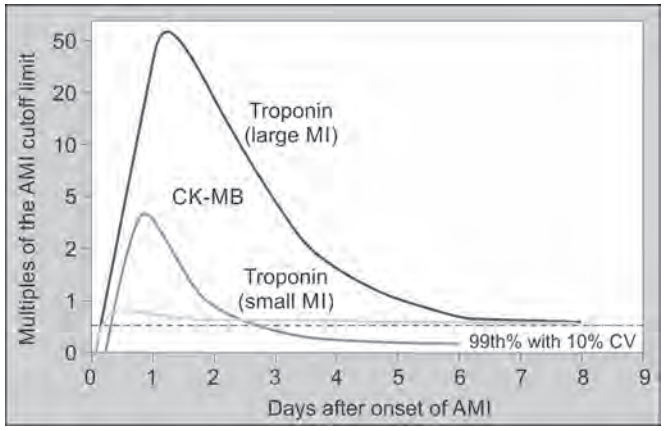
Acute Coronary Syndrome

Acute coronary syndrome is one of the most common cardiac emergencies with devastating consequences. It results from the rupture or erosion of an atherosclerotic plaque leading to formation of coronary thrombus. The working diagnosis of ACS is made based on the presence of typical symptoms, which is further characterized by ECG changes (**Flowchart 1**). The final diagnosis, however, is based on the detection of elevated cardiac specific biomarker (**Fig. 1**) preferably cardiac specific troponin. Based on these findings, ACS is subclassified into one of the three clinical syndromes: (1) ST segment elevation myocardial infarction (STEMI), (2) non-ST segment elevation



(ECG: electrocardiogram; STEMI: ST segment elevation myocardial infarction; NSTEMI: non-STEMI)

FLOWCHART 1: Algorithm for diagnosis of acute coronary syndrome (ACS).



(AMI: acute myocardial infarction; CK-MB: creatinine kinase-MB)

FIG. 1: Cardiac specific biomarkers.

myocardial infarction (NSTEMI), or (3) unstable angina. As clear from the names of these, ECG plays an important role in the working diagnosis of these entities but a key role is played by the cardiac biomarker, now almost exclusively cardiac specific troponin.

Elevated cardiac specific troponin is much more specific for cardiac tissue, is very sensitive for myocardial necrosis, and has a useful temporal profile as compared to other cardiac enzymes used previously (such as CK and CK-MB). It has also been shown to relate directly with infarct size and thus act as a prognostic marker also. It has been shown that the acute or short-term prognosis for patients with troponin-positive, CK-MB negative infarcts is better than that for patients with elevated troponin and CK-MB values.

Therefore, it is the preferred biomarker recommended for use in MI and the new definition of MI is based solely on the level of troponin. It is recommended that any patient coming to the emergency with suspected MI should have troponin

TABLE 1: Cardiac markers trends relative to time.

Cardiac biomarker	*Time to appear*	*Time to peak*	*Time to return normal*
cTn	6–12 h	24 h	Up to 14 days
cTn I/T	3–4 h	24 h	4–10 days
CK-MB	4–6 h	24 h	48–72 h
Myoglobin	2–4 h	6–12 h	24–36 h

done immediately and another value 3–6 hours later (**Table 1**). Rather than only absolute elevated values, temporal rise and fall is very important for diagnosis of MI. Although troponin is quite specific to cardiac injury, it cannot differentiate ischemic injury (in MI) from other types of myocardial injury (such as in sepsis, acidosis, and trauma). As such elevations of troponin can be seen in a variety of clinical conditions and disease states but the clinical scenario and time trend of the values should be carefully looked at in these situations to arrive at a diagnosis of MI. This approach of using troponin only for diagnosis of MI has resulted in diagnosis of more episodes of MIs correctly owing to its sensitivity and specificity, but also has been shown to be more cost effective than doing both, troponin and CK-MB. Myoglobin is also a cardiac biomarker which is detectable quite early in blood following AMI (within 2 h). However, it is not specific for cardiac injury and is also not widely available. However, it can be used sometimes as part of a multimarker strategy for diagnosis of AMI. CM-MB similarly is sometimes utilized since it remains elevated till much later after AMI. Cardiac specific troponins (I or T), however, remain the preferred biomarkers for diagnosis for ACS.

Deep Vein Thrombosis and Pulmonary Embolism

Acute PE is associated with high mortality and morbidity. Besides, there are no specific sign or symptoms of PE. As such, it is also known as the "great mimic." The clinical presentation may resemble AMI, dissection of aorta, acute heart failure, acute asthma, or even syncope. It is very important to diagnose and institute appropriate treatment for PE in the emergency department. Deep vein thrombosis (DVT) is a related entity equally important to diagnose. D-dimer is the only biomarker which is used in the scenario of DVT and PE.

Endogenous fibrinolysis breaks down the fibrin rich clot to D-dimers. The detection of elevated circulating D-dimer by enzyme-linked immunosorbent assay (ELISA) is therefore an indicator of clot formation and endogenous fibrinolysis due to any reason. *It is a sensitive indicator of DVT and PE but is not specific for DVT/PE*. Elevated D-dimer can be seen in any systemic illness such as sepsis, MI, cancer, or even postoperatively up to months. However, it has a great negative predictive value. It is most useful thus in ruling out acute PE/DVT in appropriate clinical setting. For example, in a patient presenting to emergency, suspected of having acute PE, with no other systemic illness, a negative D-dimer virtually rules out DVT/PE and no further testing is required for this purpose. In case of an elevated value in this scenario, further testing in the form of ultrasound of leg veins or computed tomography (CT) angiography of chest is required to diagnose PE. However, it has a limited role in the admitted patient with multiple

comorbidities or in a patient with recent history of trauma, surgery, or any systemic illness, owing to its nonspecificity. D-dimer can also be used as part of multimarker strategy where there is a need to rule out other conditions such as MI or acute heart failure which may have similar presentation (as discussed later). The use of D-dimer is thus very useful in the emergency for triage of patients who require costly and potentially harmful testing (like CT scanning) and potentially life-saving treatment, by optimizing the resource utilization in busy emergency room settings.

Cardiac Biomarkers in Heart Failure

B-type natriuretic peptide and NT-proBNP are polypeptides secreted mainly by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes). They have vasodilator and natriuretic properties and are also released from blood vessels and kidneys. Circulating BNP and NT-proBNP is measured by immunoassay and elevated levels are shown to be indicative of heart failure (left as well as right, acute as well as chronic). Systematic studies have shown that elevated natriuretic peptides, released as a response to myocardial stretch, can be used as indicators of elevated myocardial load. They have been found to be a useful triage tool for diagnosis, prognosis, and monitoring response to treatment in patients with acute decompensated heart failure. In a study, the negative predictive value was 96% for BNP < 50 pg/mL and the positive predictive value was 83% for a cutoff value of 100 pg/mL, relative to clinical assessment by cardiologists. BNP and NT-proBNP have been recommended for use in acute decompensated heart failure scenario by the guidelines from heart failure association of America and from the UK. It has now been shown that BNP and NT-proBNP are elevated in chronic heart failure with preserved ejection fraction (HFpEF). The European Society of Cardiology guidelines of 2016 have incorporated this approach in the diagnosis of HFpEF and cutoffs have been proposed. There is no difference between BNP and NT-proBNP when used as markers of heart failure but different cut-off values are to be used for each of these (>35 pg/mL for BNP; >125 pg/mL for NT-proBNP). Elevated BNP and NT-proBNP are also predictors of prognosis and can be used as markers of response to treatment. As discussed above, they are not specific for heart failure and elevated values can be found in diverse situations such as pulmonary hypertension, AMI, severe sepsis, renal disease, etc.

FUTURE PERSPECTIVE

Cardiac biomarkers are an indispensable tool for diagnosis, prognosis, and risk stratification in the emergency department. The use of biomarkers results in optimizing scarce resources in busy emergency departments. Judicious use of biomarkers results in rapid triage, institution of appropriate therapy in a timely manner and is also very useful in preventing mishaps on account of missing out on critical diagnosis. Some of the cardiac biomarkers such as troponin and natriuretic peptides also contribute to prediction of future risk and thus, in devising of aggressive approach for sicker patients. A multimarker approach is sometimes used as a point-of-care device but it requires more experience and refinement before it can be widely recommended. There are several biomarkers being studied for their higher sensitivity, specificity, and prognostic value in different clinical conditions. A very sensitive troponin assay is being developed for early detection and risk stratification in MI. Similarly, markers of inflammation [high-sensitivity C-reactive protein (hsCRP)] are being evaluated for defining their role in the scenario in acute coronary syndrome. Numerous other biomarkers (metalloproteinases) are being evaluated for different stages of atherosclerosis and we are likely to see greater use of low cost, easy to use biomarkers with superior diagnostic and prognostic accuracy in the emergency room.

SUMMARY

Biomarkers part is integral in defining and managing CVD. Cardiac troponin and natriuretic peptides are superior to others due to their higher sensitivity and specificity; these two are highly recommended in dealing with ACS and heart failure, respectively. When ordered correctly and judiciously biomarkers can markedly improve healthcare delivery and limit unnecessary utilization of resources.

MULTIPLE CHOICE QUESTIONS

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Echocardiography in Emergency Department

63 CHAPTER

Manish Bansal

INTRODUCTION

Prompt diagnosis and rapid institution of appropriate therapeutic measures are the most important goals in the management of patients presenting to the emergency room (ER). Given the time-sensitive and critical nature of the illnesses leading to ER presentation, the diagnosis must be established quickly, which limits the scope of the investigative work-up available for the initial evaluation of these patients. Therefore, in most patients, a focused clinical assessment combined with bedside diagnostic tools such as X-ray, electrocardiogram (ECG), and laboratory investigations need to form the basis for initial triaging. However, since a cardiac etiology may underlie almost every clinical presentation resulting in ER admission, some form of cardiac evaluation is invariably required in many of these patients. Echocardiography has emerged as a highly useful diagnostic modality for this purpose. Its portability, safety, easy availability, and ability to provide comprehensive information about cardiac structure and function within a short period of time make it ideally suited for use in the ER setting. Because of these attributes, echocardiography has now become almost an extension of clinical examination. Previous studies have shown that addition of a screening echocardiogram significantly improves the diagnostic accuracy of physical examination and reduces unwarranted downstream diagnostic and therapeutic referrals. In this chapter, we discuss the role of echocardiography in the initial evaluation and management of patients presenting to ER with various clinical presentations.

ECHO IN ASSESSMENT OF ACUTE CHEST PAIN

Chest pain is one of the most common reasons for ER visits. A number of cardiac and noncardiac conditions can cause chest pain such as acute coronary syndrome (ACS), aortic dissection, pulmonary embolism, acute pericarditis, lower respiratory tract infection, acute cholecystitis, acute pancreatitis, and costochondritis. Echocardiography plays an important role as a first-line diagnostic modality in the differential diagnosis of these conditions and plays a pivotal role in the overall management of patients presenting with ACS.

Acute Coronary Syndrome

The term ACS encompasses a wide spectrum of clinical presentations ranging from unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation MI (STEMI) to even sudden cardiac death. The diagnosis of ACS is traditionally based on clinical presentation, ECG changes, and the abnormalities in the cardiac biomarkers. However, many patients with ACS present with nondiagnostic ECGs and cardiac biomarkers typically take 6–8 hours to become abnormal. Given these constraints, echocardiography can be a useful tool for establishing the diagnosis of ACS and has a class I indication for this purpose.

In the ischemic cascade, abnormalities of left ventricular (LV) systolic and diastolic function develop very early, much before the appearance of ECG changes. Accordingly, the presence of new regional wall motion abnormalities (RWMA) on echocardiography will strongly support a diagnosis of ACS in a patient with typical chest pain but nondiagnostic baseline ECG. However, echocardiography may not be much helpful for diagnosing ACS in a patient with known coronary artery disease (CAD) when the extent of preexisting RWMA is not known.

For the purpose of initial diagnosis of ACS, a positive echocardiogram should meet one of the following criteria:

- Abnormal wall motion of two or more contiguous segments visible in two different views, or
- Global LV hypokinesia with an ejection fraction (EF) of <40%.

In patients who do not have any evidence of LV systolic dysfunction and also have normal cardiac biomarkers, stress echocardiography (either dobutamine or exercise) can be performed to rule out significant CAD prior to discharge from the ER. Such approach has ≥90% sensitivity and specificity for identifying subjects at risk for having cardiac events. Abnormalities of LV diastolic function appear even before the development of RWMA and therefore have even greater sensitivity for detection of myocardial ischemia. However, these abnormalities are too nonspecific to be used routinely for this purpose. Their utility currently lies mainly in the assessment of intracardiac hemodynamics and guiding management, rather

than in the initial diagnosis of ACS. However, the diastolic phase abnormalities may have diagnostic value on strain imaging as discussed below. Apart from establishing the diagnosis of ACS, echocardiography also permits recognition of the underlying culprit vessel, assessment of the extent of myocardial damage, and its hemodynamic consequences, and helps in detection of mechanical complications of MI, if any.

In CAD, LV-RWMA usually follows the distribution of coronary vascular territory. Therefore, the pattern of regional myocardial involvement during ACS helps in identification of the underlying culprit artery (**Fig. 1**). This information not only has diagnostic utility, but also helps in determining the choice of treatment modality and the urgency with which such treatment needs to be instituted.

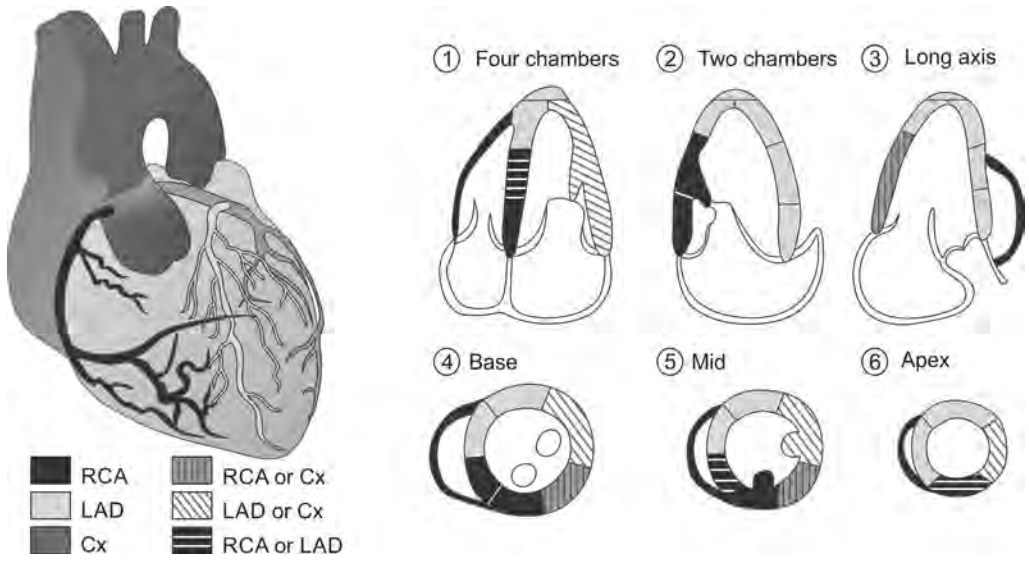
The extent of myocardial damage can be determined by estimating either *wall motion score index* (WMSI) or, more commonly, LVEF. For estimation of WMSI, segmental wall motion of each LV myocardial segment is scored as (1) normal, (2) hypokinetic, (3) akinetic, and (4) dyskinetic or aneurysmal, in a 16-segment model. The score for each segment is then added and the total score is divided by the number of segments analyzed to obtain WMSI. *WMSI provides a semiquantitative estimate of overall LV systolic function* with higher WMSI signifying greater amount of myocardial damage and thus, worse LV systolic function. In clinical practice, however, LVEF is the most commonly used measure of LV systolic function. In patients with ACS, LVEF has immense diagnostic, prognostic, and therapeutic value and is central to almost every therapeutic decision-making, not just during the acute stage, but during the entire course of illness.

Estimation of LVEF by echocardiography is simple and easy to perform. Modified biplane Simpson's technique is the recommended method for this purpose. This method requires tracing of endocardial border of the LV in apical four-chamber and two-chamber views in both end-diastolic and end-systolic frames. The automated software in the echocardiography machine performs the calculations required to estimate LV volumes and EF. Alternately, LVEF can also be estimated visually by eyeballing, which, in fact, is the most common method used in real-life clinical practice. With experienced echocardiographers, LEVF estimation by eyeballing has been shown to have high degree of accuracy. More recently, three-dimensional echocardiography has also become available and has been shown to be more accurate than two-dimensional (2D) echocardiography for estimation of LV volumes and EF.

Role of Adjunctive Techniques

As discussed above, the diagnostic evaluation of CAD by echocardiography traditionally relies on segmental wall motion analysis, either at rest or during stress. While this approach has been extensively validated over the years, it has certain limitations. Most important of these are inability to defect subtle changes in myocardial contractile function and the lack of information about myocardial perfusion. Strain imaging and myocardial contrast echocardiography (MCE) overcome these limitations and their incorporation during conventional echocardiography has been shown to have incremental value in the evaluation of chest pain patients in the ER.

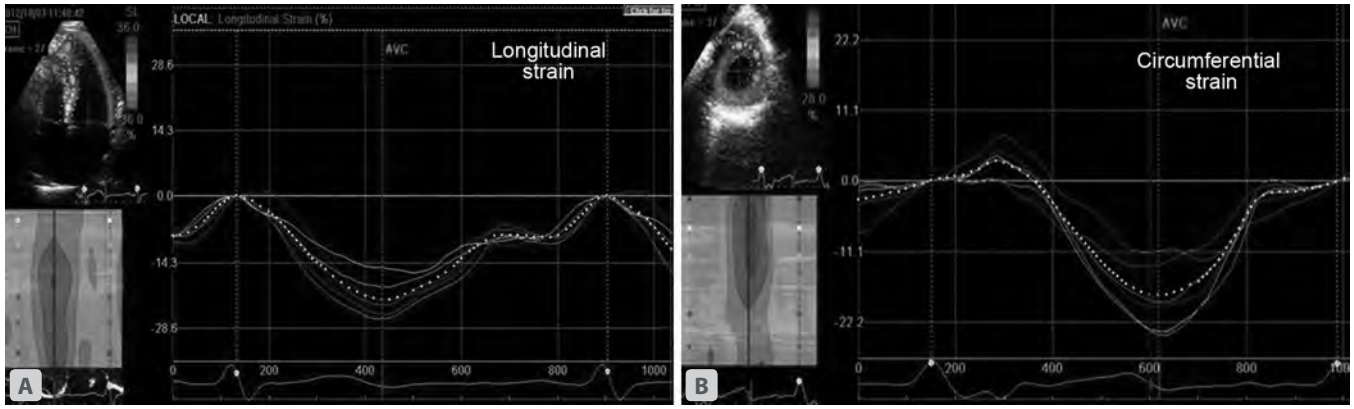
Strain imaging is a sensitive modality for detection of myocardial contractile dysfunction. The currently used speckle tracking echocardiography (STE) permits comprehensive assessment of myocardial deformation in different directions, which has important diagnostic implications in the evaluation of CAD (**Figs. 2A** and **B**). As longitudinal deformation of LV is determined predominantly by subendocardial myocardial fibers, longitudinal strain (LS) is the first one to get affected with the onset of myocardial ischemia (**Fig. 3**). In contrast, circumferential deformation which is determined primarily by the subepicardial fibers gets involved much later when the myocardial injury has become transmural. This unique



(LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery)

FIG. 1: The typical distribution of coronary vascular supply.

Source: Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-63.



FIGS. 2A AND B: Speckle tracking echocardiography-based measurement of left ventricular longitudinal and circumferential strain. ***(For color version, see plate 5)***

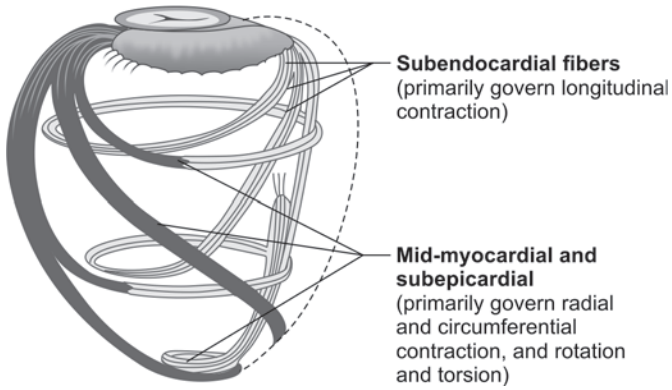

Subendocardial fibers
(primarily govern longitudinal contraction)
Mid-myocardial and subepicardial
(primarily govern radial and circumferential contraction, and rotation and torsion)

FIG. 3: Arrangement of muscle fibers in the left ventricular myocardium and their contributions in causing myocardial deformation.

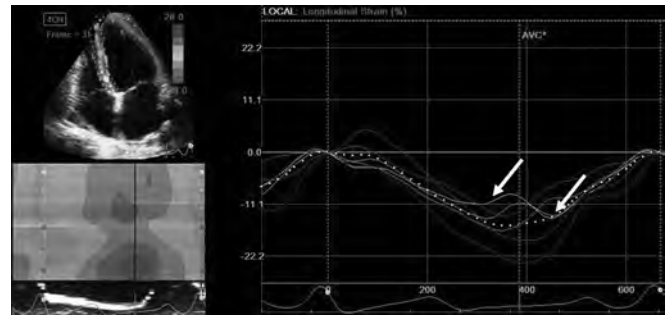


FIG. 4: Reduced systolic longitudinal strain with post-systolic shortening (arrows) in basal septum (yellow trace). ***(For color version, see plate 5)***

structural-functional relationship of LV myocardial contractile apparatus can be exploited for the purpose of early detection of myocardial ischemia, for differentiating subendocardial injury from transmural injury, and for predicting myocardial viability.

Subendocardial myocardial fiber dysfunction can be detected by strain imaging either as reduced systolic LS, increased postsystolic strain (PSS), and/or as delayed decay of peak LS during diastole (**Fig. 4**). These strain abnormalities can be used for diagnosing CAD and may have incremental value over wall motion analysis. Furthermore, increased PSS and impaired diastolic decay of strain may persist for a reasonable period of time after acute myocardial ischemia and can serve as ischemic myocardial memory.

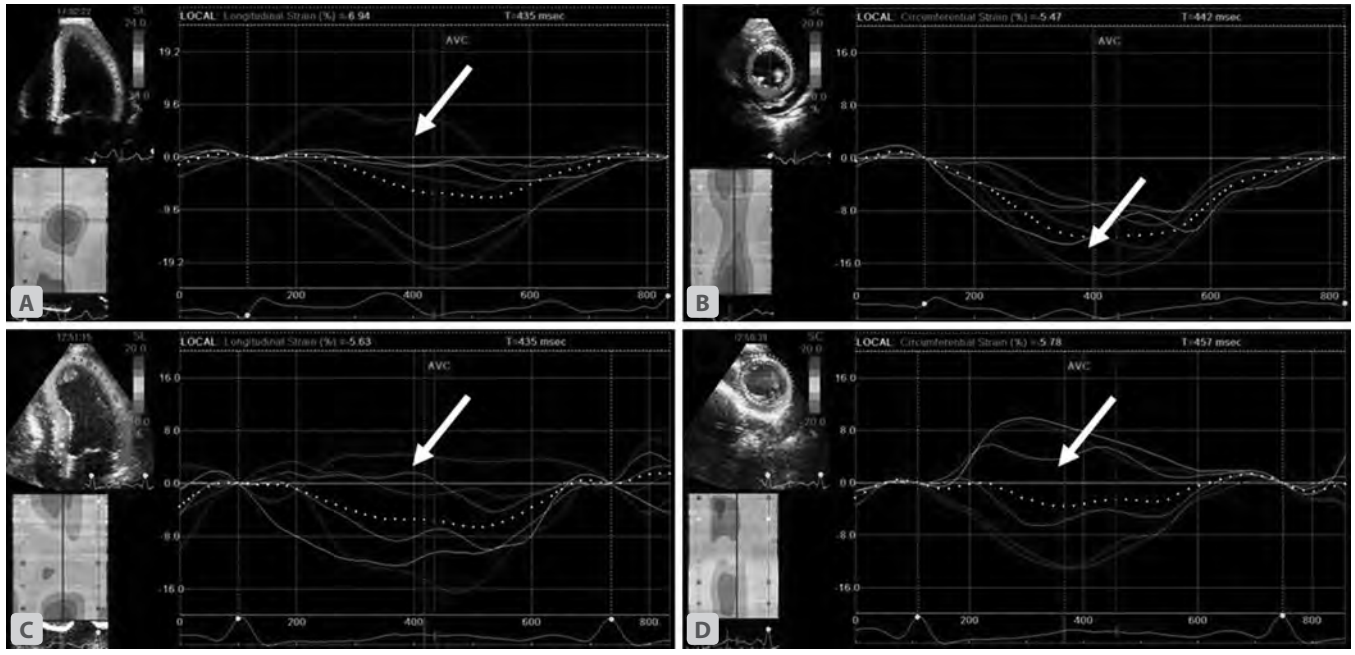
When impairment of LS is not accompanied by concomitant reduction in circumferential strain (CS), it usually indicates nontransmural injury whereas concomitant reduction of both LS and CS indicates transmural infarct. Thus, assessment of CS can be helpful not only in diagnosing ACS, but more importantly, in identifying total coronary occlusions and in predicting late LV remodeling and overall clinical outcomes (Figs. 5A to D). Furthermore, CS can also help in differentiating STEMI from acute myocarditis which may have similar clinical presentations. As myocarditis preferentially affects epicardial myocardial layers, it causes more marked impairment of CS, unlike ischemia which generally results in greater impairment of LS. Accordingly, in patients with preserved LVEF, impaired global CS (less negative than -19.3%) has been shown to differentiate acute myocarditis from STEMI with sensitivity 72% and specificity 74%.

Unlike strain imaging, MCE provides information about myocardial perfusion and thus bridges the gap between echocardiography and nuclear imaging. Because of its ability to assess myocardial perfusion, MCE has been shown to have high sensitivity for detection of subendocardial ischemia and can be useful in triaging the patients presenting with suspected ACS. In a study involving 400 patients presenting to ER with chest pain but normal ECG and biomarkers, dipyridamole-atropine stress echocardiography with MCE had significantly higher accuracy (sensitivity and specificity 97% and 74%, respectively) for diagnosing as compared to wall motion analysis alone (sensitivity and specificity 63% and 91%, respectively).

Aortic Dissection

Acute aortic dissection is a potentially fatal disease which presents as acute severe chest pain often radiating to interscapular region. Although chest pain in aortic dissection generally has typical character, it has often been misdiagnosed as ACS because of low index of suspicion and also because of occurrence of nonspecific ECG changes in aortic dissection. Sometimes, aortic dissection may result in a true STEMI also, due to occlusion of a coronary artery ostium by the dissection flap. Since the management of ACS is completely opposite of that of acute aortic dissection, accurate distinction between the two conditions is of paramount importance.

The patient profile, pattern of chest pain, and the presence unequal peripheral pulses provide important clues to the underlying diagnosis of aortic dissection, which can then



FIGS. 5A TO D: Differential involvement of left ventricular longitudinal and circumferential strain in patients with subendocardial and transmural infarcts. (A and B) Longitudinal strain is impaired (A) but circumferential strain is preserved (B) in basal segments in a patient with subendocardial infarct; (C and D) Both longitudinal and circumferential strains are impaired in apical segments in a patient with transmural infarct. ***(For color version, see plate 6)***

be confirmed with the help of imaging. Echocardiography is an excellent modality for initial evaluation of patients with aortic dissection, particularly those with proximal aortic dissection (**Figs. 6A** to **D**). Transthoracic echocardiography (TTE) has 77–80% sensitivity and 93–96% specificity for diagnosing proximal aortic dissection, whereas the same for transesophageal echocardiography (TEE) are 98% and 95% respectively. The sensitivity of TTE for detecting distal aortic dissection is much lower, but TEE can generally diagnose most of the dissections involving descending thoracic aorta. *The diagnosis of aortic dissection on echocardiography is based on detection of an undulating intimal flap within the aortic lumen that separates the true and false channels and has motion independent of that of the aortic wall. The flap should be identified in more than one view.* TEE can demonstrate intimal tear in the vast majority of cases and also permits recognition of true and false lumina. The false lumen is often larger and has less blood flow than the true lumen. Partial thrombosis of the false lumen is seen frequently and total thrombosis is an occasional finding. Doppler study can also be used for differentiating true lumen from the false lumen. Apart from diagnosing aortic dissection, echocardiography is also helpful in detecting its potential complications such as hemopericardium, coronary involvement, and aortic insufficiency.

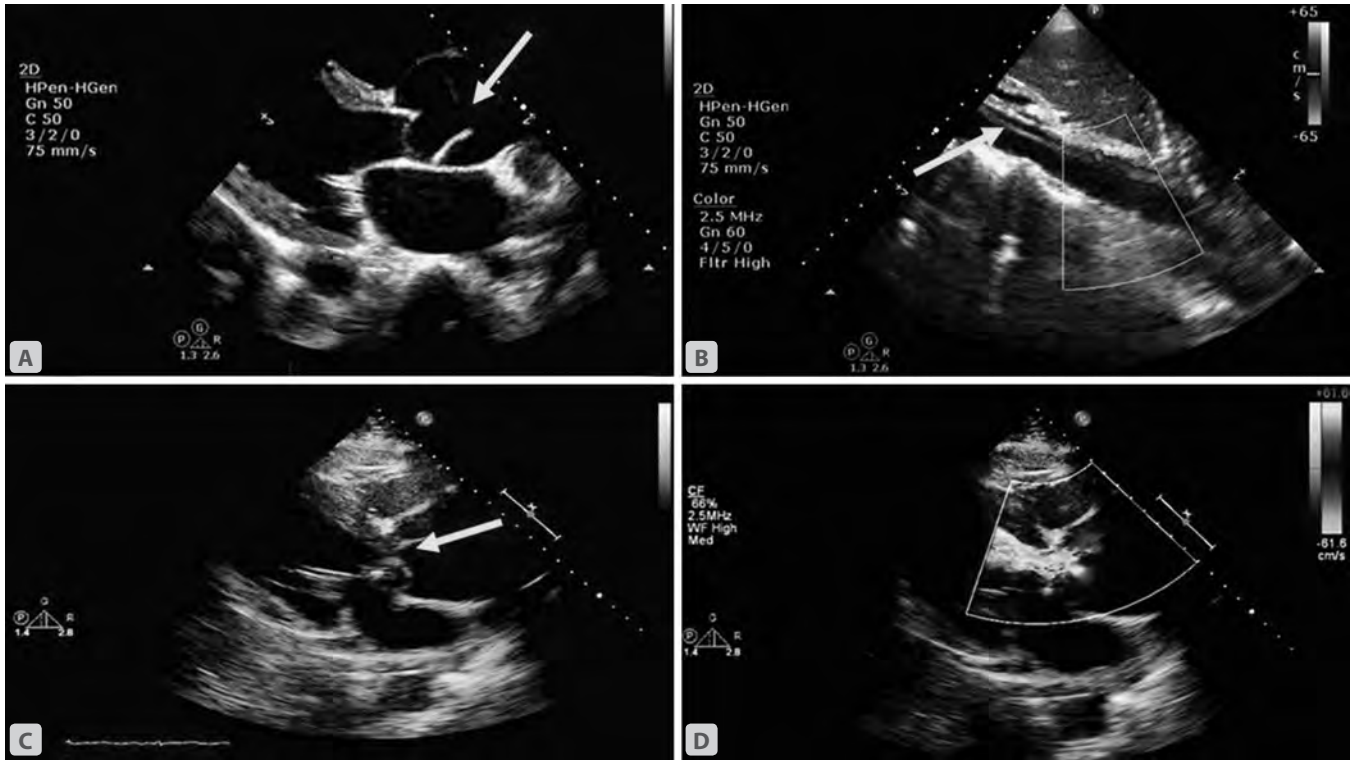
Pulmonary Embolism

Pulmonary embolism is a less common but potentially lethal cause of chest pain. It more often presents as shortness of breath or as hemodynamic collapse. Chest pain usually occurs when emboli are relatively small resulting in peripheral pulmonary infarction. *The imaging modality of choice for diagnosing acute pulmonary embolism is computed tomographic pulmonary angiography (CTPA)*. However, echocardiography provides useful initial clues toward the possibility of underlying pulmonary embolism, permits assessment of the hemodynamic significance of the embolism—an important determinant of the treatment strategy and in some cases may also reveal thrombi in main pulmonary artery and its branches, right atrium (RA), and/or right ventricle (RV) (**Figs. 7A** and **B**).

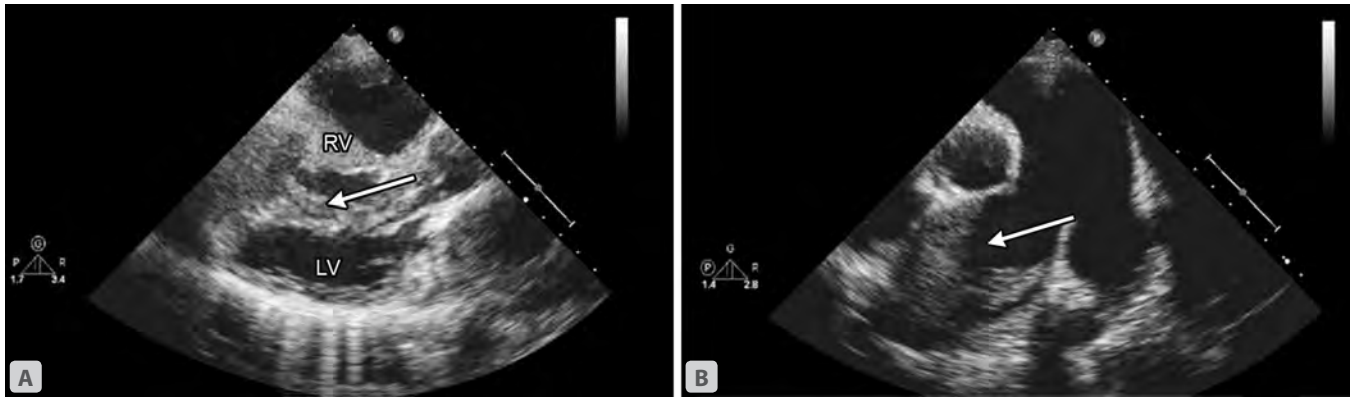
Echocardiographic features corroborative of pulmonary embolism include dilatation of pulmonary artery with evidence of increased RV afterload in the form of RV dilatation/dysfunction, D-shaped LV cavity caused by leftward shift of the interventricular septum and Doppler evidence of pulmonary hypertension with or without evidence of increased RA pressure. RV systolic dysfunction in pulmonary embolism often has a typical regional pattern, affecting mainly the free wall with sparing of RV apex. This is known as *McConnell's sign* and is highly specific for pulmonary embolism but has low sensitivity. As such, echocardiography itself has low sensitivity to rule out pulmonary embolism. Therefore, while an abnormal echocardiogram can help to confirm the diagnosis of pulmonary embolism, particularly in a hemodynamically compromised patient in whom CTPA may not be feasible, it should not be the only modality to rule out the diagnosis or for risk stratification in patient with stable hemodynamics. Additionally, emergency physicians should also be vigilant about other causes of RV pressure/volume overload such as obstructive airway disease, idiopathic pulmonary hypertension, right ventricular myocardial infarction (RVMI), and primary tricuspid regurgitation (TR), when diagnosing pulmonary embolism based on echocardiography alone.

ECHO IN ASSESSMENT OF DYSPNEA/ SHORTNESS OF BREATH

Acute onset dyspnea can be due to cardiac or noncardiac conditions. Echocardiography is very helpful in distinguishing



FIGS. 6A TO D: Two examples of acute aortic dissection. (A) Intimal flap (arrow) is seen in the aortic root; (B) In the same patient, the dissection flap (arrow) is seen extending into the abdominal aorta also; (C and D) Intimal flap (C, arrow) in another patient is prolapsing through the aortic valve causing severe aortic regurgitation. ***(For color version, see plate 6)***



(LV: left ventricle; RV: right ventricle)

FIGS. 7A AND B: A patient with massive pulmonary embolism. (A) Right ventricle is grossly dilated and the interventricular septum (arrow) is deviated towards the left ventricle; (B) Markedly dilated main pulmonary artery with complete occlusion of right pulmonary artery with thrombus (arrow).

between the two and in providing detailed description of the underlying cardiac pathology when such a condition is found. Dyspnea is therefore a class I indication for performing echocardiography. There are a number of cardiac conditions that can result in acute dyspnea. The common ones include:

- Predominant LV systolic dysfunction—due to MI, dilated cardiomyopathy, stress cardiomyopathy, etc.
- Predominant LV diastolic dysfunction—due to long-standing hypertension, hypertrophic cardiomyopathy, restrictive cardiomyopathy, aortic stenosis, etc.
- Valvular heart diseases—mitral stenosis, mitral regurgitation (MR), aortic stenosis, aortic regurgitation, prosthetic heart valve (PHV) malfunction, etc.
- Pericardial diseases such as cardiac tamponade and constrictive pericarditis
- Cardiac tumors such as LA myxoma.
- Pulmonary embolism, idiopathic pulmonary hypertension, etc.

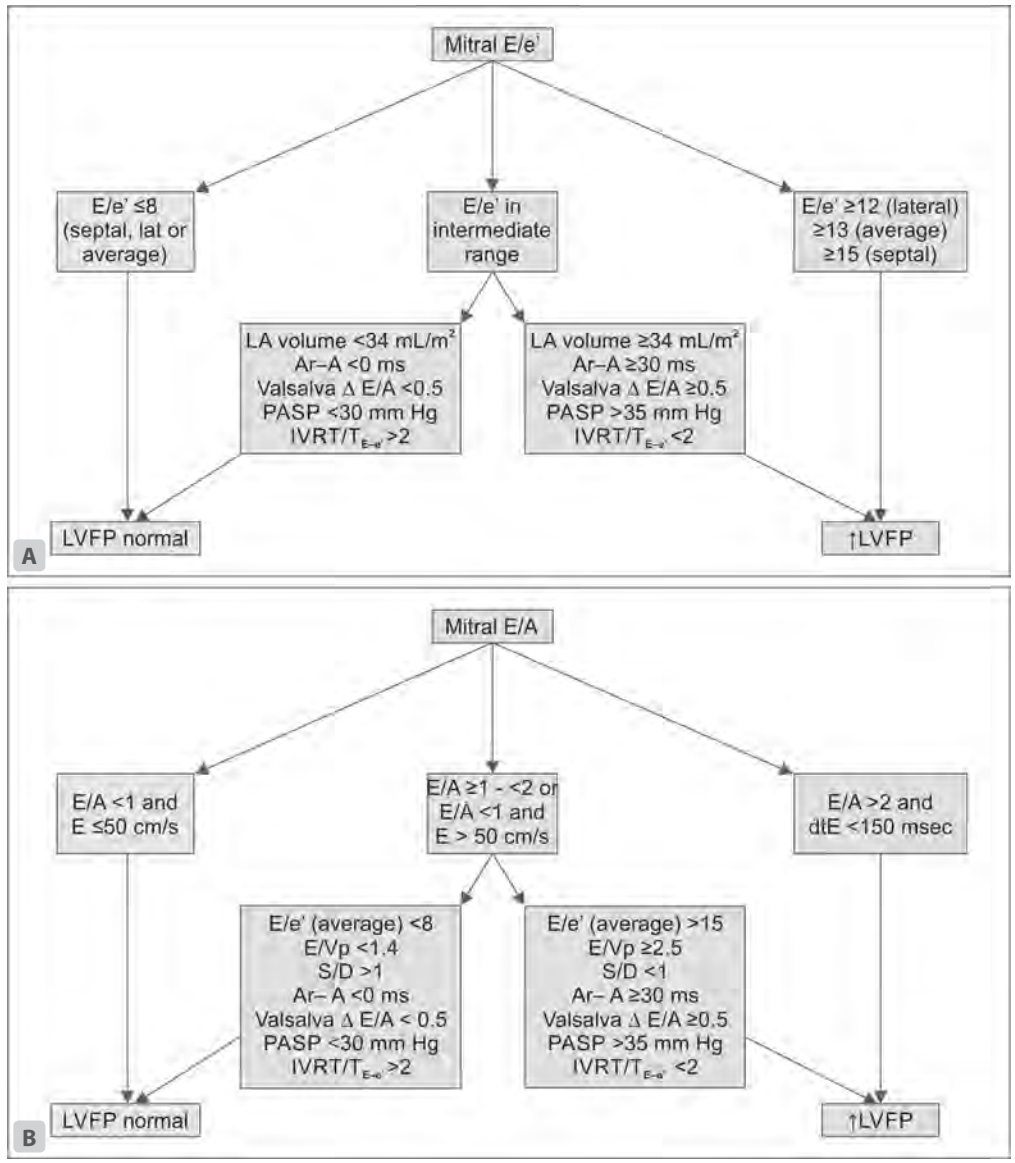
In all the above conditions, echocardiography is able to demonstrate the underlying structural abnormality in detail. In addition, it also permits comprehensive assessment of intracardiac hemodynamics which helps in determining the role of these abnormalities in causation of dyspnea and in planning appropriate treatment strategy.

Predominant LV diastolic dysfunction has recently emerged as an important cause of dyspnea. It is estimated that

almost half of all patients presenting with heart failure have normal or near-normal LVEF with LV diastolic dysfunction being the dominant abnormality. *This entity is termed as "heart failure with preserved EF" or HFpEF.* Assessment of LV diastolic function is central to the recognition of this entity and echocardiography is the most commonly utilized modality for this purpose. Using echocardiography, LV diastolic function is assessed by integrating information derived from interrogation of mitral inflow pattern, mitral annular motion, pulmonary vein flow pattern, etc. The American Society of Echocardiography has recommended algorithms for step-wise assessment of LV diastolic function and LV filling pressure in different patient populations (**Figs. 8A** and **B**).

Estimation of LV filling pressure is of paramount importance even in patients with frank LV systolic dysfunction. In these patients, elevated LV filling pressure is not only an adverse prognostic marker, it has major therapeutic implications as well. The need for diuretics, intravenous fluids, inotropes, vasodilators, etc.; timing of introduction of beta-blockers; timing of coronary intervention; ambulation and mobilization of patients after acute MI; etc. are all influenced by the status of LV filling pressure.

Among valvular lesions, mitral stenosis is the most common condition that presents with acute shortness of breath. Development of atrial fibrillation is the usual culprit in these patients. In contrast, acute shortness of breath in other



(A: mitral inflow late diastolic velocity; Ar: atrial reversal wave in pulmonary vein flow; D: pulmonary vein flow diastolic velocity; dtE: deceleration time of mitral inflow early diastolic velocity; E: mitral inflow early diastolic velocity; e': mitral annular early diastolic velocity; IVRT: isovolumic relaxation time; LA: left atrium; LVFP: left ventricular filling pressure; PASP: pulmonary artery systolic pressure; S: pulmonary vein flow systolic velocity; $T_{E-e'}$: time interval between the onset of mitral E and e' velocities, measured from the onset of QRS complex on ECG; Vp: mitral inflow propagation velocity)

FIGS. 8A AND B: Algorithm for echocardiographic assessment of left ventricular diastolic function and estimation of left ventricular filling pressure in presence of normal (A) or reduced (B) left ventricular systolic function.

Source: Nagueh SF, Appleton CP, Gillebert TC, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009;22:107-33.

valvular heart diseases generally occurs due to worsening LV systolic dysfunction, development of infective endocarditis (IE) or traumatic disruption of valvular apparatus. Aortic stenosis may result in acute dyspnea even in absence of LV systolic dysfunction because of LV hypertrophy with consequent LV diastolic dysfunction. PHV malfunction can occur because of valve thrombosis, structural degeneration, and progressively worsening pannus formation or IE.

ECHO IN ASSESSMENT OF HYPOTENSION AND HEMODYNAMIC INSTABILITY

Hypotension and shock are commonly encountered in the ER. They can be cardiogenic in origin or may result from noncardiac causes such as hemorrhage, hypovolemia, or sepsis. As shock requires aggressive early intervention in order to prevent end-organ damage due to inadequate tissue perfusion, distinguishing cardiogenic shock from shock of other etiologies is extremely important. *The major advantage of echocardiography is that it can quickly determine whether the shock is cardiogenic or noncardiogenic*, apart from also providing plenty of hemodynamic information that is useful irrespective of the type of shock. *A brief 2D echocardiographic examination itself can help in excluding common cardiac causes of hypotension such as*:

- Extensive MI with severe LV systolic dysfunction
- Right ventricular infarction
- Mechanical complication of MI
- Nonischemic severe LV systolic dysfunction
- Pericardial effusion with tamponade
- Massive pulmonary embolism, etc.

Even in patients with noncardiogenic shock, echocardiography often provides useful clues to the underlying etiology. For example, in patients with hypovolemic shock, echocardiography often reveals a small under-filled and hyperdynamic LV, which is a reliable indicator of intravascular volume depletion. Similarly, a collapsed IVC in a patient with unexplained shock indicates an urgent ultrasound evaluation of the peritoneal cavity to look for abdominal hemorrhage.

A more formal assessment of hemodynamics can also be performed by echocardiography, which helps in characterization of the type of shock. LV filling pressure can be estimated as described above, whereas RV filling pressure (same as mean RA pressure or central venous pressure) is derived from IVC size and collapsibility (**Table 1**). Mean and systolic pulmonary pressures can be estimated from pulmonary regurgitation and TR jets. For systemic cardiac output, LV stroke volume is calculated first which is then multiplied with heart rate. LV stroke volume is usually calculated by multiplying 2D-derived LV outflow tract (LVOT) area with Doppler-derived LVOT velocity time integral. Alternately, it can also be calculated by subtracting LV end-systolic volume from LV end-diastolic volume derived using the modified Simpson's method.

By combining all this data, systemic vascular resistance (SVR) can be calculated as:

SVR (Wood units) = [Mean aortic pressure (mm Hg) – mean RA pressure (mm Hg)]/systemic cardiac output (liter/min)

In the above equation, mean systemic blood pressure is used as a surrogate for mean aortic pressure whereas the other two values are obtained from echocardiography. Once systemic cardiac output, LV filling pressure, pulmonary pressures, and central venous pressure are available, it is quite easy to determine the underlying mechanism of shock, i.e., hypovolemic, cardiogenic, septic, or a combination of these.

TABLE 1: Estimating mean right atrial pressure from inferior vena cava size and collapsibility.

Inferior vena cava diameter	*Collapse on sniff*	*Mean right atrial pressure (mm Hg)*
<2.1 cm	>50%	3 (range 0–5)
>2.1 cm	<50%	15 (range 10–20)
Indeterminate cases		8 (range 5–10)

Right Ventricular Myocardial Infarction

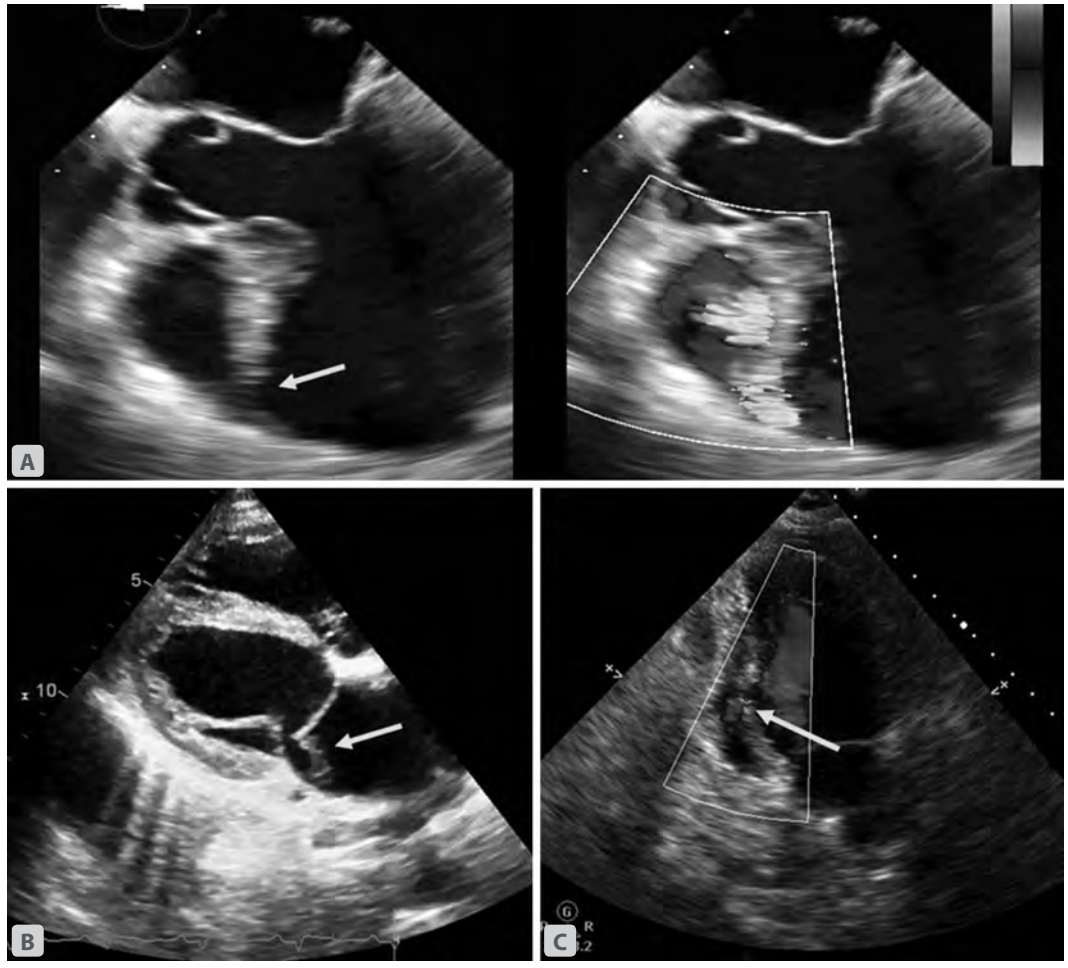
Right ventricular myocardial infarction occurs in almost 50% of all cases of inferior wall MI, but hemodynamically significant RVMI is less common. Recognition of RVMI in patients with inferior wall MI is important because not only RVMI is associated with worse prognosis, the management of the two conditions is also vastly different. *Echocardiography plays a vital role in the diagnosis of RVMI. In these patients, it usually reveals a dilated RV with regional RV hypokinesia/akinesia. TR is common due to dilatation of the tricuspid annulus.* Tissue Doppler imaging may provide additional information. A study revealed that a tricuspid annular peak systolic velocity < 12 cm/s had a sensitivity of 81%, specificity of 82%, and negative predictive value of 92% for diagnosing RVMI in patients presenting with acute inferior wall MI.

Mechanical Complications of Myocardial Infarction

Acute MI can result in several mechanical complications that are among the few most catastrophic cardiac conditions and are associated with very high mortality rates despite best treatment. Early recognition is extremely crucial for improving outcome of these conditions and echocardiography is the most useful modality for this purpose. Common mechanical complications of MI include ventricular septal rupture (VSR), chordal or papillary muscle rupture leading to acute MR, contained free wall rupture with pseudoaneurysm formation, and complete free wall rupture (**Figs. 9A** to **C**).

Post-MI VSR occurs in roughly 1–3% of all STEMI, mainly during the early phase of acute infarction. In case of anterior wall MI, the defect is usually located in the distal part of the septum whereas inferior wall MI results in basal septal rupture. 2D echocardiography may reveal a discrete defect, or there may be multiple channels traversing though the necrotic myocardium. The diagnosis of large discrete defect can be easily made by TTE but small defects may not be visible. TEE is required when TTE is suboptimal and there is high clinical suspicion.

Papillary muscle necrosis and rupture occurs in roughly 1% of all cases of STEMI. It is more common after inferior wall MI and can result from even a modest size infarct. Rupture usually involves the posteromedial papillary muscle as it has single blood supply. Echocardiography is useful in delineating the exact anatomic defect and in assessment of MR severity. However, conventional parameters of MR severity may not



FIGS. 9A TO C: *Examples of mechanical complications of myocardial infarction*. (A) There is apical ventricular septal rupture (arrow) with left to right shunt through the defect; (B) One of the *papillary muscles has got ruptured* and is seen attached to the anterior mitral leaflet and prolapsing into the left atrium. The anterior mitral leaflet itself is flail; (C) Contained *rupture of the inferior wall*. Blood flows through the defect (arrow) into a small pseudoaneurysm. ***(For color version, see plate 7)***

be applicable in this setting due to small regurgitant volume with nondilated LA and LV. Accordingly, a chordal or papillary muscle rupture should always be suspected when there is an eccentric jet of MR with a relatively normal-sized LA in a patient of acute MI.

Rupture of the free wall of the LV occurs in about 1% of the patients with MI. It mainly occurs in patients with a transmural MI involving the inferolateral wall. When there is complete free wall rupture, it usually results in immediate cardiac tamponade and sudden death. However, when the defect is small, the patients may sometimes escape immediate death. In such cases, echocardiography will reveal pericardial collection of variable magnitude with features of cardiac tamponade. However, it is often difficult to visualize the actual defect as the defect may appear just like a "slit" in the myocardium and the location of the pericardial collection also does not always correlate with the site of rupture.

A pseudoaneurysm is the contained rupture of LV free wall, but rarely it may also form as a result of VSR. Majority of pseudoaneurysms are seen in inferoposterior or inferolateral regions. It is important to distinguish a pseudoaneurysm from a true aneurysm as the former has high risk of spontaneous rupture whereas a true aneurysm seldom ruptures spontaneously. In a true aneurysm, there is continuity of the endocardium in the area of dilatation and the wall of the aneurysm is formed by the stretched but intact LV myocardium. In contrast, in a pseudoaneurysm there is breach of endocardial continuity and the wall of the sac is composed of pericardium with little or no myocardial tissue. In addition, the size of communication relative to the size of the aneurysm may also help in making this distinction. The ratio of the diameter of entry to the maximum diameter of the pseudoaneurysm is usually <0.5, whereas it is much larger in a true aneurysm. However, this feature has only 60% sensitivity.

Cardiac Tamponade

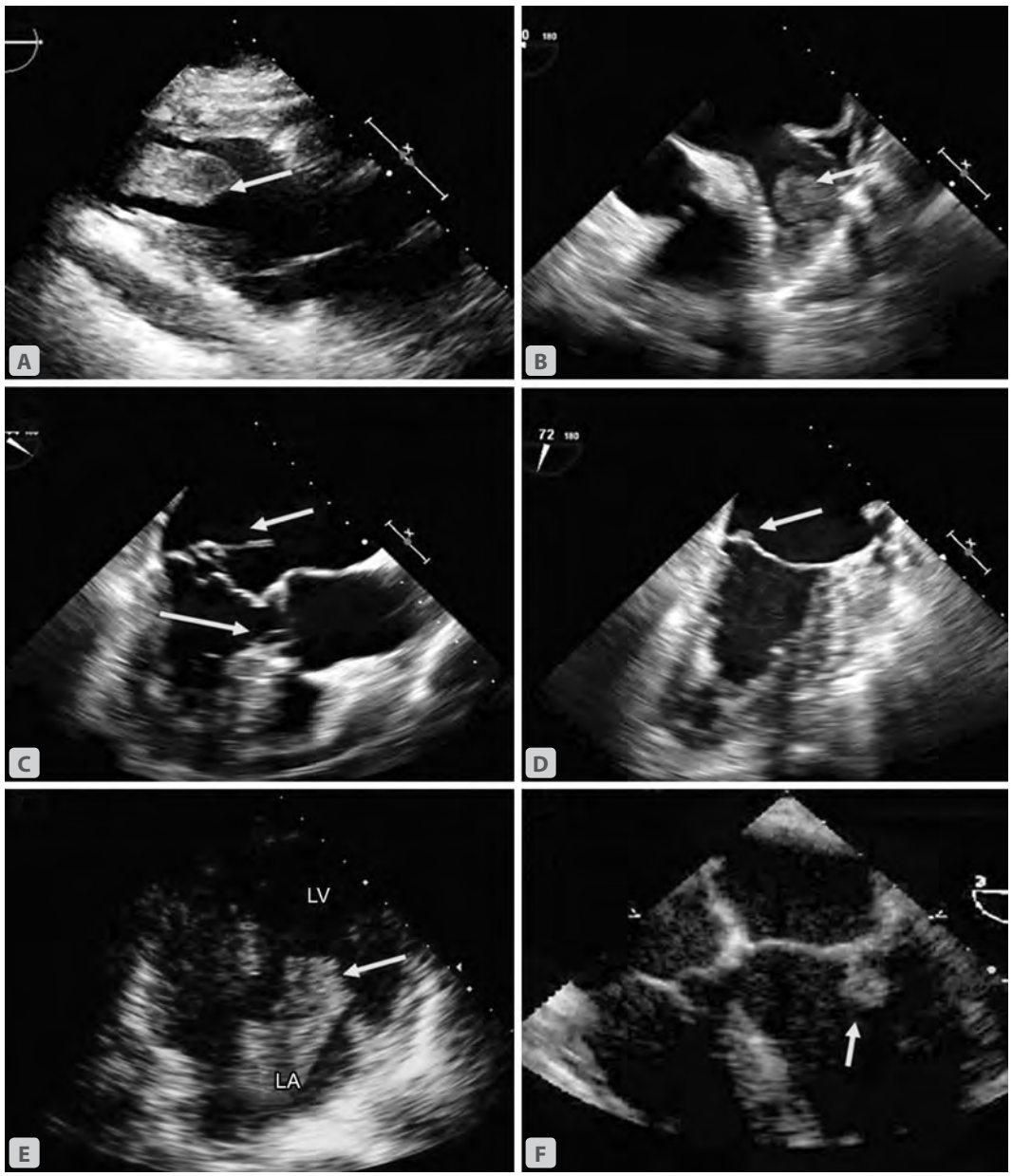
Cardiac tamponade should be suspected in every patient presenting with acute breathlessness with hypotension. Immediate pericardiocentesis is life-saving in such patients and an echocardiogram is very helpful in making the diagnosis. On echocardiography, pericardial effusion is seen as an echo-free space between pericardium and the heart. *The characteristic finding in cardiac tamponade with large effusion is a "swinging heart" appearance*. The 2D echocardiographic and Doppler signs that indicate increased intrapericardial pressure and presence of tamponade in patients with large pericardial effusion include early diastolic RV collapse, late diastolic RA

inversion, abnormal ventricular septal motion, characteristic respiratory variation in mitral and tricuspid inflow velocities, and dilated and noncollapsing IVC. Apart from establishing the diagnosis, echocardiography is also helpful in guiding pericardiocentesis by demonstrating the maximum site of fluid accumulation, suggesting the best trajectory for needle insertion, helping confirm the intrapericardial position of the needle tip, and finally by assessing the immediate postprocedure outcome.

ECHO IN ASSESSMENT OF STROKE PATIENTS

Cardiogenic embolus is an important cause of stroke, accounting for approximately 20% of all ischemic strokes. Therefore, cardiac evaluation is required in all stroke patients who present with clinical features suggestive of cardioembolism (i.e., young age, presence of atrial fibrillation, known valvular heart disease, etc.). A variety of cardiac conditions can lead to systemic embolism. *The common sources of cardioembolism include (**Figs. 10A** to **F**):*

- Left atrial (LA)/LA appendage (LAA) thrombus
- Left ventricular thrombus
- Vegetations (infective/noninfective)
- Cardiac tumors
- Prosthetic heart valve thrombi
- Paradoxical embolism through patent foramen ovale (PFO)/atrial septal defect (ASD)
- Miscellaneous—mitral annular calcification, sclerotic aortic valve, and mitral valve prolapse



FIGS. 10A TO F: *Common causes of cardioembolic stroke.* (A) Large left ventricular apical clot (arrow) in a patient with anterior wall myocardial infarction; (B) Left atrial appendage clot (arrow); (C) Vegetations (arrows) attached to both mitral and aortic valve leaflets; (D) Sessile vegetation (arrow) on the atrial surface of the mitral leaflet in a patient with non-bacterial thrombotic endocarditis; (E) Large left atrial myxoma (arrow) prolapsing into the left ventricular cavity through the mitral orifice; and (F) Papillary fibroelastoma (arrow) attached to the mitral leaflet. ***(For color version, see plate 8)***

Left Atrial/Left Atrial Appendage Thrombus

Left atrial/LAA thrombi accounts for >45% of cardiogenic thromboembolic events. They are most often associated with atrial fibrillation or rheumatic mitral stenosis. TEE is the modality of choice for detection of LA/LAA thrombi and has nearly 100% sensitivity for this purpose. In comparison, the sensitivity of TTE for detection of LA/LAA thrombi is only 39–63%. However, both TTE and TEE can easily detect spontaneous echo contrast within LA, which is a precursor to thrombus formation and has strong association with the risk of systemic embolism. Systemic emboli are frequently seen among patients with dilated cardiomyopathy as well. Though LV thrombi are supposed to be the source of emboli in these patients, LA thrombi are four times more frequent than LV thrombi.

Left Ventricular Thrombus

Left ventricular Thrombus is mainly seen in patients with recent MI, LV aneurysm, or dilated cardiomyopathy. Thrombi most often occur in the apical region of LV, in the presence of regional akinesis or dyskinesis. TTE in combination with ultrasound contrast is a good modality for detection of LV thrombi and TEE is usually not required. Echocardiography also helps in assessing the risk of embolism. A large-sized, mobile thrombus hanging in the LV cavity is associated with high risk of embolism. Similarly, hyperkinetic segments adjacent to the thrombus and an echo-lucent center (suggesting actively growing thrombus) also indicate high risk of embolization.

Valvular Sources of Systemic Embolism

Systemic embolism is a common complication in patients with PHVs, particularly mechanical PHVs. The risk is much higher in patients with subtherapeutic anticoagulation level. Although echocardiography is the modality of choice for evaluation of PHV-related thrombi, acoustic shadowing due to valve structure often proves a limiting factor. TEE provides much better visualization as compared to TTE, particularly in case of mitral PHVs.

Infective endocarditis is another common cause of valve-related embolic events. Echocardiography is useful in detecting the underlying heart disease responsible for IE, identifying vegetations and diagnosing complications of IE. A vegetation is an irregularly shaped, often flagellar, echogenic, and mobile mass, usually attached to the valve leaflets but may also be attached to chordae, chamber walls, or any intracardiac implant such as pacemaker lead, indwelling catheter, or PHV sewing ring. Vegetations may be sessile or pedunculated. Large vegetations (>10 mm size) with high mobility and multiple sites of involvement are at higher risk of embolization. For detection of vegetations and abscesses, TEE is more sensitive than TTE with overall sensitivity 90–100% as compared to only 40–63% for the latter. In a comparative study involving 66 cases of suspected IE, TEE had a sensitivity of 94% compared with 44% for TTE, but both had high specificity approaching 100%.

Vegetations can also form in absence of IE. This is known as nonbacterial thrombotic endocarditis (NBTE) and is usually seen in patients with connective tissue disorders, malignancies, etc. Vegetations in NBTE are most commonly found on the mitral valve and usually on the atrial side of the leaflets. Unlike IE, these vegetations are generally sessile and not >5–10 mm in size.

Finally, calcific specks or fragments of valve tissue can also embolize rarely in patients with mitral annular calcification, aortic sclerosis, etc.

Cardiac Tumors

Cardiac tumors that are commonly associated with systemic embolization are LA myxoma and papillary fibroelastomas. A young patient in sinus rhythm presenting with embolic stroke should raise the suspicion of cardiac tumor or IE. LA myxomas are most often attached to the interatrial septum, in the region of fossa ovalis. They are usually pedunculated and have a nonhomogeneous "cluster of grapes" appearance with areas of echolucency and calcification. LA myxomas can often be confused with LA thrombus and need to be differentiated from the latter. Unlike LA myxoma, an LA thrombus has an amorphous echogenic appearance, is usually sessile and is commonly located in the posterior portion of the LA. Papillary fibroelastomas most often arise from aortic or mitral valve. These tumors are small in size (generally 0.5–2.0 cm in diameter) and have distinct appearance. They are irregular and frond-like in shape, pedunculated, mobile, and attached to the downstream side of the valve. Mobility makes them prone to embolization. Because of the attachment on the valve, fibroelastomas are often mistaken for vegetations. However, the lack of any evidence of infection and their appearance should help in differentiating fibroelastomas from vegetations.

Paradoxical Embolism

In patients with ASD or PFO, blood flow is predominantly in left to right direction. However, there can be a transient reversal of the shunt when RA pressure exceeds LA pressure as occurs during coughing or straining. During these brief periods of shunt reversal, a thrombus from the venous system may travel to the left side of the heart, resulting in systemic embolism. While it is easier to diagnose ASD by echocardiography, diagnosis of a PFO may be challenging. Injecting agitated saline contrast along with Valsalva maneuver or coughing can help uncover intermittent right-to-left interatrial shunting. TEE with saline contrast is superior to TTE with contrast for the diagnosis of PFO. A PFO is considered potentially significant for causing stroke when >10 microbubbles appear in the LA within three cardiac cycles.

ECHO IN ASSESSMENT OF SYNCOPE

Syncope is defined as "sudden temporary loss of consciousness associated with a loss of postural tone and spontaneous recovery not requiring electrical and chemical cardioversion." It is a clinical diagnosis and a detailed history and good physical examination should be able to suggest the diagnosis in the vast majority of the cases. However, echocardiography is often required to rule out underlying structural heart disease. *Various structural heart diseases that can result in syncope include*:

- Acute MI
- Ischemic or nonischemic LV systolic dysfunction (usually due to ventricular tachyarrhythmias)
- Severe aortic stenosis—valvular, subvalvular, or supravalvular
- Hypertrophic obstructive cardiomyopathy
- Large atrial myxoma

- Cardiac tamponade
- Aortic dissection
- Massive pulmonary embolism
- Severe pulmonary hypertension
- Severe pulmonary stenosis, etc.

Echocardiography aids in the accurate diagnosis of the underlying structural heart disease when present. However, it should be remembered that echocardiography should not be a routine diagnostic tool for evaluation of syncope, unless the underlying cause is unexplained by history and physical examination or when the patient has significant cardiac history or has an abnormal ECG.

ECHO IN ASSESSMENT OF PYREXIA OF UNKNOWN ORIGIN

Echocardiography is generally not required in the evaluation of most patients with fever. However, when patients with cardiac conditions predisposing to IE present with fever, echocardiography is routinely indicated. In addition, it is also needed to rule out IE in some patients with no underlying heart disease when no other cause for fever is found despite extensive evaluation.

SUMMARY

Noninvasive nature, portability, and instantaneous diagnostic capability render echocardiography a highly suited diagnostic modality for use in the ER. It offers vital information for early diagnosis, provides extensive anatomic and hemodynamic information, and is also very useful in guiding therapeutic procedures. However, echocardiography is an operator-dependent technique and this becomes even more relevant in ER setting where diagnosis needs to be established quickly and the acoustic window may not always be good. Therefore, proper training of the users and following standardized imaging protocols are essential to maintain optimum diagnostic accuracy of this technique.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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Coronary Computed Tomography in Chest Pain Evaluation

64 CHAPTER

Devendra Richhariya

INTRODUCTION

We all know that chest pain and related symptoms such as chest discomfort with squeezing pressure, burning sensation in epigastric, and precordial or pericardial area are the most common presentation in emergency department (ED). About 60–85% of patient with chest pain presenting to ED do not have acute coronary syndrome. Presentation of patient with chest pain is increasing in ED and emergency physician has to very careful while discharging these patients from ED because mortality in wrongly discharge patient is about 25%. Meanwhile observing all the patients in emergency for longer period of time are neither logical nor economical. Initial triaging is to identify the patient with low-risk chest pain and discharge them safely but this is also true that traditional cardiovascular risk factors and clinical scores are not enough to discharge the patient safely because even in low-risk patient adverse events are about 1–2%. This is a challenge for emergency physician to accurately and efficiently diagnose the myocardial infarction (MI) and also noncardiac fatal causes of acute chest pain such as aortic dissection and pulmonary embolism at the same time. Electrocardiogram and cardiac enzyme are traditional methods used as first diagnostic tool for chest pain evaluation and in some institute exercise treadmill, stress echo, and myocardial perfusion imaging are also performed for risk stratification and to look for functional ischemia and these tests carry false-positive and false-negative results. At the same time, package of tests exerts logistic burden on emergency medical services and on patients. So early imaging is necessary for risk stratification. Coronary computed tomography (CT) is an advanced cardiac noninvasive imaging modality with excellent diagnostic accuracy for the detection of coronary artery disease (CAD) and safe efficient and cost-effective tool. Coronary CT angiography (CTA) has been shown to be a highly sensitive test for the detection of CAD with negative predictive values approaching 97–99%. *Triple rule out (TRO) CT examines coronary, pulmonary, and thoracic aorta in single test* and helpful in the diagnosing the fatal causes of acute chest pain such as acute pulmonary embolism and aortic dissection. *Coronary CT is attractive modality for rapid triaging of chest pain*, reduces the hospitalization, and cost effective without compromising the safety and quality of care. Inclusion and exclusion criteria for performing the CTA are summarized in **Table 1**.

TABLE 1: Inclusion and exclusion criteria for coronary CT.

Inclusion criteria	*Exclusion criteria*
Chest pain	Atrial fibrillation
Low-to-intermediate risk	Known CAD
TIMI score 0–2	History of PTCA
Normal ECG and cardiac enzyme	Deranged creatinine
Inconclusive cardiac enzyme	Beta blocker or
Admission to rule out CAD	contrast allergy
	obesity weight >150 kg

INDICATIONS OF CORONARY CT ANGIOGRAPHY

- Coronary CTA is useful in patients with nonacute symptoms representing an ischemic equivalent and low or intermediate group of CAD.
- It is also appropriate in patients who have low or intermediate probability of CAD and normal, nondiagnostic, or uninterpretable ECG or cardiac biomarkers.
- Cardiac CT is excellent for detection and quantification of calcified portions of coronary plaque and for differentiation of calcified, mixed, and noncalcified plaques.
- Coronary CTA is an appropriate first test in patients who are unable to exercise due to osteoarthritis, and who have either a low or intermediate probability of CAD.
- Coronary CT has promise as a novel imaging modality in the acute setting because it is readily available, rapid and requires minimal additional expertise to perform the imaging.
- Coronary CT is useful screening tool for the assessment of coronary arteries for obstructive disease in young and middle-aged patients presenting for noncoronary cardiac surgery such as valve repair, resection of cardiac masses, and aortic surgery.
- Coronary CT is safe test with newly diagnosed heart failure. The objective is to exclude CAD as a cause of heart failure.

- Coronary CT gives accurate assessment of in-stent restenosis in postpercutaneous transluminal coronary angioplasty (PTCA) patients coming in ED with nonacute chest pain.
- Coronary CT is indicated for symptomatic patients with prior CABG to evaluate for graft patency, graft thrombosis, malposition, aneurysms, and pseudoaneurysms.
- Cardiac CT can be used to differentiate between a subacute and an old MI. An acute myocardial infarct will appear as a hypoperfused, akinetic area of myocardium with normal wall thickness. In old MI, patients usually develop wall thinning in relation to normal, adjacent myocardium. In some instances, fatty metaplasia or calcification may be seen in CTA in old MI.
- Cardiac CT is a reasonable choice as the first modality in assessing all of the congenital anomalies in a single study, e.g., patients with suspected Turner's syndrome may have multiple congenital anomalies, including a bicuspid aortic valve, coarctation of the aorta, elongation of the transverse aortic arch, atrial or ventricular septal defect, and partial anomalous pulmonary venous return. All anomalies can be screened in a single study of CTA.
- Prior to invasive procedures, cardiac CT is useful for pulmonary vein mapping, coronary vein mapping, and for localizing bypass grafts and other retrosternal anatomy.
- Coronary CT is useful for evaluating the right ventricular morphology and function, including in cases of suspected arrhythmogenic right ventricular dysplasia (ARVD).
- It is useful for evaluating native or prosthetic cardiac valves in the setting of valvular dysfunction and for evaluating cardiac masses.
- Finally, cardiac CT is an appropriate test for evaluation of the pericardium.

CONTRAINDICATIONS FOR CORONARY CT

- If patient not able to hold breath, follow instruction or remain still.
- Renal insufficiency
- Cardiac arrhythmias
- Beta-blockers are given to patients undergoing CTA to bring the heart rate (HR) down so as to allow gating. If a patient has a contraindication to beta-blockade, such as asthma.
- Anaphylactic reaction to intravenous iodinated contrast agents is considered an absolute contraindication, though less severe allergic reactions may be acceptable if the patient has been adequately premedicated, usually with a combination of intravenous or oral diphenhydramine and corticosteroids.

FACTORS AFFECTING THE QUALITY OF CORONARY CT IMAGES

- *Fast HR*: Image quality will be poor if HR is >65 beats/min. Patient with high HR is unsuitable for CT coronary. Patient with HR > 70 beats/min, beta blocker should be given to achieve the HR < 65 beats/min. Calcium channel blockers are alternative to beta-blockers. HR reducing medication and fast scan (64–320 cross-section per rotation) help in acquiring the images with no artifact.
- *Atrial fibrillation*: Ectopy or ECG artifacts result in degradation of image quality.
- *Extensive coronary calcification*: It obscures the coronary lumen make analysis of segments or even entire arteries difficult.
- *Preexisting CAD*: Patients with history of CAD usually have extensive coronary calcifications, and/or coronary stents produces metal artifacts and prior coronary bypass grafting with extensively calcified native vessels and small caliber distal coronary arteries also make interpretation of images difficult.
- *Obesity (body mass index over 40 kg/m^2)*: It increases radiation scatter within the patient's body and consequently degrades image quality.

PREPARATION AND INSTRUCTIONS FOR CORONARY CT

- Patient undergoes coronary CT while in ED or after completing observation protocol.
- Troponin and creatinine test are performed simultaneously. Coronary CT is performed only after creatinine result. Usually, the troponin results are repeated while patients are in observation unit.
- Contrast is calculated on the basis of weight of the patient and given as the bolus technique.
- Radiology technician/attending physician instructs the patient about breath holding.
- Image acquisition during single breath hold
- Patient should not move during the image acquisition.
- Patient may feel warm sensation during contrast injection.
- Low radiation exposure with lower tube voltage technique and with advanced CT scan

TRIPLE RULE-OUT PROTOCOL

Acute chest pain is the most common presentation in ED. In view of wide spectrum causes of acute chest pain, not all life-threatening causes are of cardiac origin. Emergency physician should consider other noncardiac causes of chest pain such as pulmonary embolism and acute aortic syndrome which are less common than acute coronary syndrome but immediately life threatening. Apart from initial triaging, other investigations such as D-dimer are used for diagnosis but nonspecific and elevated in other conditions also. Whenever there is high clinical suspicion multidetector row CT (MDCT) used to examine three vascular territories simultaneously pulmonary aorta and coronary arteries. *"TRO"* CT protocol is associated with higher radiation dose. Coronary CT imaging with TRO protocol is modality of choice for suspected pulmonary embolism and aortic pathology such as aortic dissection and aneurysm. TRO protocol covers the whole chest and helpful in assessment of vascular as well as nonvascular pathologies of entire chest.

Patient selection—triple rule CT protocol recommended in acute chest pain patient with inconclusive cardiac enzyme and ECG and combine suspicion of acute pulmonary embolism, acute coronary syndrome, and aortic dissection.

Patient with elevated cardiac enzyme, ECG changes of acute coronary syndrome, pregnancy, previous contrast reaction, nephropathy, should be excluded. *"TRO" protocol* helpful in diagnosis of following conditions—acute aortic syndrome (including aortic dissection, aneurysm, penetrating aortic ulcer, and intramural hematoma), pulmonary embolism, and acute coronary syndrome.

INTERPRETATION OF CORONARY CT

Interpretation and reporting of CTA are done by radiologist with special training in cardiac imaging and CT angiography. Degree of stenosis is observed and measured by electronic calipers. Narrowing of left main, left anterior descending, right coronary artery, circumflex, and their branches is expressed and reported in percentage:

- Mild stenosis (<50% luminal narrowing)
- Moderate stenosis (50–69% luminal narrowing)
- Severe stenosis (>70% luminal narrowing)

Value of calcium scoring in ACS evaluation of patient in ED is debatable. Large calcium deposits in coronaries make interpretation of images difficult. Calcification in coronary arteries is a marker of atherosclerosis and may be considered for long-term management of cardiac risk in outpatient but not for acute setting in ED.

CORONARY CT AS DECISION MAKING TOOL

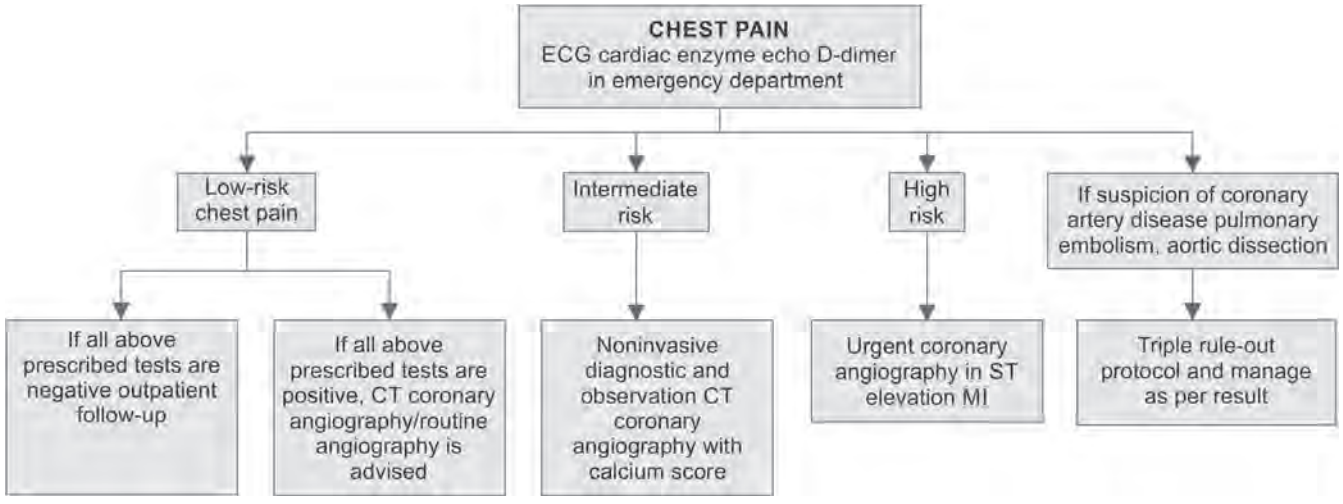
Coronary CT in ED act as a surrogate for cath lab angiography. Coronary CT helpful in risk stratification and disposition of chest pain patient in ED. Provide better understanding of disease, CT is safe, efficient, costs effective, reduces ED visits and hospitalization, physicians and patients believe the results. Higher satisfaction rates, improves chest pain triaging and helpful as *decision making tool in disposition of patient with chest pain* (**Table 2**).

SUMMARY

Coronary CT has been shown to be a safe and efficient way to determine which patients have no significant CAD. CTA is a valuable asset to clinical decision-making in that it allows for the discharge of many patients who would otherwise be admitted for further observation and testing. CTA is not without its limitations, but as technology improves, so will the detail of images, which will improve the diagnostic capabilities of the modality. TRO protocol not only diagnose acute coronary syndrome but also noncardiac life-threatening emergencies such as acute pulmonary embolism and acute aortic dissection. Early implementation of CTA in the ED, for the evaluation of low to intermediate risk chest pain associated with reduced length of stay and a safe alternative to standard ED evaluation (**Flowchart 1**). Rules out CAD by direct visualization of the coronary arteries.

TABLE 2: Coronary CT as decision making tool.

Degree of stenosis	*Recommended action*
0–25%	Patient can be discharged safely follow-up in OPD
26–49%	Patient can be discharged OPD follow-up for preventive measures
50–69%	Possible CAD further evaluation needed before discharge
>70%	Possible CAD hospitalization and evaluation


CHEST PAIN
ECG cardiac enzyme echo D-dimer in emergency department
Low-risk chest pain
Intermediate risk
High risk
If suspicion of coronary artery disease pulmonary embolism, aortic dissection
If all above prescribed tests are negative outpatient follow-up
If all above prescribed tests are positive, CT coronary angiography/routine angiography is advised
Noninvasive diagnostic and observation CT coronary angiography with calcium score
Urgent coronary angiography in ST elevation MI
Triple rule-out protocol and manage as per result

(CT: computed tomography; ECG: electrocardiography; MI: myocardial infarction)

FLOWCHART 1: Showing role of computed tomography in evaluation of chest pain.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Acute Coronary Syndrome

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INTRODUCTION

Acute coronary syndrome (ACS) refers to the clinical spectrum of coronary artery diseases (CADs) that include ST-segment elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTE-ACS). The NSTE-ACS encompasses non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). Acute myocardial infarction (AMI) is any ACS with clinical evidence of: (1) Myocardial injury with serial elevated cardiac troponin (cTn) levels and at least one cTn value above the 99th percentile of upper reference limit (URL); and (2) Cardiac tissue necrosis consistent with myocardial ischemia.

According to a recent US survey by the American Heart Association (AHA) more than one million patients were hospitalized annually with primary or recurrent ACS. Approximately one in every seven deaths in the US occurs due to CAD. Of all the premature deaths (before 70 years) due to noncommunicable diseases, 82% occur in low middle income countries, of which 37% are caused by CADs. The overall prevalence of CAD has risen dramatically in India in the last decade with CAD occurring at a much younger age in India than in Western population. Therefore, prevention, early diagnosis, and timely management of CAD including ACS based on evidence-based guidelines [European Society of Cardiology (ESC) for STEMI and the 2014 AHA guidelines for NSTE-ACS] are of utmost importance in India.

ETIOPATHOGENESIS AND RISK FACTORS

Acute coronary syndrome mainly occurs due to acute thrombus in an atherosclerotic coronary artery or its branches (**Fig. 1**) causing obstruction of blood flow to the myocardium, triggering increased myocardial oxygen demand and unbalancing oxygen demand and supply. Not all plaque ruptures result in ACS, majority remain asymptomatic. The possibility of a plaque causing ACS depends on severity of rupture, blood flow in the area, the blood thrombogenicity, and the degree of inflammation at the site. The *risk factors* associated with atherosclerosis are dyslipidemia, diabetes mellitus (DM), hypertension, obesity, family history of ACS, number of diseased vessels, history of previous ACS or MI, alcohol abuse, and smoking.

The etiopathogenesis of ACS differs with the type of clinical setting (**Table 1**) and the ACS subcategory of (STEMI/NSTE-ACS).

Clinical Presentation

Substernal chest pain is the classic symptom of ACS, often described as crushing or pressure-like feeling, radiating to the jaw, and/or left arm. If a patient has pain radiating to the left arm or both arms, there is a high possibility of ACS. A study found that even 22% of low-risk patients who had ACS presented with sharp or stabbing pain. Many times, presenting complaints can be atypical like breathing difficulty, lightheadedness, isolated jaw or left arm pain, nausea, epigastric pain, diaphoresis, and weakness. Although atypical symptoms could typically mean no possibility of ACS, however, physicians should be alert that these could be low ACS-risk patients. About 10–40% of patients with MI present without any chest pain. Female gender, DM, and older age are associated with atypical symptoms or MI without chest pain. Patients with NSTEMI are more likely to present without chest pain than those having STEMI. Mortality rate is higher in this patient group. Differentiating cardiac pain from noncoronary pain is very critical for an accurate diagnosis. Few examples of ailments causing noncardiac chest pain include pneumonia, pulmonary embolism, renal calculus, rib fracture, abdominal disorders, acute aortic dissection, splenic infarction, or esophageal spasm. Physical findings that may be suggestive of ACS include new mitral regurgitation murmur, hypotension, S3 gallop, and a new jugular venous distention. Frequently, physical examination of patients with ACS turns out to be normal.

MANAGEMENT OF ACUTE CORONARY SYNDROME

Initial Evaluation at Emergency Department/ When First Seen

Initial evaluation is aimed at establishing diagnosis of ACS, assessing risk and differentiating into STEMI, NSTEMI, and unstable angina for further management. Physicians initially make a working diagnosis of ACS based on the symptoms, medical history (including assessing risk factors for CAD),

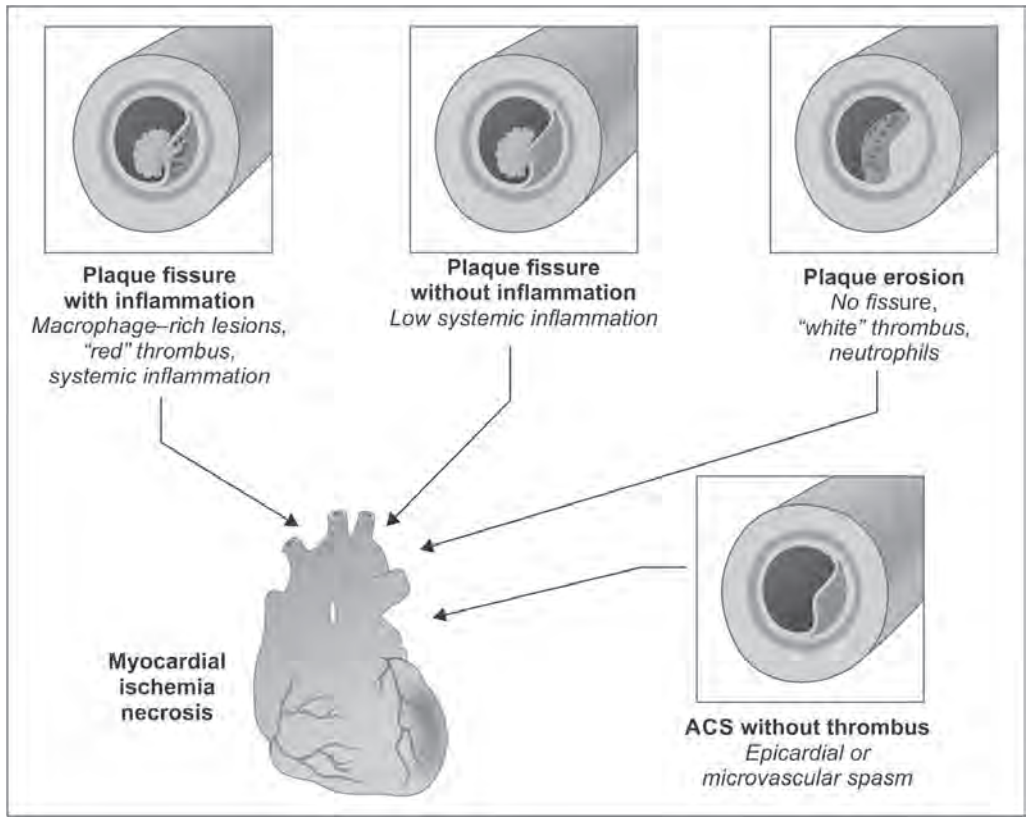


FIG. 1: Four diverse mechanisms causing acute coronary syndromes (ACS).

TABLE 1: Types of ACS presentation.

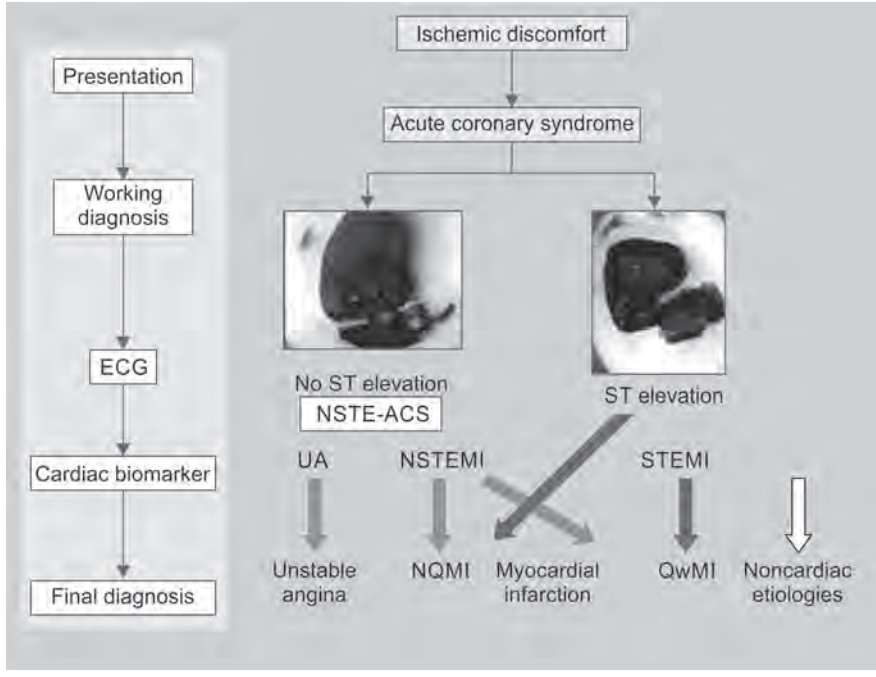
Type	*Clinical setting*	*Etiology/Findings*
Type 1	Spontaneous MI	• Rupture, ulceration, fissuring, erosion, or dissection of atherosclerotic plaque • Distal platelet emboli with resultant myocyte necrosis
Type 2	MI secondary to ischemic imbalance	Non-CAD-related condition such as arrhythmia, coronary embolus, coronary endothelial dysfunction, coronary artery spasm, anemia, tachycardia, respiratory failure, pulmonary embolism, severe aortic stenosis, hypotension, hypertension, sepsis, use of cardiotoxic drugs, stress, cocaine, and tobacco use
Type 3	MI resulting in death when biomarker values are unavailable	Death due to cardiac arrest before blood samples could be obtained or before cardiac biomarkers could rise ECG shows new ischemic changes or new LBBB
Type 4a	MI related to PCI (recurrent MI)	cTn elevation to >5 times the 99th percentile of URL or >20% in patients with normal pre-PCI values and one of the following: • Angina • *ECG*: New ischemic changes • *Angiography*: Either reduced blood flow or blockage • *Imaging studies*: New regional wall motion abnormality
Type 4b	MI related to stent thrombosis (recurrent MI)	Stent thrombosis on angiography or autopsy and rise and/or fall in cardiac biomarker levels
Type 5	MI related to CABG (recurrent MI)	Cardiac biomarkers values >10 times with 99th percentile of URL in patients with normal pre-CABG values and one of the following: • *ECG*: New pathological Q waves or LBBB • *Angiography*: Occlusion of a new graft or native coronary artery • *Imaging*: New regional wall motion abnormality

(CABG: coronary artery bypass surgery; CAD: coronary artery disease; cTn: cardiac troponin; ECG: electrocardiogram; LBBB: left bundle branch block; MI: myocardial infarction; PCI: percutaneous coronary intervention; URL: upper reference level)

and physical evaluation, which is further confirmed by serial electrocardiograms (ECG) and serial serologic cardiac markers (**Fig. 2**). Further management is based on risk prognosis assessed by *two commonly used risk assessment tools*—(1) thrombolysis in myocardial infarction (TIMI) risk score and (2) the Global Registry of Acute Coronary Events (GRACE) risk score (**Table 2**). After initial evaluation and risk stratification, treatment depends on whether patient has STEMI, NSTEMI, or UA. The primary aim of the treatment for ACS is to relieve distress, reduce cardiac workload, reverse ischemia, interrupt thrombosis, and prevent complications. Patients having confirmed STEMI require more intensive management and monitoring than NSTE-ACS.

Initial Electrocardiogram (ECG)

Timing of ECG, a 12-lead ECG is performed within 10 minutes of patient's arrival at an emergency facility. If the initial ECG is nondiagnostic and patient continues to be symptomatic, ECG is repeated at 15–30-minute intervals during the first hour. Serial ECGs are recommended for better diagnosis and management of ACS. Establishing diagnosis with ECG, in patients with



(ACS: acute coronary syndrome; NSTE-ACS: non-ST elevation ACS: NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina)

FIG. 2: Initial evaluation of an individual presenting with symptoms suggestive of acute coronary syndrome (ACS): ascertaining the type of ACS. ***(For color version, see plate 9)***

TABLE 2: Risk scores for risk stratification of acute coronary syndrome.

TIMI risk score for STEMI	*TIMI risk score for NSTE-ACS*	*GRACE risk score for entire spectrum of ACS*
Score: 0–14 *(scores ≥3—high risk)*	*Score: 0–7* *(scores ≥3—high risk)*	*Range: 1–372* *Low risk <109* *Intermediate risk: 109–140* *High risk: >141*
Based on eight variables at admission: • ≥65 years • Risk factors: Diabetes mellitus, angina, and hypertension • SBP <100 • Heart rate >100 • Weight < 67 kg • Anterior STE or LBBB • Treatment start > 4 hours	*Based on one point each for seven variables at admission:* • ≥65 years of age • ≥3 risk factors for CAD • Prior ≥50% coronary stenosis • ST deviation on ECG • ≥2 anginal events in prior 24 hours • Aspirin use in prior 7 days • Elevated cardiac biomarkers	*Based on eight variables at admission:* • Age • Heart rate • SBP • Serum creatinine • Killip class • Cardiac arrest • ST-segment deviation on ECG • Elevated cardiac enzymes/markers

(ACS: acute coronary syndrome; ECG: electrocardiogram; LBBB: left bundle branch block; NSTE-ACS: non-ST elevation ACS; SBP: systolic blood pressure; STE: ST-segment elevation; STEMI: ST-segment elevation myocardial infarction)

STEMI, initial ECG shows ST-segment elevation (≥1 mm) in ≥2 contiguous leads reflecting the damaged area **(Fig. 3A)**. Conversely, in NSTE-ACS, there is horizontal or down-sloping ST depression **(Fig. 3B)**. Based on initial ECG findings or in patients with intermediate/high risk for ACS with initial nondiagnostic ECG, the following additional ECG recordings may be required.

- Posterior chest wall leads (V_7–V_9) in patients with high suspicion of posterior MI
- Right precordial leads (V_3R and V_4R) in patients with inferior MI
- Continuous monitoring with 12-lead ECG, if required

The ECG assists in risk stratification, diagnosing, and treatment decisions; however, accuracy improves when ECG is obtained in patients with ongoing chest pain.

Cardiac Markers for Diagnosis and Risk Stratification

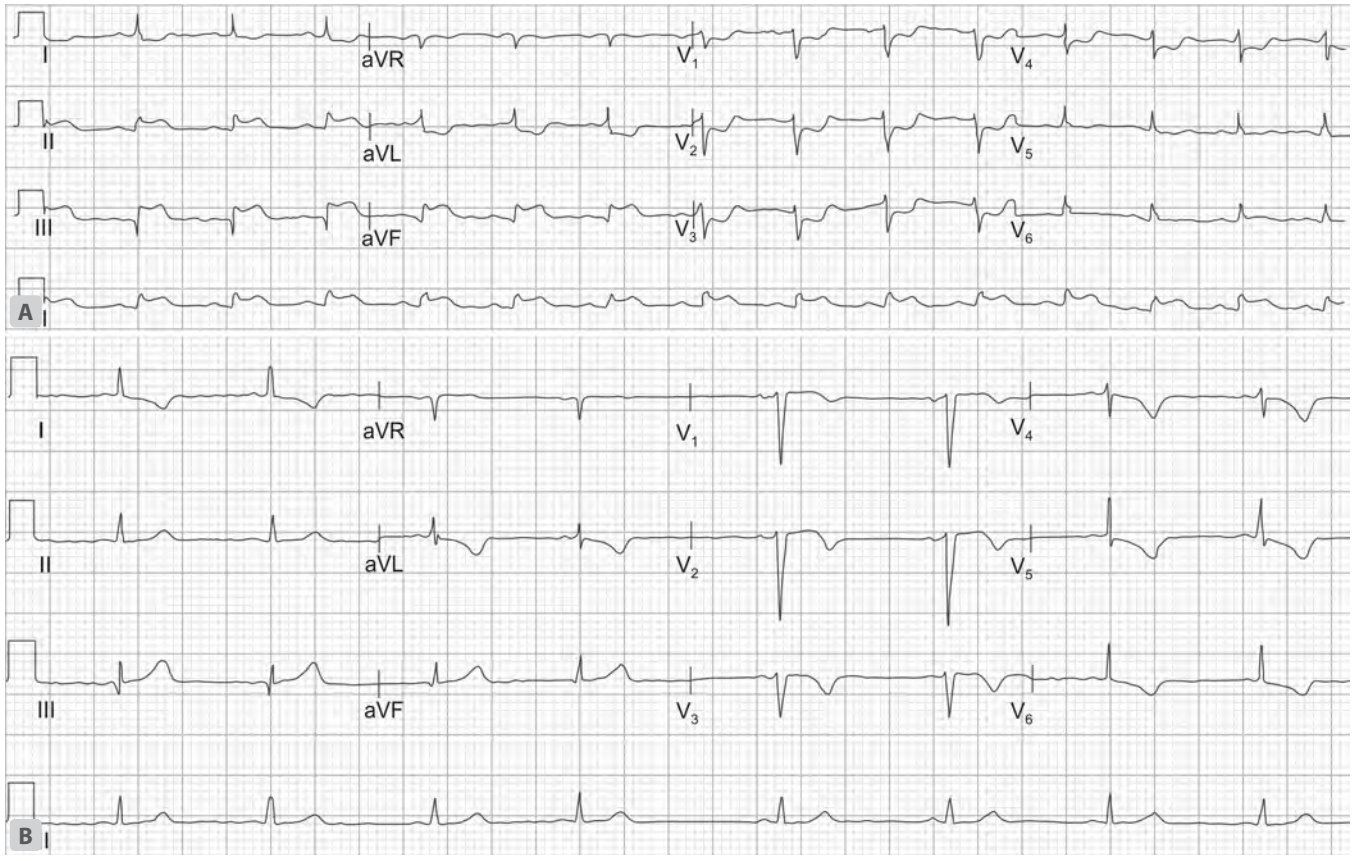
Timing of cardiac markers, in patients with symptoms consistent with ACS:

- Immediately send blood samples for cardiac troponin I (cTnI) or cardiac troponin T (cTnT)
- Reassess cTnI or cTnT 3–6 hours after symptom onset
- *After 6 hours*: If initial and serial cTn values are normal, and/or patient has ECG changes, and/or patient is in immediate-/high-risk category
- *Day 3 or 4*: In patients with MI to assess infarct size

An increased cTn suggests myocardial cell injury but does not throw light on cause of the injury as cTn values increase in many other cardiac/noncardiac causes. Imaging techniques such as angiography are used to find the cause and actual site of injury.

Role of Other Cardiac Markers in ACS Diagnosis

Other cardiac markers include creatinine kinase (CK), myoglobin, and B-type natriuretic peptide (BNP). The sensitivity and specificity of CK levels for cardiac damage are lower compared to other markers as raised CK levels are usually associated with many noncardiac conditions as well. CK myocardial isoenzyme (CK-MB) is useful for early diagnosis of acute MI. Unlike CK level, CK-MB is more specific to cardiac injury but it cannot help in ascertaining infarct size; however, it is useful in detecting early reinfarction. CK-MB and myoglobin are not required if contemporary troponin assays are being performed as they do not add any additional diagnostic value. BNP or N-terminal (NT)-pro-hormone BNP (NT–pro-BNP) is



FIGS. 3A AND B: (A) (STEMI): 12-lead electrocardiogram showing ST-segment elevation in the inferior leads (II, III, and aVF) with reciprocal ST-segment depression in leads V_1–V_4, I, and aVL. (B) (NSTEMI): 12-lead electrocardiogram showing anterolateral T-wave inversion (leads V_2–V_6, I, and aVL).

sometimes done in patients with suspected ACS to assess risk and as a prognostic marker.

COMMON STRATEGIES FOR STEMI AND NSTEMI MANAGEMENT

- Patients with confirmed MI are admitted to hospital care immediately:
  - *Low risk*: Admitted to intermediate step-down
  - *High risk*: Admitted to a coronary care unit (CCU). Nurses trained in rapid cardioversion and defibrillation should be deployed in such CCUs.
- Continuous ECG monitoring
- Supplemental oxygen is started only if oxygen saturation < 90% or there are respiratory distress/other hypoxemia features
- Antianginal, antiplatelet, and anticoagulant therapy are started.
  - *Antianginal*: Sublingual [nitroglycerin (NTG) is given every 5 minutes (three times) for continuing angina; then switched to intravenous (IV)] NTG for persistent angina, heart failure (HF), or hypertension. Nitrates are contraindicated if patient was recently on phosphodiesterase inhibitors.
  - *Antianginal*: IV morphine sulfate for persistent angina not relieved by nitrates. Nonsteroidal anti-inflammatory drugs are contraindicated, except aspirin as these are associated with high risk for major adverse cardiovascular event (MACE).
  - *Mild tranquillizer (usually a benzodiazepine)*: If patient is very anxious.
  - Nonenteric-coated, chewable aspirin (162–325 mg) is started immediately followed by maintenance dose (81–325 mg/day) indefinitely. This can be given before and after percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG).
- *Antiplatelet*: P2Y12 inhibitor—ticagrelor (preferred), clopidogrel, or prasugrel is usually started with aspirin as part of dual antiplatelet therapy (DAPT).
- Lipid profile is obtained in first 24 hours; high-intensity statins started, unless contraindicated.
- Beta-blockers (calcium channel blockers if beta-blockers contraindicated) can be started within first 24 hours.
- Angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blocker (ARB) recommended especially for patients with impaired left ventricular ejection fraction (≤40%), early HF, hypertension, and DM.
- Patients remain on bed/chair rest with minimal ambulation.
- Nurse-patient ratio should allow continuous cardiac monitoring and repeated assessment of vitals and mental status.

NON-ST ELEVATION—ACS MANAGEMENT

Unstable angina patient group with ACS symptoms but normal serial cTn and inconclusive/normal serial ECGs:

- Before discharge from emergency unit or within 72 hours postdischarge; only if patients have been angina-free for 12–24 hours; and very low-risk patients:
  - Perform treadmill ECG if no ST changes in resting ECG
  - Perform stress echocardiography or stress myocardial perfusion imaging if ST changes in resting ECG.
- In case of persisting symptoms and clinical suspicion of ACS, perform coronary CT angiography or resting technetium-99m myocardial perfusion imaging.

Patients with low risk are referred for outpatient management and follow-up. These patients are usually prescribed aspirin, short-acting NTG, and other medications as required. If patients develop STEMI/NSTEMI changes on treadmill ECG or stress imaging, then further treatment depends on patient's condition and MACE risk.

STEMI MANAGEMENT

Reperfusion is indicated for all patients with ≤12 hours duration of symptoms and persistent ST-segment elevation (**Table 3**). Fibrinolysis with tenecteplase, alteplase, or reteplase is recommended if revascularization is expected to be delayed beyond 2 hours (**Table 4**). It is also important to distinguish between left ventricular myocardial infarction (LVMI) and the right ventricular myocardial infarction (RVMI) with the help of clinical features, ECG and the hemodynamic features because mortality risk due to primary RV dysfunction nearly as high as LV dysfunction. Differentiating features between LV and RV MI are shown in **Table 5**. Literature shows that primary PCI is better in terms of reducing mortality, nonfatal myocardial infarction, and stroke compared with fibrinolysis if performed on time.

Preferred Infarct-related Artery Reperfusion

- *Primary PCI*: Stenting recommended over balloon angioplasty
- New-generation drug-eluting stent (DES)—DESs are recommended over bare-metal stent.
- Radial access recommended over femoral access
- Routine use of thrombus aspiration or deferred stenting is not recommended.
- If infarct-related artery (IRA), PCI cannot be performed—CABG for patients with ongoing ischemia/jeopardized myocardium covering large areas

Non-IRA-related Reperfusion

- Routine preventive strategy in STEMI patients with multivessel disease
- During index IRA procedure in patients with cardiogenic shock

SPECIAL CONSIDERATION IN STEMI/NSTEMI MANAGEMENT

Further NSTEMI management involves either invasive strategy or an ischemia-guided strategy. Invasive strategy involves diagnostic angiography with intent to perform PCI; it can be immediate, early, or late invasive depending on patient's condition. CABG is another option for revascularization. On the contrary, early ischemic strategy is used for patients with low-risk score (conservative management). Patients with STEMI are usually intensively managed with invasive techniques such as angiography followed by PCI or CABG.

TABLE 3: Invasive treatment strategy for NSTEMI and STEMI.

Treatment strategy	*Timing*	*Patient group (NSTEMI)*	*Patient group (STEMI)*
Immediate	≤2 h (120 min)	• Refractory angina • Recurrent angina • Ischemia at rest/low activity level despite intensive medical therapy • HF • New or worsening MR • Hemodynamic instability • Sustained VT or VF	• Primary PCI within 120 min of presentation/ECG • IRA should ideally be perfused within 60 min • If a delay is expected then immediate fibrinolysis • Primary PCI in absence of ST segment elevation + persisting symptoms: ○ Hemodynamic instability ○ Cardiogenic shock ○ Life-threatening arrhythmias ○ Cardiac arrest ○ Mechanical complications of MI ○ Acute heart failure ○ Recurrent dynamic ST-segment or T-wave changes
Early	≤24 h	Not a candidate for immediate invasive GRACE risk score >140 Temporal change in cTn New or presumably new ST depression	• Early angiography if complete symptom relief and complete normalization of ST-segment elevation spontaneously or after NTG • *Routine primary PCI*: Symptoms onset of 12–24 h • If symptom onset is >12 h, primary PCI is indicated in the presence of persistent symptoms of ischemia, hemodynamic instability, and arrhythmias (life-threatening)
Delayed	≤25–72 h	Not a candidate for immediate/early invasive but patient has: • Diabetes mellitus • Renal insufficiency (GFR < 60 mL/min/1.73 m^2) • Reduced LV systolic function (EF < 0.40) • Early postinfarction angina • PCI within 6 months • Prior CABG • GRACE risk score 109–140; TIMI score ≥ 2	• Routine primary PCI: symptoms onset of 25-48 h • Routine PCI of an occluded IRA > 48 h after onset of STEMI is not indicated in asymptomatic patients

(CABG: coronary artery bypass surgery; EF: ejection fraction; GFR: glomerular filtration rate; GRACE: Global Registry of Acute Coronary Events; HF: heart failure; IRA: infarct-related artery; LV: left ventricular; MI: myocardial ischemia; NSTE-ACS: non-ST-elevation acute coronary syndrome; NTG: nitroglycerin; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction; Tn: troponin; VF: ventricular fibrillation; VT: ventricular tachycardia; MR: mitral regurgitation)

TABLE 4: Fibrinolytic agents and doses.

Streptokinase	1.5 million IU Infused over 1 h in 45 mL NaCl
Alteplase	15 mg loading dose followed by 50 mg over 30 min and 35 mg over next 1 h (Total duration of infusion 90 min) and concurrent use of heparin 0.75 mg/kg not to exceed 50 mg over 30 min and 0.50 mg/kg and not to exceed 35 mg over next 1 h
Reteplase	• Given as double bolus by 10 U + 10 U (no infusion) • 10 U bolus over 2 min wait for 30 min and repeat 10 U over 2 min and concurrent use of heparin
Tenecteplase	30–50 mg single weight-based bolus over 5–10 sec and concurrent use of heparin

TABLE 5: Differentiating features of LVMI and RVMI.

	LV MI	*RVMI*
Clinical features	Pulmonary congestion S3, S4 new MR	Clear lung fields right-sided S3 new TR, hypotension with distended neck veins
ECG	ST elevation in standard leads	ST elevation in V_4R
Hemodynamics	Raised pulmonary wedge pressure	RAP > 10 mm Hg RAP/PAWP > 0.8
Specific management	• Fluid restriction • Preload and after-load reduction • Reperfusion therapy • Inotropes	• Fluid resuscitation • Avoid preload reduction • Reperfusion therapy • Inotropes

Anticoagulation: Special Considerations

Long-term anticoagulation is not routinely prescribed following ACS.

Commonly used anticoagulants in specific situations include:

- Bivalirudin until diagnostic angiography or until PCI
- Subcutaneous enoxaparin or fondaparinux for the hospitalized duration or until PCI
- Intravenous unfractionated heparin for 48 hours or until PCI
- *Antiplatelets*: P2Y12 inhibitor in loading dose followed by maintenance therapy; given in addition to aspirin, and continued for at least 12 months, especially in patients receiving a DES during PCI. DAPT can significantly reduce the risk of stent thrombosis and MACE. The STOPDAPT-2 trial showed that DAPT can be reduced up to one month with the new generation DES without any significant increase in MACE.
- Ticagrelor (loading dose: 180 mg; maintenance: 90 mg twice daily), clopidogrel (loading dose: 600 mg; maintenance: 75 mg daily), or prasugrel (loading dose: 60 mg; maintenance: 10 mg daily)
- In high-risk patients, glycoprotein (GP) IIb/IIIa inhibitors (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) can be given at the time of PCI.

Stopping Anticoagulation before CABG

- *Elective CABG*: Clopidogrel or ticagrelor discontinued for at least 5 days and prasugrel for at least 7 days before surgery, if possible.
- *Urgent CABG*: Clopidogrel or ticagrelor discontinued for at least 24 hours before surgery to reduce major bleeding.
- Short-acting IV GP IIb/IIIa inhibitors (eptifibatide or tirofiban) are discontinued for at least 2–4 hours and abciximab for at least 12 hours before surgery to reduce major bleeding.

DISPOSITION

Patients are discharged from hospital once they are stable with detailed instructions on medications, activity level, recognition of warning symptoms requiring urgent care and follow-up details. Long-term cardiac rehabilitation that includes exercise, lifestyle changes, and education is stressed upon during routine cardiac follow-ups.

SUMMARY

Acute coronary syndrome encompasses NSTE-ACS—UA, NSTEMI, and STEMI. Diagnosis is based on medical history, physical assessment, ECG, and serum cardiac markers; cTn is most sensitive. Treatment and management of ACS based typically on the ACS subtypes and patient characteristics. STEMI needs more aggressive treatment approach than NSTE-ACS. Prolonged anticoagulation not recommended but aspirin should be continued indefinitely. DAPT is preferred over aspirin alone especially in patients who undergo PCI with DES.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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66
CHAPTER

Cardiogenic Shock

Devendra Richhariya

INTRODUCTION

Shock is the final outcome of the circulatory collapse and inadequate supply of oxygenated blood to the tissues and the vital organs. Traditionally *shock is classified in-to four major types*—(1) Hypovolemic shock (excessive fluid loss from the body), (2) Obstructive shock (blood flow obstruction in the large blood vessels, conditions like pulmonary embolism, cardiac tamponade, and tension pneumothorax), (3) Distributive shock (sepsis and anaphylactic reaction), and (4) Cardiogenic shock caused by various conditions affecting the myocardium. Various characteristics of different types of shock are described in Chapter 48 "Approach to Shock". According to epidemiological data, septic shock (distributive shock) is the most common shock followed by cardiogenic and hypovolemic shock.

Cardiogenic shock is the syndrome develops due to primary cardiac dysfunction resulting in tissue and organ hypoperfusion with progressive multiorgan failure. Most common cause of cardiogenic shock is acute myocardial infarction (AMI) particularly involving the anterior wall. Other causes include impairment of mechanical function of the heart, cardiomyopathies, and arrhythmias. Sometime establishing the etiology of cardiogenic shock is not easy. Invasive hemodynamic monitoring, specific biomarkers echocardiography are helpful in establishing the cause. Management of cardiogenic shock is always difficult and mortality in cardiogenic shock is still high about 50–70%. Since myocardial infarction is common cause of cardiogenic shock, early recognition, utilization of advanced revascularization therapy, and circulatory support help in reducing the mortality and improve the survival also.

DEFINITION

Cardiogenic shock is defined by presence of specific clinical and hemodynamic criteria.

- *Clinical criteria*: Systolic blood pressure <90 mm Hg for >30 min or requirement of vasopressor to maintain BP >90 mm Hg. Clinical features of tissue and organ hypoperfusion such as altered mental status, cold and clammy skin, decreased urine output, and raised serum lactate.
- *Hemodynamic criteria*: Low cardiac output state with cardiac index <1.8 L/min/m^2 or <2–2.2 L/min/m^2 (on pharmacological or mechanical support) with elevated pulmonary capillary wedge presser 15 mm Hg, elevated indices of cardiac preload left ventricular end-diastolic pressure (LVEDP) >18 mm Hg and right ventricular end-diastolic pressure (RVEDP) >10–15 mm Hg.

Cardiogenic shock can easily be diagnosed by easy to assess clinical criteria. This is possible that hypotension may not present in early stage of compensated shock where normotension is maintained by high systemic vascular resistance compensating for low cardiac index. Group of people who are prone to cardiogenic shock are older age, female, myocardial infarction (anterior wall), hypertension, diabetes, multivessels coronary artery disease, and history of heart failure.

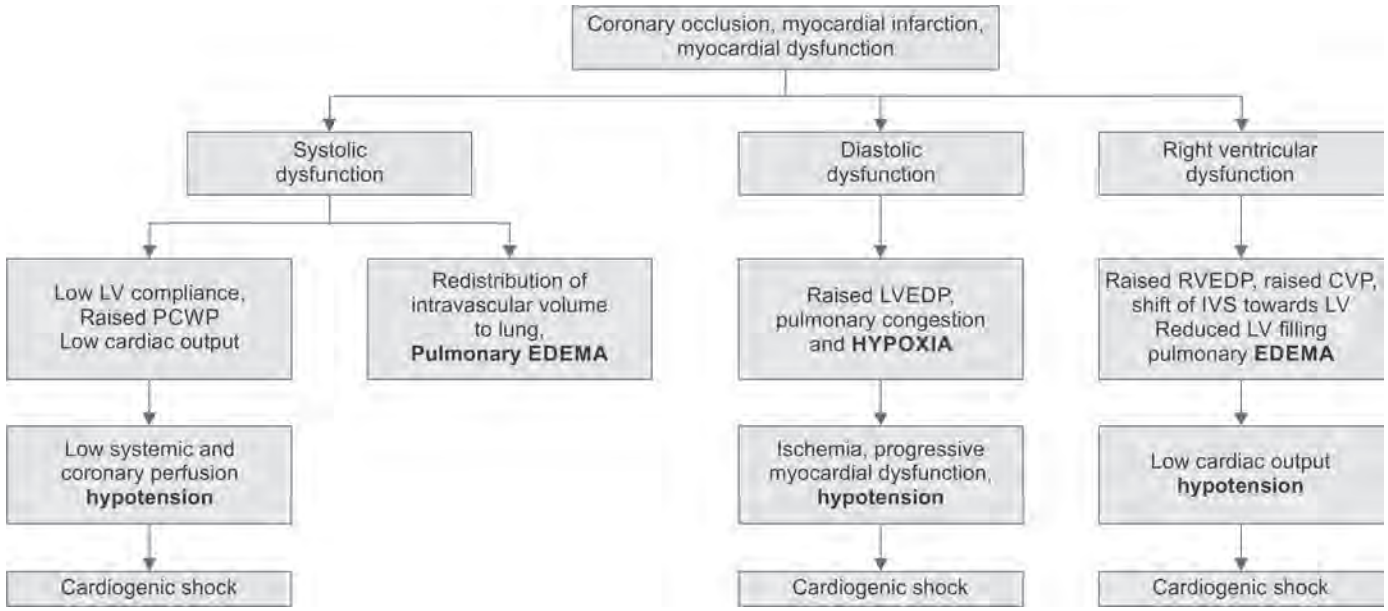
ETIOLOGY

Knowledge of etiology is important for management of cardiogenic shock. Etiology of cardiogenic shock is classified as conditions affecting the myocardium, mechanical cause, and arrhythmic causes. Most common cause of cardiogenic shock is AMI and related complications such as acute mitral regurgitation, ventricular septal defect, and cardiac tamponade due to cardiac free wall rupture. Other important causes of cardiogenic shock are right ventricular failure, myocarditis, valvular heart disease, arrhythmias, and advanced stage cardiomyopathies (**Table 1**).

PATHOPHYSIOLOGY

Cardiogenic shock occurs when about 40% of left ventricle is damaged predominantly due to ischemia. Right ventricular infarction is also recognized as the cause of cardiogenic shock in few cases. Thrombotic occlusion of artery supplying the major part of the heart is underlying pathology of the cardiogenic shock. Coronary occlusion induces depression of myocardial contractility. Reduction in myocardial contractility produces the low cardiac index and hypotension. Low cardiac index and hypotension cause severe tissue hypoperfusion which is measured by the raised serum lactate. Initially, compensatory vasoconstriction occurs in which normotensive state is maintained. If this preshock stage is not recognized early and not treated well, this condition progresses to severe or refractory cardiogenic shock (**Flowchart 1**). Inflammatory

TABLE 1: Etiology of cardiogenic shock.		
Myocardial causes	***Mechanical causes***	***Arrhythmic causes***
• Myocardial infarction left or right infarction • Cardiomyopathy • Myocarditis • Toxins and cytotoxic drugs • Medication (CCB, beta blockers, digoxin, antiarrhythmic drugs, and antidepressant) • Ventricular hypertrophy	• Valvular heart disease • Mechanical complications of MI (papillary muscle dysfunction, ventricular septal rupture, and cardiac free wall rupture) • Hypertrophic cardiomyopathy • Outflow tract obstruction • Atrial thrombus and atrial tumor • Aortic dissection • Cardiac trauma (myocardial contusion)	• Supraventricular or ventricular arrhythmia • Bradycardia


Coronary occlusion, myocardial infarction, myocardial dysfunction
Systolic dysfunction
Diastolic dysfunction
Right ventricular dysfunction
Low LV compliance, Raised PCWP Low cardiac output
Redistribution of intravascular volume to lung, Pulmonary EDEMA
Raised LVEDP, pulmonary congestion and HYPOXIA
Raised RVEDP, raised CVP, shift of IVS towards LV Reduced LV filling pulmonary EDEMA
Low systemic and coronary perfusion hypotension
Ischemia, progressive myocardial dysfunction, hypotension
Low cardiac output hypotension
Cardiogenic shock
Cardiogenic shock
Cardiogenic shock

(CVP: central venous pressure; IVS: interventricular septum; LVEDP: left ventricular end-diastolic pressure)

FLOWCHART 1: Pathophysiology of the cardiogenic shock.

derangement capillary leakage and microcirculatory derangement also contribute to development of severe/refractory shock. According to various studies, older age group, low LVEF, low cardiac index, low systolic BP, requirement of vasopressor and mechanical support, and high serum lactate level are associated with high mortality rates in cardiogenic shock.

DIAGNOSIS

Cardiogenic shock develops gradually and can be categorised as Preshock stage (patient at risk of cardiogenic shock), mild shock (responsive to low dose inotropic support), severe shock [responsive to high dose inotropic support/Intra-aortic balloon pump (IABP)], and refractory shock (when mechanical support is required). Diagnosing the cardiogenic shock in early stage is challenging and vital as reversibility almost impossible in advanced and refractory stage. *Various clinical features and hemodynamics are suggestive of cardiogenic shock* (**Table 2**). This is also important to establish the type of shock for appropriate management. Emergency physician should be aware about the differentiating features of hypovolemic, distributive, and cardiogenic shock (**Table 3**).

TABLE 2: Diagnosis of cardiogenic shock on the basis of clinical and hemodynamic features.	
Clinical features	***Hemodynamic features***
• Signs of hypo-perfusion such as cool moist skin, pale or cyanosis, slow speech, low sensory perception, lethargy, confusion • Oliguria or anuria	• Systolic BP < 90 mm of Hg for >30 min • Requirement of vasopressors to maintain the systolic BP > 90 mm of Hg • Low cardiac index (<2.2 L/min/m^2) • Raised pulmonary wedge pressure (>15 mm Hg)

Various supporting test such as biochemical test hemodynamic monitoring and echocardiography also helpful in this regard. Bedside echocardiography is key investigations along with electrocardiogram (ECG) and biochemical test for acute coronary syndrome as myocardial infarction is important cause of cardiogenic shock. Important cardiac parameters such as global systolic function, pressers, pericardial fluid, and inferior vena cava can be assessed by the bedside echocardiography. Pulmonary artery catheterization is helpful

in providing the information about left or right ventricular filling pressures, systemic and pulmonary vascular résistance, right ventricular ejection fraction, and oxygen saturation. Monitoring of mixed venous oxygen saturation (SvO_2) not only useful for diagnostic purpose but maintaining the therapeutic target of SvO_2 during the initial hours of shock treatment helpful in reducing the mortality. It is also important to distinguish between left ventricular myocardial infarction (LVMI) and the right ventricular myocardial infarction (RVMI) as the cause of cardiogenic shock with the help of clinical features, ECG, and the hemodynamic features because mortality risk for cardiogenic shock due to primary RV dysfunction nearly as high as LV dysfunction. Differentiating features between LV and RV MI are shown in **Table 4**.

TABLE 3: Hemodynamic features of various types of shock.

	Hypovolemic shock	*Distributive shock*	*Cardiogenic shock*
Pulmonary wedge pressure	Low	Low or normal	Raised
Cardiac output	Low	Raised	Low
SVR	Raised	Low	Raised
Mixed venous O_2 saturation	Low	Raised	Low

(SVR: systemic vascular resistance)

TABLE 4: Differentiating features of LVMI and RVMI.

	LVMI	*RVMI*
Clinical features	Pulmonary congestion S_3, S_4 new MR	Clear lung fields right-sided S_3 new TR, hypotension with distended neck veins
ECG	ST elevation in standard leads	ST elevation in V_4R
Hemodynamics	Raised pulmonary wedge pressure	RAP > 10 mm Hg RAP/PAWP > 0.8
Specific management	• Fluid restriction • Preload and after-load reduction • Reperfusion therapy • Inotropes	• Fluid resuscitation • Avoid preload reduction • Reperfusion therapy • Inotropes

(ECG: electrocardiogram; LVMI: left ventricular myocardial infarction; PAWP: pulmonary artery wedge pressure; RVMI: right ventricular myocardial infarction; RAP: right atrial pressure)

MANAGEMENT

Management of cardiogenic shock should be started as early as possible to normalize hemodynamic parameter and to prevent the further damage of organ and deterioration of the patient. Management of the cardiogenic shock should target to maintain hemodynamic parameter within therapeutic range (**Fig. 1**). Maintaining the hemodynamic parameters within therapeutic range suggestive of adequate management strategies and positive outcome.

Management of cardiogenic shock is multiphasic, and various modalities of treatment used in cardiogenic shock are summarized in **Figure 2**. Immediate management of shock includes fluid therapy, vasoactive therapy, and ventilator therapy along with correction of electrolyte imbalance. Along with the symptomatic treatment therapy should be directed at the underlying cause. Most cases of cardiogenic shock are due to myocardial infarction, prompt reperfusion therapy should be instituted. Revascularization therapy [percutaneous transluminal coronary angioplasty or coronary artery bypass grafting (PTCA or CABG)] reduce the hospitalization, long-term mortality and MI-related mechanical complication.

CRITICAL CARE SUPPORT

Fluid Administration

First step of management is assessment of intravascular fluid status and fluid responsiveness. Fluid therapy should be used cautiously under the guidance of invasive monitoring and maintenance of target CVP. Generally, 250–500 mL of crystalloid fluid given over 30 minutes.

Vasopressor and Inotrope Support

Vasopressor agents are added to the ongoing therapy when hypotension persists despite fluid therapy. For maintaining the MAP (>60 mm Hg), vasopressor agents are required to maintain adequate coronary and tissue perfusion. *Noradrenaline*—primarily is vasoconstrictor and weak inotrope. Noradrenaline is vasopressor of choice in cardiogenic shock, helpful in increasing the coronary blood flow. Dose of noradrenaline is 0.02–1 μg/kg/min. *Vasopressin*—primarily a vasoconstrictor usually added to the noradrenaline when requirement to noradrenaline exceeds 0.4 μg/kg/min. *Phenylephrine*—pure vasoconstrictors are used when hypotension associated with tachycardia. Mean arterial pressure (MAP) mostly correlating to central hemodynamics but does not correlate peripheral tissue perfusion. There is compensatory peripheral vasoconstriction mechanism due to which compromised tissue perfusion occurs. Inotropes are indicated when feature of tissue hypoperfusion despite adequate fluid and target

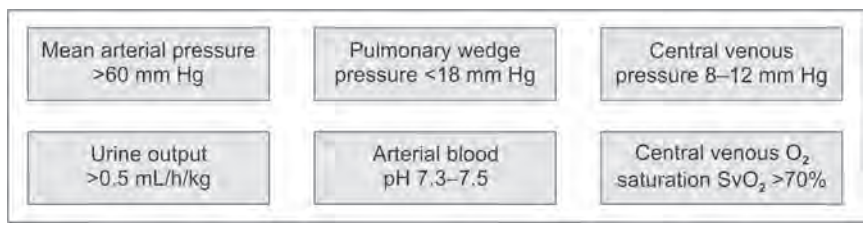
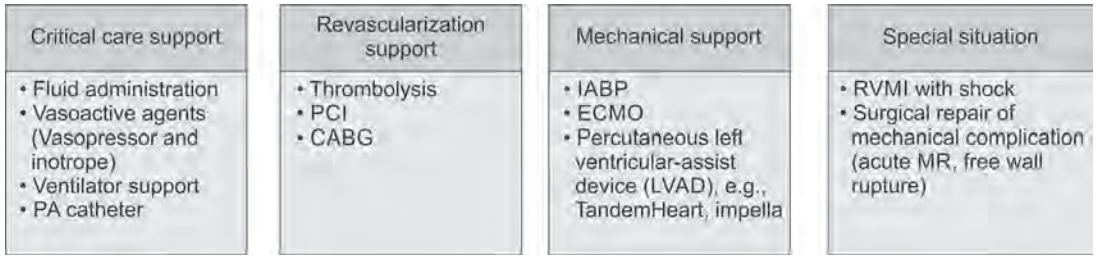


FIG. 1: Therapeutic target for hemodynamic parameters.



(CABG: coronary artery bypass grafting; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; RVMI: right ventricular myocardial infarction; PCI: primary coronary intervention; PA: pulmonary artery)

FIG. 2: Modalities of treatment in cardiogenic shock.

TABLE 5: Vasopressors and inotropes for cardiogenic shock.

Medication	*Vasopressor/Inotropes*	*Use in cardiogenic shock*
Phenylephrine	Vasopressors	• Increased afterload of systemic and pulmonary circulations • Generally, not used in CS, useful in LVOTO to decrease gradient across outflow tract
Vasopressin	Vasopressors	• Increased afterload of systemic but not pulmonary circulation • Useful in isolated RV disease or vasoplegia with tachycardia
Norepinephrine	Vasopressors mild inotropes	First-line vasopressor for CS in ED
Epinephrine	Inopressor	• Increased risk of arrhythmias • Recommended for symptomatic bradycardia or refractory hypotension
Dopamine	Inopressor	• Increased risk of arrhythmias • Only used in symptomatic bradycardia
Dobutamine	Inodilator	• First-line inotrope for CS in ED • Fast-acting, easily titratable
Milrinone	Inodilator	• Second-line agent, slower-acting with 2.5 h half-life • Renally cleared, can accumulate in AKI or CKD less arrhythmogenic than other inotropes, better pulmonary vasodilation

(AKI: acute kidney injury; CKD: chronic kidney disease; CS: cardiogenic shock; ED: emergency department; LVOTO: left ventricular outflow tract obstruction)

MAP. *Dobutamine*—inotrope of choice in cardiogenic shock. Started with the dose of 2–20 μg/kg/min when systolic BP > 90 mm Hg. It improves the peripheral perfusion but produces hypotension and tachyarrhythmia due to mild systemic vasodilatory and positive chronotropic effect. *Milrinone*—the main use of milrinone is in decreasing the RV load in advanced nonischemic cardiomyopathies. Milrinone provides inotropic with less chronotropic and less arrhythmic effects. *Dopamine and adrenaline* are less commonly used in cardiogenic shock due to their arrhythmic and undesirable hemodynamic results.

This is very important that emergency physician should be aware about characteristics of vasopressors and inotropes (**Table 5**) and also be able to select the appropriate vasopressors and inotropes in specific situation (**Flowchart 2**).

Positive Pressure Ventilation Support

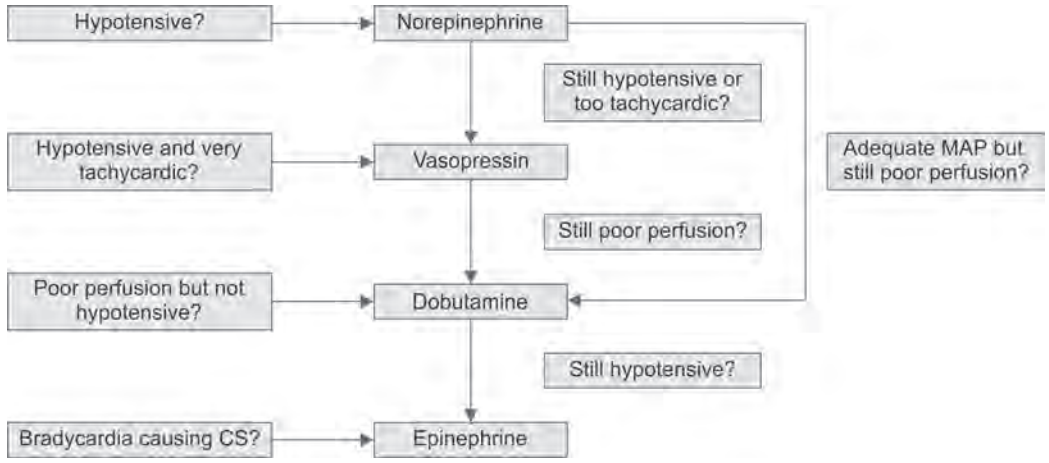
Positive pressure ventilation (PPV) provides different effects for the RV and the LV, as shown in **Figure 3**. In cases of LV failure leading to cardiogenic shock, PPV may unload the LV by decreasing preload and afterload. However, if patients are preload dependent, or in RV failure, intubation may precipitate hemodynamic collapse. For patients in overt shock, intubation may be warranted to minimize work of breathing and oxygen consumption by respiratory muscles**.** Mechanical ventilation improves patient comfort, reduces stress, fatigue and correct acidosis, and hypoxia and improves tissue perfusion. Intensive care support summarized as VIP mnemonic *V* (ventilation), *I* (infuse-fluid therapy), *P* (pump-vasoactive drugs).

Pulmonary Artery Catheterization

Pulmonary artery catheter (PAC) insertion may be helpful in monitoring of patient with cardiogenic shock. It gives information about hemodynamic parameters such as right and left ventricular filling pressures, systemic and pulmonary vascular resistance, right ventricular ejection fraction, and SvO_2 saturation, and thermodilution derived cardiac out. PAC associated with various periprocedural complications so should be performed by expert. Appropriate interpretation of data of PAC is helpful in differentiating the different type of shock and guide appropriate management.

REVASCULARIZATION SUPPORT

Myocardial infarction is important cause of cardiogenic shock. Early revascularization (PCI or CABG) is the lifesaving intervention in cardiogenic shock management. Urgent coronary angiography with support of IABP and PTCA or CABG is recommended in patient with cardiogenic shock due to left ventricular failure complication acute MI or new left bundle branch block (LBBB) MI.



FLOWCHART 2: Algorithm for selecting vasopressors and inotropes in cardiogenic shock in the emergency department.

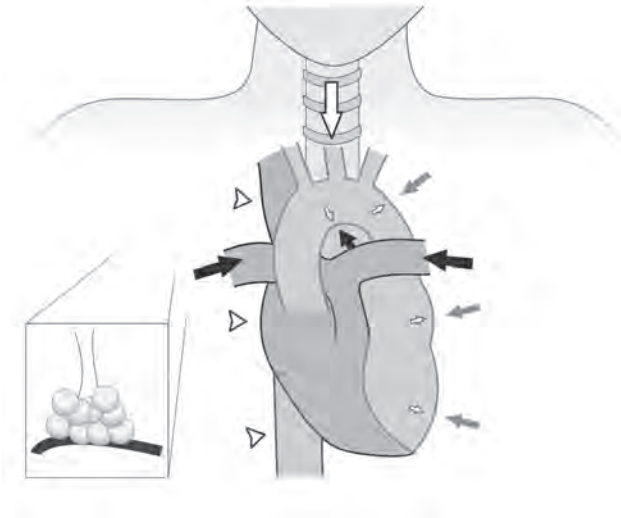


FIG. 3: Effects of positive pressure ventilation (PPV) can vary. PPV decreases preload (open black arrowheads) for the interior vena cava, superior vena cava, and right heart. PPV can also lead to alveolar distention, crimping capillaries (inset), thereby increasing RV afterload, as indicated by the large black arrows. PPV can also decrease afterload on the LV (black arrows) by decreasing the transmural gradient (small gray arrows).

TABLE 6: Fibrinolytic agents and doses.

Streptokinase	• 1.5 million IU • Infused over 1 h in 45 mL NaCl
Alteplase	• 15 mg loading dose followed by 50 mg over 30 min and 35 mg over next 1 h • Total duration of infusion 90 min and concurrent use of heparin 0.75 mg/kg not to exceed 50 mg over 30 min and 0.50 mg/kg and not to exceed 35 mg over next 1 h
Reteplase	• Given as double bolus by 10 U + 10 U (no infusion) • 10 U bolus over 2 min wait for 30 min and repeat 10 U over 2 min and concurrent use of heparin
Tenecteplase	30–50 mg single weight-based bolus over 5–10 sec and concurrent use of heparin

Fibrinolytic Therapy

Fibrinolytic therapy started if presentation of early or compensatory stage of cardiogenic shock with STEMI to hospital <3 hours, no contraindications to therapy and PCI intervention facility not available. Concurrent use of IABP is also beneficial. Currently available fibrinolytic agents are streptokinase, alteplase, reteplase, and tenecteplase. *Streptokinase*—1.5 million IU (infused over 1 h in 45 mL NaCl). *Alteplase*—15 mg loading dose followed by 50 mg over 30 minutes and 35 mg over next 1 hour (total duration of infusion 90 min) and concurrent use of heparin (0.75 mg/kg not to exceed 50 mg over 30 min and 0.50 mg/kg and not to exceed 35 mg over next 1 h). *Reteplase*—given as double bolus by 10 U + 10 U (no infusion), 10 U bolus over 2 minutes wait for 30 minutes and repeat 10 U over 2 minutes and concurrent use of heparin. *Tenecteplase*—30–50 mg single weight-based bolus over 5–10 s and concurrent use of heparin. Other fibrinolytic agents though less used, e.g., urokinase, prourokinase, and anistreplase are also available. Fibrinolytic agents and doses are summarized in **Table 6**.

Percutaneous Transluminal Coronary Angioplasty

Various studies show decrease in mortality rates if successful reperfusion done in cardiogenic shock caused by AMI. PTCA is especially helpful as reperfusion therapy in single or double vessels coronary artery disease.

Coronary Artery Bypass Grafting

Patient with cardiogenic shock with triple vessel disease or left main coronary artery disease, CABG provides favorable outcome.

MECHANICAL SUPPORT

Mechanical support is ultimate approach to improve hemodynamic parameters. Nowadays, a number of devices are available with different mechanism of action and effectiveness.

These devices provide cardiac chambers (right left biventricular) support. IABPs, extracorporeal membrane oxygenation (ECMO), and percutaneous left ventricular assist device (LVAD) are available for mechanical support. These devices are indicated when all ICU measures fail to provide adequate tissue and organ perfusion and risk of multiorgan failure develops. 30-day mortality was not reduced by use of IABP in cardiogenic shock complicating MI according to IABP-SHOCK II trials. No reduction of short-term mortality is noted by use of IABP and Impella pump and TandemHeart device are not found superior to IABP according to few randomized studies. Thus, further improvement in mechanical device is required which provides not only hemodynamic stabilization but also improves patient outcome.

Intra-aortic Balloon Pump

Several physiological parameters are improved with the use of IABP. Use of IABP commonly used to improve hemodynamic parameters. IABP provides reduction in myocardial oxygen demand, pulmonary wedge pressure, LV afterload along with Improvement in coronary blood flow, and cardiac output (**Figs. 4A to C**).

Indications

Various indications of IABP are summarized in **Table 7**.

Selection of Balloon and Mechanism of Action

For optimal hemodynamics effect, balloon should be deflated just before LV ejection (at QRS complex). Ideal balloon function in 1:3 sequence where every third ventricular beat is augmented by IABP. If heart rate >140 switch to 1:2 sequence until rate slow. Hemodynamic effect of IABP depends on the balloon volume, heart rate and rhythm, and systemic vascular resistance. Selection of balloon size (**Table 8**) in specific patient is helpful in achieving maximum output.

Complication of Intra-aortic Balloon Pump

Be aware of presence of pulse in left arm, indicate tip of balloon not obstructing subclavian orifice, and subclavian flow is not occluding. IABP associated with various complications such as arterial wall trauma, limb ischemia, thrombus dislodgement, thrombocytopenia hemolysis, hemorrhage, balloon rupture or leak, and infection.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation consists of blood pump, the heat exchanger, and the oxygenator. Indicated in severe hypercapnia with pH < 7.20, PaO_2:FiO_2 < 50–1,000 mm Hg, alveolar—arterial oxygen gradient >600 mm Hg, transpulmonary shunt >30%. Main challenges in ECMO are patient selection system logistic and complication such as limb ischemia bleeding complications. Currently ECMO is used as bridge therapy to heart transplantation.

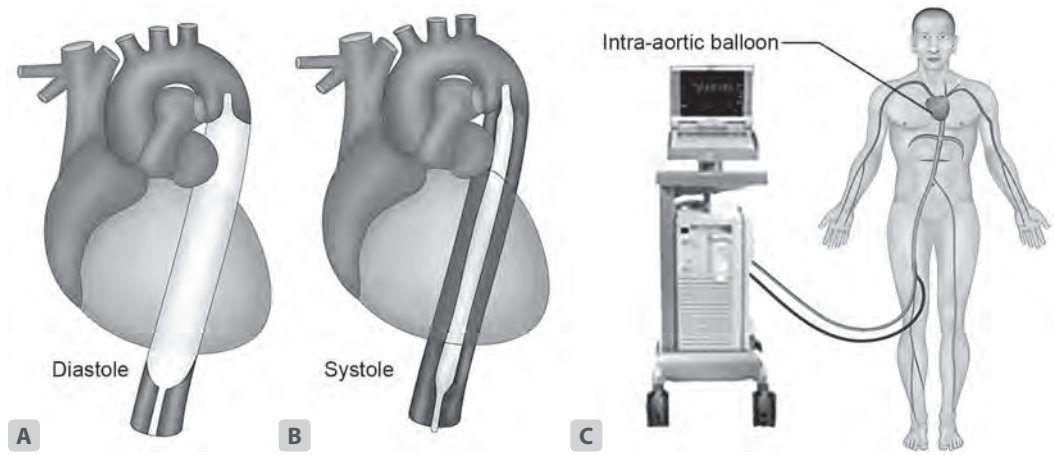
TABLE 7: Indication of IABP in various conditions apart from cardiogenic shock.

Medical	*Surgical*	*Others*
• Cardiogenic shock • Acute anterior wall MI • Complications of MI like acute MR VSR • High-risk angioplasty • Ventricular arrhythmia secondary to ischemia	• High-risk cardiac patient • Bridge to CABG and heart transplant • Postoperative low cardiac output • Weaning from bypass open heart surgery	• Drug-induced heart failure • Myocardial contusion aortic stenosis
IABP contraindicated in acute aortic dissection, aortic regurgitation, chronic end-stage heart disease, and irreversible brain damage		

(CABG: coronary artery bypass grafting; IABP: intra-aortic balloon pump; MI: myocardial infarction; MR: mitral regurgitation; VSR: ventricular septal rupture)

TABLE 8: Selection of IABP balloon size.

Height of patient	<5′	5′–5′4″	5′4″–6′
Balloon volume	25 mL	34 mL	40 mL
Length	165 mm	221 mm	258 mm
Diameter	15 mm	15 mm	15 mm
Catheter size	7.5 F	7.5 F	7.5 F



FIGS. 4A TO C: Intra-aortic balloon pump (IABP) and mechanism of action: Balloon inflated in diastole with closure of aortic valve. Balloon remains inflated till ventricular systole inflation of balloon displaces the blood toward aorta and coronaries and promotes coronary perfusion and blood flow. Collapse of balloon decreases the LV work by reducing the resistance of LV ejection.

Percutaneous Left Ventricular Assist Device

Currently available percutaneous LVADs are TandemHeart and Impella. They are inserted percutaneously through femoral artery and provide pulsatile support via pump. LVADs provide higher cardiac index, higher MAP, and lower pulmonary wedge pressure. There are no 30 days survival benefits by using LVAD. They are used in refractory cardiogenic shock as bridging strategies to heart transplantation.

Heart Transplantation

Heart transplantation is particularly indicated in patient who required biventricular mechanical circulatory support and is the only hope for long-term survival. LVADs are used in patient refractory to treatment and as bridging therapy to heart transplantation. All currently used durable mechanical circulatory support devices are continuous-flow devices, include an inflow cannula placed directly into the LV cavity and an outflow graft sutured into the ascending aorta, and can provide hemodynamic support with flow rates ranging from 5 to 10 L/min. In view of few organ availability, unpredictable donor availability, and various logistic factor, heart transplant is unreliable primary therapy in cardiogenic shock.

SPECIAL SITUATION

Right Ventricular Myocardial Infarction with Shock

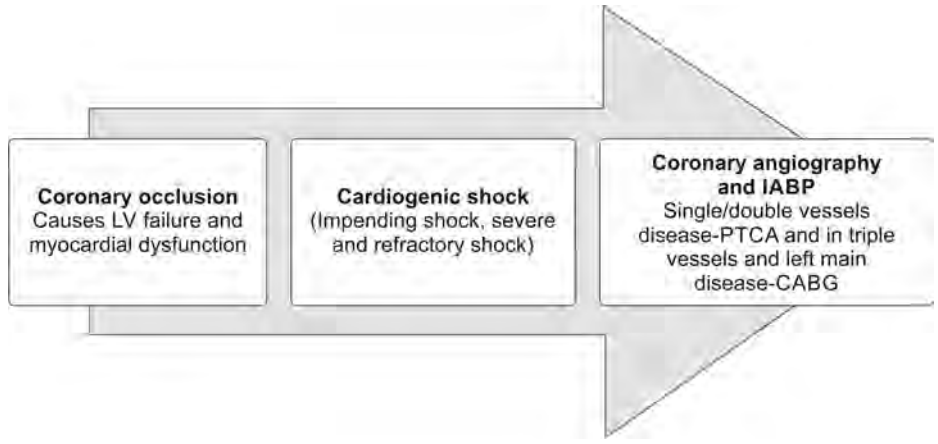
Right ventricular myocardial infarction is suspected in all patient with inferior wall MI with shock. RVMI mostly associated with inferior and posterior wall MI and mortality is also high. Clinically triad of raised JVP, clear lung fields in the presence of inferior or posterior MI, present ECG shows ST segment elevation in V_3R and V_4R echocardiography also helpful in diagnosis. Therapeutic approach is quite different from left ventricular failure. Maintain right ventricular preload with intravenous fluid, avoid use of nitrates and diuretics, and maintain A-V synchrony with the help of pacing in case of high degree of heart block. Use of pharmacological circulatory support revascularization support, mechanical support is the mainstay of therapy (**Table 9**).

Mechanical Complication of Acute MI (Acute Mitral Regurgitation, Papillary Muscle Rupture, Ventricular Septal Rupture, and Free Wall Rupture)

Acute mitral regurgitation is usually associated with inferior wall MI and ischemia of posterior papillary muscle. Acute MR develops within 2–7 days after the myocardial infarction and clinically present as pulmonary edema hypotension and cardiogenic shock. Echocardiography is extremely useful. All therapeutic measures should be implemented as described above. However, definitive therapy is surgical valve repair or replacement. Patient with ventricular septal rupture present with severe or refractory cardiogenic shock. Characteristic pansystolic murmur and parasternal thrill present on examination and echocardiography is diagnostic modality of choice. Early use of circulatory and mechanical support followed by surgical repair is definitive therapy.

TABLE 9: Management of cardiogenic shock from right heart failure.

Parameters	*Pathophysiology*	*Management*
Recognition	• Recognizing is often challenging such as RV infarct, or acute-on-chronic, such as with pulmonary hypertension	• Management complex • Consult, usually pulmonologist or cardiologist, early in course
Preload	• Acute RV dysfunction can be preload dependent • May be volume depleted, based on history (e.g., recent gastrointestinal illness) • Pulmonary hypertension patients often chronically overloaded because of neurohormonal upregulation • Volume status assessment challenging because of chronic adaptations	• If patient needs volume from acute RV dysfunction or by history, provide in small volume • Reassess frequently with vital signs, echocardiography, markers, or perfusion • In cases of volume overload, may benefit from diuresis • Often benefit from PA line placement
Contractility	• Hypotension can lead to decreased coronary perfusion, leading to worse contractility • Cannot tolerate arrhythmias	• Add early vasopressors to maintain coronary perfusion • Add inotropes for RV support • Manage arrhythmias aggressively
Afterload	• Hypoxemic vasoconstriction, acidemia increase RV afterload • Positive pressure ventilation can increase afterload • Inhaled pulmonary vasodilators can dilate pulmonary vasculature	• Avoid hypoxia and hypercapnia • Support oxygenation with high-flow nasal cannula • Judicious noninvasive ventilation • Avoid intubation if possible, • Prevent hypotension, hypoventilation/hyperventilation with intubation • Consider inhaled epoprostenol or nitric oxide


Coronary occlusion
Causes LV failure and myocardial dysfunction
Cardiogenic shock
(Impending shock, severe and refractory shock)
Coronary angiography and IABP
Single/double vessels disease-PTCA and in triple vessels and left main disease-CABG

(CABG: coronary artery bypass grafting; IABP: intra-aortic balloon pump; LV: left ventricular; PTCA: percutaneous transluminal coronary angioplasty)

FIG. 5: Summary approach to cardiogenic shock.

REVERSIBLE MYOCARDIAL DYSFUNCTION (MYOCARDITIS, SEPSIS-INDUCED MYOCARDIAL DYSFUNCTION)

Few reversible causes of myocardial dysfunctions such as sepsis-induced myocardial dysfunction, inflammatory myocarditis, and myocardial dysfunction after cardiopulmonary bypass. Inflammatory cytokines [tumor necrosis factor-alpha and interleukin-1 (TNF-α and IL-1)] play important role in sepsis and myocarditis. Combination of inotropic support, IABP required for days to week to allow sufficient time for recovery. If these measures fail, mechanical support with LVAD can be considered.

SUMMARY

Left ventricular failure and myocardial dysfunction occur due to coronary occlusion. Cardiogenic shock can be present as different stages, e.g., impending shock to severe and refractory shock. Cardiogenic shock develops due to multiple causes such as myocardial infarction cardiomyopathies and myocarditis. Restoration of effective tissue perfusion and cellular metabolism is the ultimate goal for the prescribed therapy. Early circulatory support (IABP) and revascularization (PTCA or CABG) are the mainstay of treatment and also improve the survival in cardiogenic shock complication of AMI (**Fig. 5)**.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Acute Heart Failure

Devendra Richhariya

INTRODUCTION

Acute heart failure (AHF) is one of the most common causes of emergency admissions in India and the incidence is steadily rising. Increasing prevalence of coronary artery disease, greater survival after myocardial infarction and rising incidence of diabetes mellitus in our country are some of the important factors. Of late, there has been a greater awareness of heart failure with preserved ejection fraction where left ventricular ejection fraction (LVEF) is over 40%.

Quality of life and survival after heart failure have improved significantly for the last three decades. This has largely been due to understanding of the basic pathophysiology especially the role of neurohormonal activation, definitive interventional therapies, and support devices. New drugs on the horizon especially angiotensin receptor neprilysin inhibitor (ARNI) appear to be very promising and may yet to be the most significant advance in pharmacotherapy after angiotensin-converting enzyme (ACE) inhibitors. The readmission rate often AHF is still disturbingly high. This may be due to failure to uptitrate the doses and inadequate counseling regarding lifestyle modification. It is important to quickly triage these patients on presentation to the emergency ward to decide who requires or more aggressive approach to their disease. Such patients should be offered high tech solution to reduce mortality and morbidity.

Survivals of patients presenting with AHF have improved dramatically since 1980, the medical advances reflect understanding of the role of neurohormonal stimulation and antagonism, the physiology and evaluation of congestion leading to decompensation, and the indications for devices to avert sudden death and enhance synchrony.

PATHOPHYSIOLOGY

The key components of AHF are elevation of filling pressure and reduction of cardiac output which do not necessary occur together. Cardiac output is frequently reduced from normal but reaches critical levels only with patients with cardiogenic shock. In these patients, severe compromise of resting cardiac output and perfusion generally does not occur unless a patient has severe restrictive, infiltrative, or hypertrophic disease with very small left ventricular cavity or severe mitral regurgitation.

PRECIPITATING FACTORS

The most common cause of AHF is exacerbation of chronic heart failure. However, other important causes are accelerated hypertension, acute myocardial infarction, valvular disease, myocarditis, and renal failure. For patients with preexisting chronic heart failure, one should identify the precipitating factors and the status of fluid overload and perfusion. For patients with known coronary artery disease, new-onset ischemia is an important cause. Other common exacerbating factors are tachyarrhythmia, thyroid disease, anemia, infection, chronic kidney disease, chronic pulmonary disease, and pulmonary emboli. Excessive fluid and salt intake and coadministration of certain drugs are known to worsen heart failure and should also be enquired into. Common precipitating factors frequently lead to heart failure are shown in **Box 1**.

CLASSIFICATION

The European Society of Cardiology has classified AHF (**Box 2**) in various clinical syndromes and their presenting features may be overlapping but for specific therapeutic approach classification is important. Since the features are overlapping and due to heterogenicity of patient population, it is important to divide the patient with AHF on the basis of initial systolic blood pressure (important prognostic marker) and distinct clinical approach for management can be implemented for each group of the patient.

- Acute heart failure with hypertension (systolic blood pressure > 140 mm Hg)

BOX 1: Precipitating factors for acute heart failure.

- Medication noncompliance
- Dietary noncompliance
- Acute coronary syndrome
- Arrhythmias
- Acute valve dysfunction
- Anemia
- Infections

BOX 2: Classification of acute heart failure.

- Acute decompensated heart failure
- Hypertensive acute heart failure
- Pulmonary edema
- Cardiogenic shock
- Right heart failure
- Acute coronary syndrome complicated by acute heart failure

Source: Dickstein K, Cohen-Solal A, Filippatos G, McMurray JV, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute heart failure 2008. Eur J Heart Fail. 2008;10:968.

- Acute heat failure with hypotension (systolic blood pressure < 90 mm Hg)
- Acute heart failure with normal blood pressure (systolic blood pressure 90–140 mm Hg)

CLINICAL FEATURES

Dyspnea is the most common complaint due to AHF. Additional features such as orthopnea paroxysmal nocturnal dyspnea and peripheral edema fatigue weakness are also present. Depending on cause, AHF condition may present with either hypertension or hypotension. Usually patient is tachycardic but due to medications (β-blockers) or high-degree atrioventricular (AV) block, bradycardia may be present. Clinical estimation of perfusion can be made by temperature of extremities, examination of pulses and sensorium, and presence of cyanosis. A good history and a thorough physical examination can yield important information. Orthopnea, nocturnal cough, and progressive effort intolerance are indicative of elevated filling pressure in this setting. Raised jugular venous pressure (JVP), hepatojugular reflux, pulmonary edema, hepatomegaly and bilateral crepitation third heart sound is usually present.

DIAGNOSIS

Diagnosing AHF is critical step as patient present with signs and symptoms, and need to differentiate AHF from other overlapping conditions. Electrocardiogram (ECG), chest X-ray, elevated natriuretic peptides, and echocardiography are the most important initial investigations. In the absence of pulmonary edema, arterial desaturation may or may not be present. Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) used in emergency department for patient with undifferentiated dyspnea. BNP has both diagnostic and prognostic role and released from myocytes in response to volume overload. In doubtful case, BNP < 100 pg/mL rules out heart failure and >400 pg/mL strongly suggests heart failure, though these are only guide and NT-proBNP have similar role but different half-life and cut-off value than BNP.

EMERGENCY DEPARTMENT TREATMENT

Most of the time, patient with AHF present in emergency department in very distress state and needs rapid initiation of treatment. Obtain intravenous access. Cardiac monitoring, pulse oximetry, and oxygen supplementation should be started immediately. Appropriate laboratory studies should be performed. *Early initiation of noninvasive positive pressure ventilation (NIPPV) and appropriate pharmacological therapy are the basics of AHF therapy in emergency department.*

- Noninvasive positive pressure ventilation reduces the afterload (by reducing transmural pressure of entire left ventricle)
- Noninvasive positive pressure ventilation reduces preload (by increasing intrathoracic pressure and reducing venous return)
- Reducing both preload and afterload significantly benefits the acutely failing heart
- Finally, by these mechanisms, NIPPV reduces work of breathing and improves oxygenation.
- Bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) have similar benefits, start with initial setting of iPAP/ePAP—10/5 mm Hg for BiPAP and 10 mm Hg for CPAP.

Hemodynamic Monitoring

In patients with AHF, hemodynamic monitoring may provide valuable information and guide titration of pressor agents and the need for mechanical circulatory support. Hemodynamic monitoring is strongly recommended to help reevaluate optimization of filling pressures and systematic vascular resistance while oral agents are adjusted during weaning from inotropic infusions in patients who appear to be dependent on them. It is not recommended as a routine practice, if a patient is responding to the usual treatment. In a carefully selected patient, a good beside echocardiography can yield useful information regarding cardiac hemodynamic and can be used repeatedly. As discussed in classification section, the patient with AHF can be categorized into three subgroups on the basis of systolic blood pressure on presentation in emergency department. Further clinical approach is based on hypotensive/hypertensive/normotensive AHF (**Fig. 1**).

High-risk features: Poor response to therapy, inadequate urine output, uncontrolled BP (SBP < 90/>200 mm Hg), elevated troponin, tachycardia, high respiratory rate, and high urea creatine hypoxia in spite of early NIPPV.

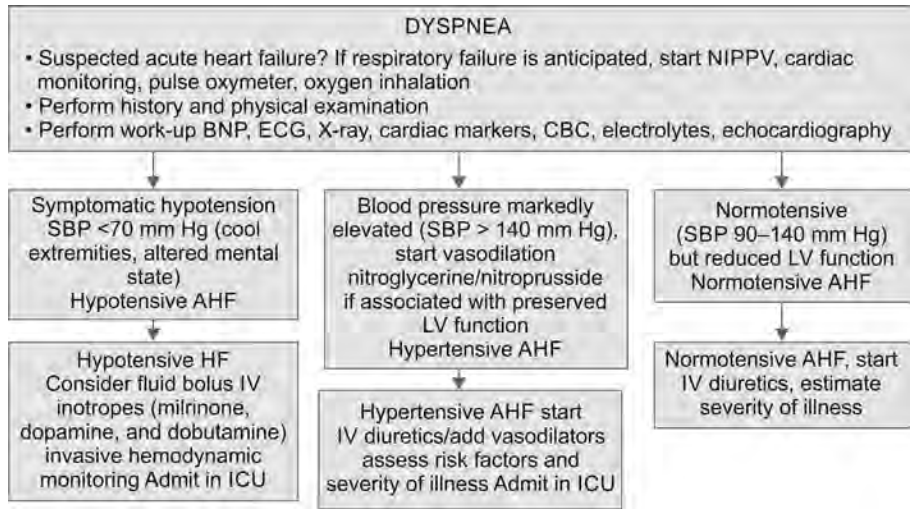
Nonhigh-risk features: Good response to therapy, adequate urine output, controlled blood pressure, and negative troponin.

PHARMACOLOGIC THERAPY

Diuretics, IV vasodilators, and IV inotropes are the major drugs used during acute management of decompensated heart failure.

Diuretics

Loop diuretic is generally considered as the first-line therapy. They are effective and well tolerated. Rapid IV administration of furosemide may rarely cause ototoxicity. A common problem is under dosing with these drugs. When glomerular filtration rate (GFR) is reduced, higher doses must be used because they are secreted in the proximal tubule and act from the luminal side on the loop of Henle. Thiazides and spironolactone are weaker diuretics and may be ineffective when GFR is below 40 mL. In patients with more advanced heart failure, distal tubule reabsorption may limit the efficacy of loop diuretics. In this situation, a *combination of metolazone and loop*



(AHF: acute heart failure; BNP: brain natriuretic peptide; CBC: complete blood cell; ECG: electrocardiogram; IV: intravenous; ICU: intensive care unit; LV: left ventricular; SBP: systolic blood pressure)

FIG. 1: Approach to acute heart failure.

diuretics is very effective. However, potassium levels need to be watched for carefully with this combination as hypokalemia may occur and can precipitate ventricular arrhythmias. Muscle aches are common with brisk diuresis. Most patients with heart failure receive potassium-sparing ACE inhibitors and frequently spironolactone also. In patients with diabetes and renal dysfunction, hyperkalemia can result in this situation. Potassium-rich fruits and salt substitutes containing potassium are often given to these patients and can further aggravate hyperkalemia. Metabolic alkalosis, increased uric acid, hyponatremia, and neurohormonal activation are the other side effects of potent diuretics and need to be watched for.

In certain patients when IV diuretics have suboptimal effect, IV infusion of loop diuretics are beneficial. Ultrafiltration and other form of dialysis may be useful in patients with inadequate diuresis and are very useful in patients who have difficulty achieving diuresis with conventional medications.

Intravenous Vasodilators

After diuretics, IV vasodilator is the most useful medicine for acute management of heart failure. They reduce filling pressures, increase cardiac output, and reduce mitral regurgitation, resulting in immediate improvement of symptoms. When used carefully, they generally do not increase heart rate or result in arrhythmias unless there is severe hypotension.

- *Nitroglycerine*: This is one of the safest and most widely used agents in AHF for both acute ischemia and heart failure due to ischemia or vasoconstriction. The individual responses are highly variable and thus require careful monitoring. *Nitroglycerine indicated in features of pulmonary congestion/edema, BP > 90 mm Hg. Start with 10–20 μg/min and increase to 200 μg/min*. Headache and tachycardia may occur in some patients and tolerance on continuous use.
- *Nitroprusside*: This was the first vasodilator to be used in heart failure and is very effective in patients with severe hypertension with increased systemic vascular resistance. Nitroprusside hypertensive HF congestion/edema BP > 90 mm Hg. Start with 0.3 μg/kg/min and increase to 5 μg/kg/min. The onset and offset of action are very rapid with a half-life of approximately 2 minutes. Once filling pressures are nearly normal, further vasodilator may not be necessary. Its major limitation is hypotension, gastrointestinal and central nervous system (CNS) side effects from cyanide toxicity which are more likely to occur with impaired hepatic perfusion or hepatic dysfunction and in patients receiving large doses for >48 hours. Reduction and cessation of nitroprusside are generally enough to treat this complication.
- *Nesiritide*: It is a recombinant form of BNP and lowers filling pressures and improves symptoms in decompensated heart failure. Nesiritide should be started with features of pulmonary congestion/edema BP > 90 mm Hg, bolus 2 μg/kg + infusion 0.015–0.03 μg/kg/min. Hypotension is major concern so blood pressure needs to be monitored because it has a longer half-life of 18 minutes. Bradycardia and headache may occur occasionally. It potentiates the effect of concomitant diuretics. This effect may persist after infusion is stopped. It has been shown to be effective for decreasing filling pressures and relieving symptoms.
- *Angiotensin receptor neprilysin*: A recent welcome addition is a new drug called angiotensin receptor and neprilysin inhibitor. This is an oral drug which upon ingestion breaks down into valsartan [angiotensin receptor blocker (ARB)] and sacubitril, which inhibits neprilysin. Neprilysin is a natural enzyme which results in breakdown of natriuretic peptides. Thus, the administration of this drug results in elevated levels of natriuretic peptides due to inhibition of their breakdown and ARB valsartan. In recent trials, this drug has shown dramatic results in reducing mortality and morbidity in chronic heart failure and currently a trial is under way to assess its efficacy in AHF.

Intravenous Inotropic Agents

Though widely used, inotropic agents pose their own problems. They are associated with more tachyarrhythmias and ischemic events. Also, the efficacy of diuretics and tolerability of ACE inhibitors may be overestimated in the presence of inotropic stimulation. This may prolong hospitalization or increase the chances of early rehospitalization. The appropriate use of

inotropic agents therefore is in a situation when they provide benefits not offered by initial therapies. They should be used until the cause of hypotension and deranged hemodynamic profile has been elucidated till diuresis becomes effective in patients with refractory heart failure and till renal, lung, or liver functions have improved significantly. Tapering of inotropes at times becomes difficult due to hypotension and in this situation temporary or permanent discontinuation of β-blockers and ACE inhibitors in severely compromised patients may help. Despite all these limitations, they are still extremely useful, especially in situations where despite adequate therapy congestion or hypotension is persistent.

- *Dobutamine*: This is the most commonly used inotropic agent. It stimulates β-adrenergic receptor with little effect on alpha-adrenergic receptors so that contractility is increased with peripheral and pulmonary vasodilation. Cardiac output is increased, filling pressures are reduced, and diuresis is potentiated. However, it causes tachycardia, especially in patients with atrial fibrillation and also results in increased ventricular arrhythmias and ischemia. When indicated the lowest dose possible should be used. Increase in diuresis and improvement in renal function can be seen at 1–2 μg/kg/min. Treatment for more severe hypoperfusion requires higher doses and tachyphylaxis is generally seen. Maximum doses are usually 10–15 μg/kg/min. Occasionally, its prolonged administration is accompanied by increased eosinophil count, skin rash, and eosinophilic myocarditis.
- *Dopamine*: Dopamine stimulates β-receptors, α-receptors, and dopaminergic receptors that cause vasodilation in renal and peripheral vasculature. At doses up to 5 μg/kg/min, it is predominantly vasodilatory. After 5 μg/kg/min, α-receptor stimulation dominates, resulting is vasoconstriction. Dopamine also causes release of norepinephrine, resulting in independent stimulation of α- and β-receptors. In low doses, its beneficial effects are clinically similar to dobutamine with similar adverse effects. It is usually indicated in rapidly changing situations in which modest inotropy and vasodilation may be adequate but further increase in pressure is required. In this situation, one can start with 4 μg/kg/min and wean off when a dose of 3 μg/kg/min is reached. There is no significant advantage of combining dobutamine and dopamine for enhanced renal function in heart failure and it increases the risk of arrhythmias and ischemia.
- *Milrinone*: Milrinone increases cyclic adenosine monophosphate (AMP) by inhibiting its breakdown rather than increasing its production through stimulation of β-receptor. It acts synergistically with β-agent stimulating to achieve further increase in cardiac output than either agent alone. These are more effective than β-adrenergic agent, when β-blockers have already been given. The degree to which cardiac output increases and systemic resistance decreases is variable and therefore some patients may exhibit predominant vasodilator. Thus, there is a significant incidence of hypotension with milrinone unlike dobutamine. It results in lesser tachycardia than dopamine and dobutamine but has a similar incidence of arrhythmias and ischemia. It has a longer half-life of 6 hours unlike dopamine and dobutamine which are in minutes. It is generally started as an infusion at a dose of 0.5 μg/kg/min and titrated up to a maximum of .75 μg/kg/min. It is excreted renally and therefore in renal dysfunction dose adjustment is needed. Its prolonged use can increase its half-life to up to 18 hours. Therefore, after discontinuing, its infusion at least 48 hours of observation is required.
- *Epinephrine and norepinephrine*: These are full β-receptor agonists, which increase contractility, heart rate and peripheral resistance while promoting arrhythmias and ischemia. They can provide significant additional short-term inotropic and blood pressure support over minutes to hours before other therapies. Kidney failure, hepatic failure, and gangrene can result from the use of these agents. When fatal hypotension is imminent, they are used at a starting dose of 0.1 μg/min. This can be preceded by a stat dose of 0.25 mg of epinephrine to maintain survival for a brief period. Boluses of calcium may be helpful particularly in the presence of conditions that may lower serum calcium such as transfusions, dialysis, and cardiopulmonary bypass. They are highly arrhythmogenic and may exaggerate ongoing myocardial necrosis.
- *Vasopressin:* It is used to potentiate the use of catecholamines in patients who remain severely hypotensive despite high dose pressor support. It can be used for hours to days in doses of 0.052–0.1 unit/min. When added to norepinephrine, it can result in about 30 mm Hg increase in systolic blood pressure. It is sometimes associated with profound water diuresis. As with other vasoconstrictors, it can result in ischemic injury and necrosis of organs and limbs.

MECHANICAL ASSISTANCE

In a small minority of patients with rapid deteriorating hemodynamic which threatens their survival, a quick, aggressive support for stabilization or for definitive intervention is required. The goal in these cases is stabilization of patient to a point at which definitive intervention or surgical therapy can be offered or spontaneous recovery occurs. It is important to identify these patients quickly the evidence of this situation usually includes more than one of the following:

- Systolic blood pressure below 75 mm Hg
- Cardiac index below 1.5–1.8 L/min/m^2
- Along with systemic acidosis with positive lactate levels, anuria, obtundation, and shock with rise of transaminase level and altered sensorium
- Escalation of therapy would include more intense inotropic support with epinephrine at escalating doses. Vasopressin is frequently added as well, as discussed previously. For the patients with otherwise robust health, consultation regarding surgical options should be obtained immediately.

Intra-aortic Balloon Pump

The role of intra-aortic balloon pump (IABP) for intermediate stabilization has been well established for cardiogenic shock caused by acute myocardial infarction. The pump is usually inserted while other therapies are underway by the bedside or in the cardiac catheterization suite. When it can be performed expeditiously, balloon pump insertion seems reasonable for other cases of cardiogenic shock with underlying coronary artery disease. For cardiogenic shock of other causes, its role is less clear, and plans for insertion should not detract from progress to more definitive intervention. Some experts advocate its use for stabilization of medical therapy and anesthesia regardless of cause, whereas others believe that

it offers little benefit for patients without epicardial coronary artery disease and moreover, increases the risk of vascular and infectious complications.

Extracorporeal Membrane Oxygenator and LV-assist Devices

These are available in some specialized centers used judiciously; they are lifesaving as a bridge to recovery, surgery, or heart transplant.

DISPOSITION

Postdischarge mortality and morbidity is high in patient with AHF. In the absence of definitive guidelines whom to discharge safely, various factors other than clinical status should be taken in account like their socioeconomic and understanding about health. High-risk features or nonhigh-risk features described earlier play important role in deciding the safe discharge of patient after therapy. So patient can be discharged, if high-risk features are absent, precipitants of AHF are identified and adequately treated, baseline parameters have been achieved, follow-up discharged plan is in place, and condition is low risk in view of clinician.

SUMMARY

Acute heart failure is one of the common presentations in emergency department, usually critically ill and needs rapid initiation of therapy. In contrast to traditional teaching, not all patients are with volume overload. Clinical approach is largely based on hypertensive, hypotensive, and normotensive classification. NIPPV diuretics vasodilators and inotropic support (in hypotensive AHF) are the mainstay of the therapy. Mechanical support [IABP and extracorporeal membrane oxygenator (ECMO)] not used as routine therapy.

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68 CHAPTER

Cardiac Arrhythmias: Identification and Management

Ives Hubloue, Jamal Yusuf

INTRODUCTION

Cardiac arrhythmias or dysrhythmias are a group of abnormalities of the heart rate and or rhythm originating from abnormalities in the electric conduction system. They can occur in adults (most common) as well as in children. Most of the arrhythmias are harmless but some of them can cause serious complications (e.g., stroke) and/or life-threatening events such as sudden cardiac death. Arrhythmias can be divided in two main groups—(1) Bradycardias when the heart rate (corresponding to ventricular rate) is below 60 beats/min; and (2) Tachycardias when the heart rate exceeds 100 beats/min (in adults). In children, the normal range for the heart rate is different and depends on age. The choice of the treatment depends on various factors (life-threatening versus nonlife-threatening arrhythmia) and includes medications, medical procedures (e.g., defibrillation and pacemaker), and/or surgery.

BRADYARRHYTHMIAS

Etiology

Bradycardia could be due to either intrinsic or extrinsic causes or a combination of the two. The most important *intrinsic cause* is age-related degenerative disease. Other intrinsic causes include ischemia affecting sinus node or conduction tissue, infiltrative diseases (e.g., sarcoidosis and amyloidosis), collagen vascular diseases [e.g., systemic lupus erythematosus (SLE)], congenital heart diseases affecting sinus node or conduction system [e.g., congenitally corrected transposition of the great arteries (ccTGA)], infections (e.g., diphtheritic myocarditis), genetic cardiomyopathies, primary genetic conduction disorders, postcardiac surgery, and post-catheter ablation. *Extrinsic causes* include vagotonia due to physical conditioning or in vasovagal reflex or carotid sinus hypersensitivity. Rate-limiting drugs (e.g., beta-blockers), dyselectrolytemia (e.g., hyperkalemia), metabolic derangements (e.g., hypothyroidism), and raised intracranial pressure are some other extrinsic causes that need to be kept in mind while evaluating a case of bradycardia; the clinical and electrocardiogram (ECG) manifestation of each of these is unique enough to provide a hint to the alert mind and help guide further testing.

Symptoms

Symptoms of bradycardia may be subtle and persistent due to a chronic low-output state (easy fatigability, poor functional capacity, exertional dyspnea, cognitive impairment, and dizziness) or episodic and dramatic in intermittent bradycardias (syncope or presyncope associated with traumatic falls).

Classification

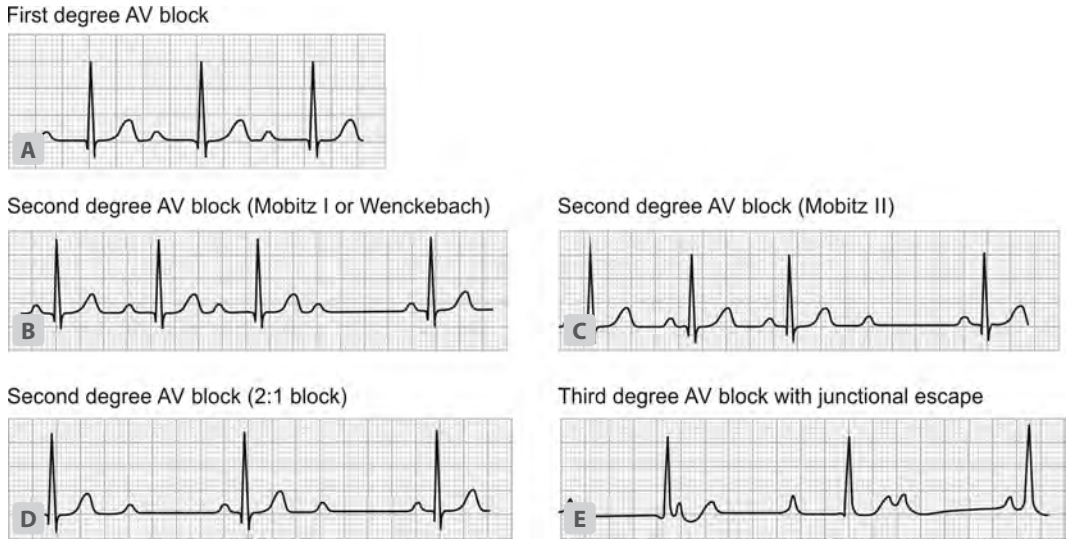
The most useful classification of bradyarrhythmia is based on the site of abnormality in impulse generation and/or propagation. Broadly, there are two groups:

1. Abnormalities of sinus node and intra-atrial conduction (includes abnormalities in impulse generation as well as conduction)
2. Abnormalities at level of AV node and below (includes abnormalities in impulse conduction only)

Abnormalities of Sinus Node and Intra-atrial Conduction (Includes Abnormalities in Impulse Generation as well as Conduction)

- *Sinus bradycardia*: In an adult, sinus bradycardia is diagnosed when there are <60 P-waves per minute on the ECG (or P-P interval of >1 second), with a regular P-P interval, every P-wave being followed by a QRS interval, PR interval between 0.12 and 0.2 seconds and a normal P-wave axis (upright in leads I and II, inverted in aVR). When the P-wave axis is consistently abnormal (beyond 0–75°), it generally indicates that there is sinus arrest and an alternative atrial pacemaker has taken over (atrial rhythm rather than sinus bradycardia). Persistent sinus bradycardia is frequently physiological (e.g., in well-conditioned athletes) or may be due to the effect of rate-limiting drugs such as beta-blockers. Conditions causing parasympathetic stimulation may lead to transient sinus bradycardia (as during a vasovagal episode). Symptomatic sinus bradycardia, when a part of sick sinus syndrome, may require a permanent pacemaker implant.

- *Sinus pause*: A sudden drop in the P-wave frequency indicates a sinus pause. This is to be differentiated from both, a sinus exit block and sinus arrhythmia. While sinus arrhythmia results in a gradual and cyclical change in P-P interval (frequently related to the respiratory cycle), sinus pauses are abrupt and noncyclical. On the other hand, a type II second degree sinoatrial (SA) exit block leads to an abrupt increase in the P-P interval, which is an exact multiple of the normal P-P interval; however, with superimposed sinus arrhythmia the differentiation between type II second degree SA exit block and a sinus pause may be difficult on the surface ECG. Practically though, this differentiation is not of much significance as the management of both would be on similar lines.
- *Sino-atrial exit block*: SA exit block refers to the delay in or inability of formed impulse to conduct to the right atrium. As the P-wave is generated on the surface ECG due to atrial depolarization, whether the impulse is not generated or whether it is generated but not conducted to the atrium, both manifest as dropped P waves. *SA exit block includes (**Figs. 1A** to **E**)*:
  - *First-degree SA exit block:* This is due to delayed conduction of the generated impulse to the right atrium; as no P wave is dropped it cannot be diagnosed from the surface ECG.
  - *Type I second degree SA exit block (Wenckebach):* This is due to progressive delay in impulse transmission to the atrium, finally resulting in a dropped impulse. It manifests on the surface ECG as progressive shortening of the P-P interval culminating in a dropped P wave, with the P-P interval preceding the dropped beat being the shortest. It is frequently mistaken for sinus arrhythmia.
  - *Type II second degree SA exit block:* This is manifested as abrupt increase in P-P interval, due to sudden blocked P wave, with the increased P-P interval being an exact multiple of normal P-P interval. As discussed earlier, this may at times be difficult to differentiate from a sinus pause on the surface ECG.
  - *Complete (type III) SA exit block*: None of the generated impulses is conducted to the atrium, resulting in complete absence of normal P waves. An atrial or junctional pacemaker may take over, providing an atrial escape rhythm (with abnormal P waves, as discussed in the section on sinus bradycardia) or a junctional escape rhythm (with no visible P waves).
- *Sinus arrest*: This is due to nongeneration of the sinus impulse, leading to complete absence of normal P waves. It is indistinguishable from type III SA exit block on the surface ECG; the two can only be distinguished with a sinus node electrode during electrophysiologic evaluation.
  i. *Hypersensitive carotid sinus syndrome*: The cardio-inhibitory type of hypersensitive carotid sinus syndrome is characterized by sinus arrest or complete SA exit block during carotid sinus stimulation, leading to a ventricular pause exceeding 3 seconds; less commonly the ventricular pause may be due to AV block. Patients with symptomatic ventricular pauses exceeding 3 seconds or documented asymptomatic pauses exceeding 6 seconds on prolonged monitoring, with little or no prodromal symptoms, leading to frequent syncope and falls, are most likely to benefit from a permanent pacemaker. A dual chamber pacemaker with a rate-drop algorithm and rate hysteresis is appropriate in this situation.
  ii. *Sick sinus syndrome*: Sick sinus syndrome refers to a combination of various sinus node abnormalities (pathological sinus bradycardia, prolonged sinus pauses, SA exit block, and sinus arrest); more than one of these may be seen at different times. *The brady-tachy syndrome*, characterized by alternation of paroxysms of rapid regular or irregular atrial tachyarrhythmias with periods of slow atrial and ventricular rates, is also a part of this spectrum. The anatomic basis of sick sinus syndrome may involve total or subtotal destruction of sinus node, areas of nodal-atrial discontinuity, inflammatory or degenerative changes in nerves and ganglia around the node, and pathologic changes in the atrial wall; occlusion of sinus node artery may have a role. Symptomatic patients of sick sinus syndrome are candidates for permanent pacemaker implant, with dual chamber pacing likely superior to ventricular-only pacing with regard to incidence of atrial fibrillation (AF) and pacemaker syndrome. Atrial-only pacing is



FIGS. 1A TO E: Sinoatrial exit blocks.

usually avoided for fear of pacing failure, in case patient goes on to develop AV conduction defect in future. Also, a recent trial has shown an increased incidence of paroxysmal AF as well as pacemaker reoperation with atrial-only pacing vis-à-vis dual chamber pacing. Tachy-brady syndrome patients require a combination of pacemaker for the bradycardia and pharmacotherapy for tachycardia control.

Abnormalities at Level of AV Node and Below Includes Abnormalities in Impulse Conduction Only

- *First-degree AV block*: Every atrial impulse is conducted to the ventricle, although with a delay, evident on the surface ECG as a prolongation of the PR interval beyond 0.2 seconds. PR intervals as long as one second have been noted, and may even exceed the P-P interval, a phenomenon known as skipped P waves. First-degree AV block may occur due to conduction delay in the AV node (A-H interval), in the His-Purkinje system (H-V interval), or at both sites. Uncommonly, equally delayed conduction over both bundle branches can produce PR prolongation without significant QRS widening. Occasionally, intra-atrial conduction delay can also prolong the PR interval. Practically, first-degree AV block with a normal QRS is most likely due to delay at AV node with a wide QRS, delay could be at the AV node or the His-Purkinje system or both. While first-degree AV block by itself is considered benign, select patients with marked PR prolongation (beyond 300 ms) and persistent symptoms owing to shortening of LV filling time and diastolic mitral regurgitation, may be considered for *DDD pacing*.
- *Mobitz type I second-degree AV block (Wenckebach)*: This is characterized by serial prolongation of the PR interval till a P wave is blocked completely. The increment in PR interval is maximum in the second beat of the Wenckebach group and each subsequent increment is progressively smaller. While a classic Wenckebach phenomenon is easy to recognize, certain caveats must be kept in mind. For one, a pure 2:1 AV block can be either type I or type II; if the QRS is normal, the block is more likely to be type I—a careful search for transition to 3:2 block at some stage (with PR prolongation in the second cycle) may be useful. Secondly, type I AV block with a high ratio of conducted beats (e.g., 8:7) may give an impression of having a constant PR interval due to the small increments in consecutive beats; here comparing the PR interval just before and just after the dropped beat readily reveals the variation in PR interval. Prognosis-wise, a type I AV block is more likely to be supra-Hisian, especially when accompanied with a narrow QRS, and have a relatively benign course.
- *Mobitz Type II second-degree AV block*: In Mobitz type II block, some P waves are blocked abruptly, but PR interval of the conducted beats is constant. Type II AV block is more likely to be infranodal, worsening with atropine, exercise or isoproterenol, and improving with carotid sinus massage. Infranodal blocks are more likely to progress to complete AV block as compared to blocks at level of AV node; and may present with Stokes-Adams attacks. Most cases require a permanent pacemaker implant once reversible causes are ruled out; a dual chamber pacemaker that maintains AV synchrony is an appropriate choice.
- *Third-degree (Complete) AV block*: Complete AV block is a type of complete AV dissociation, where none of the P waves is conducted to the ventricles; both atria and ventricles are controlled by independent pacemakers. Symptoms are predominantly governed by the stability and rate of escape rhythm. For blocks at the level of AV node (usually congenital), the escape focus is generally within or close to the His bundle—this focus is relatively more stable and can provide ventricular rates up to 60 beats/min. Acquired complete heart block is, however, frequently infra-Hisian, due to trifascicular involvement, and the distal escape foci can rarely provide rates beyond 40 beats/min. Acquired complete AV block, unless reversible, almost invariably requires permanent pacing; even where reversible causes are suspected, temporary pacing support needs to be provided. Congenital complete AV block may, however, be observed, without any intervention, if it is asymptomatic and the patient consistently has an escape rate above 50 beats/min with normal QRS duration and normal left ventricular function; whenever symptoms or high-risk features appear permanent, pacing is indicated.

Management

The trickiest aspect in the management of bradyarrhythmia is not implanting a pacemaker (which is possibly the simplest aspect); rather it is reaching an accurate diagnosis and then deciding whether or not to treat the condition in a given patient.

While persistent bradycardia is easy to diagnose from the resting ECG, the diagnosis of intermittent bradycardia can be elusive and the diagnostic modality needs to be chosen as per the patient's symptom frequency. When the symptoms occur on a daily basis, 24-hour Holter monitoring is likely to have a good yield. However, extended Holter or external loop recorder may be required for less frequent (e.g., weekly) symptoms and an implantable loop recorder may be required for occasional symptoms (frequency less than once a month). A carotid sinus massage (in absence of contraindications) may prove useful in patients above 40 years of age, when carotid sinus hypersensitivity is suspected. While evaluating a patient for symptoms of intermittent bradycardia (e.g., syncope) other causes with similar presentation must also be ruled out (e.g., tachyarrhythmias, severe aortic stenosis, etc.).

Once a diagnosis of bradyarrhythmia is established, the next step is correlating it with the patient's symptoms. This is because benefit of treatment is much better established when bradycardia is shown to reproduce the symptoms in a given patient; otherwise there always lies the possibility that the bradycardia is an incidental finding and the symptoms are due to a different etiology. However, the same is easier said than done; and frequently patients are implanted a permanent pacemaker based on reasonable level of suspicion even when recorded bradyarrhythmic events have not reproduced the symptoms. In this scenario, it is worthwhile to have a lower threshold for treatment of advanced AV blocks vis-à-vis sinus node dysfunction.

Once a decision to treat a persistent or recurrent bradyarrhythmia (not attributable to reversible causes) is taken, drug therapy has no role; the choice is only of the type of pacemaker to be implanted. The choice of pacemaker device and specific algorithms (for conditions like carotid sinus hypersensitivity) has already been discussed in the relevant

sections. Suffice to say that as of date, with the exception of patients with permanent AF, dual chamber pacing is preferable to single chamber pacing; cost constrains, however, must be taken into account.

TACHYARRHYTHMIAS

Clinical Presentation

Signs and symptoms related to the tachyarrhythmia may include shock, hypotension, heart failure, shortness of breath, chest pain, acute myocardial infarction, palpitations, and/or decreased level of consciousness. Tachyarrhythmias are broadly characterized as supraventricular tachycardia (SVT), defined as a tachycardia in which the driving circuit or focus originates, at least in part, in tissue above the level of the ventricle (i.e., sinus node, atria, AV node, or His bundle) and ventricular tachycardia (VT), defined as a tachycardia in which the driving circuit or focus solely originates in ventricular tissue or Purkinje fibers. Because of differences in prognosis and management, the distinction between SVT and VT is critical early in the acute management of a tachyarrhythmia. In general (with the exception of idiopathic VT), VT often carries a much graver prognosis, usually implies the presence of significant heart disease, results in more profound hemodynamic compromise, and therefore requires immediate attention and measures to revert to sinus rhythm. On the other hand, SVT is usually not lethal and often does not result in hemodynamic collapse; therefore, more conservative measures can be applied initially to convert to sinus rhythm.

Electrocardiographic Diagnosis

The ECG is the most important tool in arrhythmia analysis. An electrophysiological study is more definitive, however, is not available at every center. Initially, a 12-lead ECG and a long continuous recording with use of the lead that shows distinct P waves (usually leads II, III, aVF, V_1, or aVR) is recorded and analyzed. The ECG obtained during an episode of arrhythmia may be diagnostic by itself, obviating the need for further diagnostic testing. **Flowchart 1** depicts an algorithm for diagnosis of specific tachyarrhythmias from the 12-lead ECG. The following important questions are to be asked in order, while analyzing an ECG with a tachyarrhythmia. Once these questions have been addressed, one needs to assess the significance of the arrhythmia in view of the clinical setting. Should it be treated, and if so, how?

- *What is the QRS duration?* In general, if the QRS is narrow (duration <120 ms, referred to as narrow-complex tachycardias) during the tachycardia, the ventricle is being activated via the normal His-Purkinje system and thus the origin of the tachycardia is supraventricular. A wide QRS (duration exceeding 120 ms) during tachycardia suggests VT or a SVT in specific scenarios. SVT with a concurrent bundle branch block (BBB) or intraventricular conduction defect can produce wide-complex tachycardias despite a supraventricular origin. A narrow-complex tachycardia almost always makes the diagnosis of SVT, but a wide-complex tachycardia can be supraventricular or ventricular. Fusion or capture beats and AV dissociation are diagnostic of VT but are often not present or are difficult to detect.
- *What is regularity of rhythm?* An irregularly irregular rhythm point toward AF. A regular or a regularly irregular rhythm can be seen in either SVT's or VT's.
- *What is characteristic of P waves?* P-wave morphology, association with QRS complexes, atrial rate, P-R and R-P intervals and the response of the P waves to carotid sinus massage, or adenosine further helps to narrow down the differential diagnosis of the tachyarrhythmia.

SUPRAVENTRICULAR TACHYCARDIAS

A SVT is a paroxysmal tachycardia arising above the level of His bundle. It is a commonly encountered tachycardia in emergency department. Sinus tachycardia and paroxysmal supraventricular tachycardia (PSVT) are mostly without complication easily manageable. Atrial flutter and AF are serious tachycardias. Patient with multifocal atrial tachycardia (MAT) usually has underlying pulmonary or cardiac disease. PSVT is classified on the basis of the specific conduction pathway involved: atrioventricular reentry tachycardia (AVRT) and atrioventricular nodal reentry tachycardia (AVNRT).

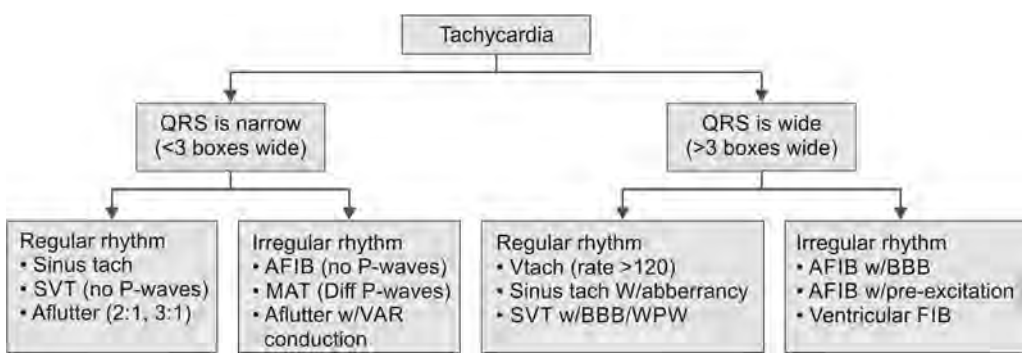
Clinical Presentation

Common complaints by patient are Increased heart beats anxious feeling, dizziness, chest heavy ness/discomfort, and pulsatile feeling in neck breathlessness.

Supraventricular tachycardia is usually seen in a structurally normal heart and in the presence of precipitating factors such as excessive intake of coffee, alcohol, or thyroid dysfunction.

Clinical Approach of a Patient with a SVT

A detailed patient's history physical examination is important to rule out structural heart disease (**Table 1**). History regarding duration and frequency of episodes, possible precipitating factors (caffeine, exercise, etc.) History of heart and lung



FLOWCHART 1: A simplified approach to tachyarrhythmias.

TABLE 1: Differentiating features of SV tachycardia.

Tachycardia	*Age*	*Underlying conditions*	*Presentation*	*Baseline ECG*
Paroxysmal SVT	All ages	Structurally normal heart	Fast onset and offset palpitation	Preexcitation common in AVRT
Atrial fibrillation **Atrial flutter** **Multifocal atrial tachycardia**	>50 years	HTN, IHD, RHD, pulmonary disease	Abrupt onset and offset irregular palpitation	LVH repolarization abnormalities
Sinus tachycardia	10–30 years	Normal heart	Progressive onset and slow termination	Normal

(AVRT: atrioventricular reentry tachycardia; ECG: electrocardiogram; HTN: hypertension; IHD: Ischemic heart disease; LVH: left ventricular hypertrophy; RHD: rheumatic heart disease)

disease should be obtained, SVT is sudden in onset and offset. Sinus tachycardia accelerates and decelerates gradually.

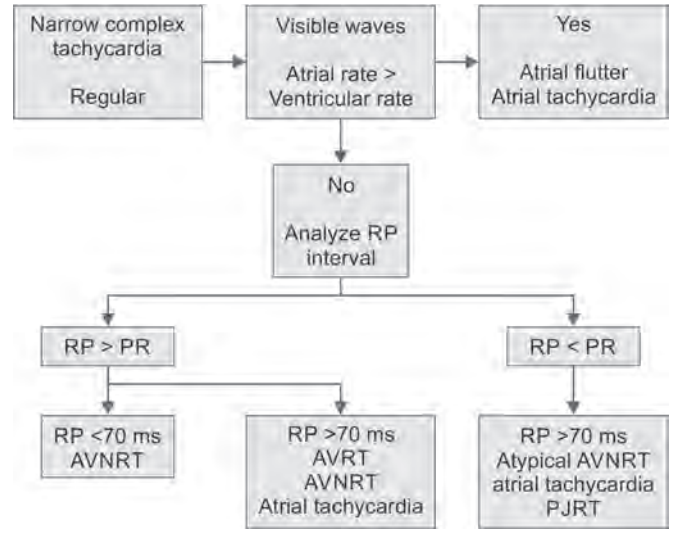
An echocardiography is helpful to rule out structural heart disease. Laboratory investigations such as serum electrolytes, thyroid profile can identify precipitating factors. *An Electrophysiological study (EPS) is done to identify the exact mechanism of the arrhythmia and catheter ablation is reserved for patients with drug resistant SVT, SVT associated with syncope, wide QRS tachycardia and individuals who do not wish to take long term medications.*

Electrocardiographic Findings

Supraventricular tachycardias present with narrow complex tachycardia with QRS duration of <120 ms. Few cases of SVT cases can have a QRS duration of >120 ms (**Flowchart 2**).

Types of Supraventricular Tachycardia

- *Atrioventricular Nodal Reentry Tachycardia:* AV nodal reentry tachycardia has a rate between 150 and 230 beats/min. The R-R interval is regular and a retrograde P wave may be present. The retrograde P wave may be difficult to distinguish in the standard ECG trace. PSVT may produce aberrant conduction and a widened QRS The reentrant pathway is functionally permitted by a fast and slow pathway that exists within the AV node.
- *Atrioventricular reentry tachycardia:* AVRT is due to a concealed AV bypass tract which creates the re-entrant circuit. The AV bypass tract usually allows retrograde conduction only.
- *Sinus node and intra-atrial reentry tachycardia (IART):* IART is commonly seen in postcardiac surgery patients caused by reentry in sinus node and atria, respectively.
- *Wolff–Parkinson–White syndrome (WPW):* Activation of ventricular muscle by impulses originating in atria and conducted by bypass tracts causes preexcitation. Many forms of aberrant connections are possible. These patients present with episodic SVT. Specific ECG abnormalities can be elicited: PR interval < 120 ms, delta wave—slurring of the initial part of QRS complex, QRS duration >120 ms, an association of WPW is seen with mitral valve prolapse syndrome (MVPS), ischemic heart disease (IHD), hypertrophic obstructive cardiomyopathy (HOCM), sick sinus syndrome, Epstein's anomaly, and rheumatic fever.



FLOWCHART 2: Electrocardiographic approach to narrow complex tachyarrhythmia.

Treatment of Supraventricular Tachycardia

Vagal Maneuvers

Carotid sinus massage stimulates baroreceptors triggering a reflexive increase in the activity of the vagal nerve and sympathetic withdrawal. Both of these causes, a slowing conduction through the AV node, thus helping in blocking reentry. A physical examination to rule out a carotid bruit is necessary. Resuscitation equipment should be ready. Attach the monitor for continuous ECG monitoring. Pressure is applied in a firm circular manner at the level of the cricoid cartilage for about 5 seconds. Repeat the procedure on the opposite side, if the tachyarrhythmia persists.

Drug Therapy

Antiarrhythmic drugs which are helpful for immediate control and long-term maintenance therapy are summarized in **Tables 2** and **3**.

Catheter Ablation

Catheter ablation has a very high success rate (>95%) and a low recurrence rate (<5%) in patients with accessory pathways.

TABLE 2: Drugs therapy for immediate control of SVT.

Drugs	*Doses*	*Side effects*
	SVT without preexcitation	
Adenosine	Give 6 mg rapid intravenous followed by fluid bolus; if no response within 1–2 min, give 12 mg more	Facial flushing, chest pain, and hypotension common; transient asystole bronchospasm, atrial fibrillation, and ventricular fibrillation
Verapamil	5 mg every 3–5 min, to max 15 mg	Hypotension, heart block, and inotropic effect negative
Diltiazem	0.25 mg/kg of body weight over a 2-min period; if no response, additional dose of 0.35 mg/kg over a 2-min period; maintenance infusion of 5–15 mg/h	Hypotension, heart block, and inotropic effect negative
Metoprolol	5 mg over a 2-min period; up to 3 doses in 15 min	Hypotension, heart block, and bradycardia bronchospasm
	SVT with preexcitation or WPW with AF	
Procainamide	30 mg/min continuous infusion to a maximal dose of 17 mg/kg (maintenance infusion of 2–4 mg/min)	Hypotension, widening of QRS complex, torsade de pointes
Flecainide	2 mg/kg over a 10-min period	Negative inotropic effect conducting atrial flutter, widening of QRS
Ibutilide	*If ≥60 kg*: 1 mg over a 10-min period *If <60 kg*: 0.01 mg/kg over a 10-min period Repeat once if no response after 10 min	Prolongation of QT interval, torsade de pointes

TABLE 3: Drugs for long-term management of SVT.

Drugs	*Doses*	*Side effects*	*Contraindication*
		SVT without preexcitation	
Beta-blockers			
Metoprolol	50–200 mg daily	Hypotension and heart block	Asthma, CHF
Atenolol	80–240 mg daily		
Calcium channel blockers			
Diltiazem	180–360 mg daily	Hypotension and heart block	CHF
Verapamil	120–480 mg daily		
Digoxin	0.125–0.375 mg daily	Digitalis toxicity	Preexcitation
		SVT with preexcitation	
First-line drugs			
Flecainide	100–300 mg daily	VT enhanced AV nodal conduction interaction with digoxin	Ischemic and structural heart disease
Propafenone	450–900 mg daily		
Second-line drugs			
Amiodarone	200 mg daily	Skin discoloration thyroid dysfunction GI pulmonary and hepatotoxicity corneal deposit tremor optic neuritis	
Sotalol	160–320 mg daily	Hypotension heart block bradycardia	

Complications of catheter ablation include perforation, bleeding, AV fistula, venous thrombosis, pulmonary embolism, myocardial perforation, valve damage, systemic embolism and rarely, death.

VENTRICULAR TACHYCARDIAS

Ventricular tachycardias are the common cause for sudden cardiac death. They are aberrant cardiac rhythms from single premature ventricular complexes (PVC) to sustained monomorphic VT, polymorphic VT, and ventricular fibrillation (VF). Ischemic and dilated cardiomyopathies are the common cause for VT. Patient should be investigated for the presence of underlying structural heart disease as the prognosis depends on it.

Clinical Approach of a Patient with a Wide Complex Tachycardia

QRS >120 ms in ECG is called wide complex tachycardia and are common in clinical practice. Wide QRS complex is seen in VT, SVT with aberrancy or BBB, and SVT with antegrade conduction over an accessory pathway (preexcited tachycardia). Drug toxicities and electrolyte imbalances are also presenting as QRS abnormalities.

Medical history and physical examination are very important and helpful in diagnosis. A history of angina, myocardial infarction, or congestive cardiac failure is strong indicators for the presence of VT. Young patients are more likely to have idiopathic VT. Hemodynamic tolerance for the arrhythmia is a poor guide to diagnosis as both SVT and VT can present with hemodynamic collapse. On the contrary, idiopathic VT's may be well-tolerated hemodynamically.

Clinical examination of the patient can help in differentiating and categorizing these patients. Clinical signs of AV dissociation include 'cannon A' wave in the jugular venous pulse, variability in the intensity of the first heart sound and variability in arterial blood pressure. Vagal maneuvers that result in termination of tachycardia indicate the presence of SVT. However, these tests are not very reliable as a few VT's can also terminate with vagal maneuvers.

Electrocardiographic Findings

Various electrocardiographic features are suggestive of VT (**Table 4**):

- Atrioventricular dissociation, fusion or capture beats, QRS width [left bundle branch block (LBBB) >160 ms and right bundle branch block (RBBB) >140 ms]
- Extreme left axis, concordance in all precordial leads, LBBB morphology with right axis deviation

Types of Ventricular Tachycardia

Monomorphic Ventricular Tachycardia

Various structural heart diseases are known to predispose to monomorphic VT. The scars present in the myocardium act as substrates for reentry. Large ventricular scars seem to predispose more frequent VT's. The most common substrate for VT is ventricular scarring related to IHD, which is present in approximately 60% of patients. Patients with dilated cardiomyopathies, ARVC, prior cardiac surgery (particularly for correction of congenital anomalies or valve surgery), sarcoidosis, or hypertrophic cardiomyopathy can also have ventricular scarring and VT.

Polymorphic Ventricular Tachycardia

Polymorphic VT or torsade de pointes is characterized by a changing of the QRS morphology from beat to beat. The term literally means "twisting of points." It is commonly a sustained arrhythmia often requiring emergency cardioversion. It can be self-limiting in some patients. Evaluation of the underlying substrate for polymorphic VT is important. Acute ischemia is common cause of polymorphic VT in most cases. Other conditions associated with polymorphic VT are long QT syndrome and Brugada syndrome. Coronary angiography is an important investigation to exclude ischemia. Correction of electrolyte abnormalities is also a very important step. Special consideration should be given to hypokalemia and hypomagnesemia. Stabilization of heart failure is of utmost importance. Amiodarone is also effective in controlling episodes of polymorphic VT.

Management of Ventricular Tachycardias

Acute Management

The initial management of a patient with sustained monomorphic VT caused by underlying structural heart disease is determined by the nature of the symptoms and the patient's hemodynamic state. Patients presenting with hemodynamic instability, myocardial ischemia, and pulmonary edema should be promptly electrically cardioverted. Reversible causes of VT, such as electrolyte imbalances, acute ischemia, hypoxia, and drug toxicities should be corrected.

In patients who are hemodynamically stable, pharmacological reversion of VT can be attempted. Lidocaine is the first-line agent and is very useful in the setting of myocardial ischemia. In other settings, especially in patients with slow and stable VT not related to ischemia, the efficacy of lidocaine is limited. Intravenous procainamide is a better choice in such patients. Procainamide has the ability to rapidly slow and terminates VT in the nonischemic setting. Use of procainamide is limited by hypotension, which occurs in approximately 20% of these individuals. Overall, it is acutely effective in 75% patients. Amiodarone is also useful, but its onset of action is slower than lidocaine or procainamide. If used it should be loaded with an intravenous dose and still the results of acute termination studies have been variable. However, at many centers' amiodarone is preferred as it is less likely to produce hypotension and prolong QTc predisposing to torsade de pointes.

Secondary Prevention

Recurrence of VT is frequent problem. Medical therapy can also be beneficial in the secondary prevention of VT. Mexiletine can be used as a second-line therapeutic agent for recurrent ventricular arrhythmias, particularly in combination

TABLE 4: ECG differences between SVT and VT.

Features in favor of SVT	*Features in favor of VT*
• Initiation with a premature P wave	• Initiation with a premature QRS complex
• Tachycardia complexes identical to those in resting rhythm	• Tachycardia beats identical to PVCs during sinus rhythm
• Long-short" sequence preceding initiation	• "Short-long" sequence preceding initiation
• Changes in the P-P interval preceding changes in the R-R interval	• Changes in the R-R interval preceding changes in the P-P interval
• QRS contours consistent with aberrant conduction (V_1 and V_6)	• QRS contours inconsistent with aberrant conduction (V_1 and V_6)
• Slowing or termination with vagal maneuvers	• AV dissociation or other non-1:1 AV relationship
• Onset of the QRS to its peak (positive or negative) <50 ms	• Onset of the QRS to its peak (positive or negative) ≥50 ms
• Fusion beats, capture beats QRS duration ≤0.14 s	• QRS duration >0.14 s, left axis deviation (especially −90–180°)

(PVC: premature ventricular complex; SVT: supraventricular tachycardia; VT: ventricular tachycardia)

TABLE 5: Classification of antiarrhythmic drugs.			
Class I: Membrane stabilizing (Na channel blockers) • Class I A—Moderately prolong conduction • Class I B—Minimal effect on conduction • Class I C—Marked prolongation of conduction	**IA** • Quinidine • Procainamide • Disopyramide	**IB** • Lidocaine • Mexiletine	**IC** • Propafenone • Flecainide
Class II (blockade of β-adrenergic receptors)	• Propranolol • Esmolol • Sotalol (Class III properties also)		
Class III (prolongation of repolarization)	• Amiodarone • Dronedarone • Dofetilide • Ibutilide		
Class IV (calcium channel blockers)	• Verapamil • Diltiazem		
Drugs for paroxysmal supraventricular tachycardia	• Adenosine • Digoxin		

with other antiarrhythmic medications (**Table 5**), although adverse effects can limit its use. Catheter ablation is an option in patients who have recurrent VT or shocks in spite of optimal medical therapy or who have unacceptable side effects with medical therapy. Catheter ablation can also be lifesaving in patients with incessant VT. Catheter ablation is also beneficial in controlling recurrent VT in patients with dilated cardiomyopathies and ARVD. Implantable cardioverter-defibrillators (ICDs) effectively treat ventricular arrhythmias. But ICDs provide inappropriate shocks and can produce a huge psychological impact as well as increase mortality.

SUMMARY

Cardiac arrhythmia is a common terminology used for any of a heterogeneous group of conditions in which there is abnormal electrical activity in the heart. Clinical presentation of arrhythmias may vary from mild, i.e., only irritating symptoms such as an awareness of the heart beating very fast to potentially life-threatening conditions such as a stroke or cardiac arrest. Emergency physician must keep in mind that an arrhythmia is only part of a patient's presentation, and before analyzing the arrhythmia the patient should be assessed and airway, breathing, and circulation (ABC) must be maintained. Systematic approach when managing an arrhythmia, finding the components of the ECG complex and their relationship can simplify its description. Knowledge of how arrhythmia treatments work makes their effects on the patient clearer. The ability of emergency physician to follow clear and scientifically derived guidelines for management of cardiac arrhythmias optimizes the patient's chances of survival.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Cardiomyopathies

Jamal Yusuf, Saurabh Sharma, Bhushan Shah

INTRODUCTION

Cardiomyopathies are a group of diseases of various etiologies in which cardiac structure, myocardial functions, and electrical properties of the heart are grossly disturbed. In 2006, American heart association scientific statement proposed the following definition:

> *"Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electric dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders."*

Primary cardiomyopathies are generally familial and myocardium is affected most common causes of primary cardiomyopathies are summarized in **Table1**. AHA classified primary cardiomyopathies as genetic, mixed, and acquired. Secondary cardiomyopathies usually involve heart muscle and mostly associated with systemic cause **Table 2**.

PATHOPHYSIOLOGY

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by a thickened but nondilated left ventricle in the absence of another cardiac or systemic condition (e.g., aortic valve stenosis, systemic hypertension, and some expressions of physiologic athlete's heart) capable of producing the magnitude of left ventricular (LV) hypertrophy evident. Left ventricular outflow tract (LVOT) obstruction is major hallmark of the disease with dynamic gradient of 30 mm Hg at rest or with exercise. It is caused by systolic anterior motion (SAM) of mitral valve resulting in contact with ventricular septum in mid systole due to drag effect, ultimately resulting in dynamic subaortic obstruction. HCM has autosomal dominant inheritance and is known to be caused by mutations in genes encoding proteins for thick and thin filaments of cardiac sarcomere. Most commonly β-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) genes are involved.

Dilated Cardiomyopathy

The European Cardiac Society has defined dilated cardiomyopathy (DCM) as dilatation of the left or both ventricles that is not explained by abnormal loading conditions or coronary artery disease. It is characterized by cardiac enlargement with normal thickness of ventricular walls and varying extents of fibrosis resulting in systolic and varying degrees of diastolic dysfunction. It can be caused by genetic mutations (usually autosomal dominant inheritance), toxins, e.g., alcohol and myocarditis.

Arrhythmogenic Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrofatty replacement of the myocardium.

TABLE 1: Primary cardiomyopathies.

Genetic	*Mixed (genetic and nongenetic)*	*Acquired*
• Hypertrophic cardiomyopathy • Arrhythmogenic right ventricular cardiomyopathy • Left ventricular noncompaction • Glycogen storage disease • Conduction system defects *(Long QT syndrome, Short QT syndrome Brugada syndrome)* • Mitochondrial myopathies • Ion channel disorders	• Dilated cardiomyopathies • Restrictive nonhypertrophied cardiomyopathy	• Inflammatory (myocarditis) • Stress-provoked (Takotsubo) • Peripartum • Tachycardia induced • Infants of insulin-dependent diabetic mothers

TABLE 2: Causes of secondary cardiomyopathies.	
Infectious causes	Viral (Adenovirus, Coxsackie virus, HIV, CMV, and influenza virus), bacterial (streptococci), spirochaetal (syphilis), Rickettsia, parasitic (trypanosomiasis-Chagas disease)
Toxins	Ethanol. Chemotherapeutic agents *(doxorubicin)*, antiretroviral agents *(zidovudine and didanosine)*, phenothiazines, cocaine, and methamphetamine
Deposition disease	Amyloidosis and hemochromatosis
Autoimmune disorders	Scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and dermatomyositis
Metabolic	• Endocrine disorders-*(diabetes mellitus, hypothyroidism, hyperthyroidism)* • Nutritional *(thiamine, carnitine, and selenium) and electrolytes (hypophosphatemia and hypocalcemia)*
Neuromuscular dystrophies	Muscular dystrophies, Friedreich's ataxia

TABLE 3: Clinical features of cardiomyopathies with systolic and diastolic dysfunctions.	
Cardiomyopathies with systolic and diastolic dysfunction	**Cardiomyopathies with diastolic dysfunction**
Dilated cardiomyopathies: Presents with congestive heart failure, chest pain, and regurgitation murmur with left ventricular hypertrophy and poor R wave progression in electrocardiograph	**Hypertrophic cardiomyopathies**: Presents with dyspnea, chest pain palpitation, syncope pulsus bisferiens, and ejection systolic murmur with features of left ventricular hypertrophy and large septal Q wave in electrocardiograph
Myocarditis: Presents with fever tachycardia, chest pain, and myalgias with nonspecific ST-T changes in electrocardiograph	**Restrictive cardiomyopathies**: Presents with feature of heart failure with preserved ejection fraction with low voltage QRS conduction abnormalities and atrial fibrillation

It is caused by mutations in genes encoding plakophilin 2 (*PKP2)*, desmoglein 2 *(DSG2),* and desmoplakin (*DSP)*. There is increasing incidence of LV involvement as well.

Restrictive Cardiomyopathies

It is characterized by nondilated left or right ventricle with diastolic dysfunction. It is mainly caused by cardiac amyloidosis, cardiac sarcoidosis, or hemochromatosis. Amyloidosis is caused by the extracellular deposition of a misfolded protein as amyloid which causes cardiac dysfunction. Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Noncaseating granulomas are the histological hallmark. It frequently invades the conduction system and causes atrioventricular block and sometimes sudden death.

Other Cardiomyopathies

Exact pathophysiology of *takotsubo cardiomyopathy* is not known. It is hypothesized that emotional and physical stress result in release of catecholamines and neuropeptide Y which have direct cardioinhibitory effects and result in acute microvascular dysfunction. *Left ventricular noncompaction (LVNC)*—LVNC is caused by premature arrest of normal myocardial compaction resulting in persistence of embryonic trabeculated myocardium.

CLINICAL PRESENTATION

The cardiomyopathies usually present in emergency department as signs of systolic or diastolic ventricular dysfunctions. Dyspnea, angina syncope, heart failure (HF) arrhythmias, and sudden cardiac death (SCD) are common features and summarized in **Table 3**.

- *Dyspnea*: It is frequent presenting complaint in patients with cardiomyopathy and may be due to either systolic or diastolic dysfunction as manifestation of HF with reduced ejection fraction (EF) or with preserved EF respectively.
- *Angina*: Frequently patients with HCM can present with exertional angina due to dynamic LVOT obstruction. *Syncope*—syncope can be exertional as in HCM due to LVOT obstruction or can be arrhythmic, e.g., due to VT which may be the first presentation in many of the cardiomyopathies. *Sudden cardiac death*—many of the cardiomyopathies such as ARVC, HCM, amyloidosis, and sarcoidosis can present catastrophically as SCD.
- *Heart failure:* Cardiomyopathies frequently present with HF with reduced EF, e.g., DCM, LVNC, ARVC, burnt out HCM, or with HF with preserved EF, e.g., restrictive cardiomyopathies (RCM) and HCM.
- *Arrhythmias*: Cardiomyopathies frequently present with arrhythmias, e.g., VT, VF which may be life threatening, e.g., in HCM, ARVC, amyloidosis, and sarcoidosis.
- *Heart block:* It is commonly seen in sarcoidosis due to conduction system involvement requiring permanent pacemaker implantation.
- *Stroke and thromboembolism*: These are frequent in LVNC. However, there is no consensus on anticoagulation in LVNC patients.

DIAGNOSTIC EVALUATION

Echocardiography

Echocardiographic evaluation is the first step in diagnosis and is fairly accurate in recognition of these cardiomyopathies.

- *Systolic dysfunction*: It is characterized by a decrease in myocardial contractility. Cardiac output is maintained by LV enlargement and Frank-Starling relationship resulting in higher stroke volume. However, when these compensatory mechanisms fail cardiac output decreases, resulting in HF. Systolic dysfunction is characteristic of DCM. It is also seen in end stage HCM due to progressive LV wall thinning.
- *Diastolic dysfunction*: It is characterized by dysfunction in LV relaxation resulting in filling abnormalities and elevated filling pressures. It may or may not be accompanied by systolic dysfunction. It is characteristically seen in HCM and restrictive cardiomyopathy.

- *Hypertrophic cardiomyopathy* is characterized by LV wall thickness of 15 mm or more. Doppler imaging generally reveals resting gradient of 30 mm Hg or more. SAM of mitral valve can be easily seen on M-mode echocardiogram.
- *Dilated cardiomyopathy* is seen as varying degrees of LV dilation with systolic and diastolic dysfunction.
- *Arrhythmogenic cardiomyopathy* is characterized by regional RV akinesia, dyskinesia, or aneurysm. *Left ventricular noncompaction* is seen as thick noncompacted layer of myocardium with deep recesses.
- *Restrictive cardiomyopathy* is characterized by biatrial enlargement with diastolic dysfunction with preserved systolic function. Amyloidosis is generally characterized by LV hypertrophy and speckled appearance of the myocardium. Sarcoidosis is seen as marked thinning and increased echogenicity of basal septum which is characteristic, however, at times it seen as global LV hypokinesia with LV dysfunction.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMRI) is very helpful in diagnosis as well as risk stratification. In cases of borderline hypertrophy, CMRI may be helpful in differentiating HCM from athlete's heart. CMRI reveals late gadolinium enhancement (LGE) in HCM. LGE >15% of LV mass is independent predictor of SCD in HCM and its presence should be considered as need for implantation of ICD (implantable cardioverter defibrillator) for primary prevention of SCD. In LVNC, >20% of LV mass is trabeculated is one of the criteria for diagnosis along with ratio of noncompacted to compacted layer of 2.3:1. CMRI is very accurate in assessing RV dilatation and dysfunction, thus making it useful in diagnosis of ARVC. CMRI has very high spatial and soft tissue resolution. It can differentiate myocardial edema and scar. It is one of the preferred imaging modalities in sarcoidosis. Circumferential subendocardial LGE most noted at the base and middle of the ventricle is frequently seen in cardiac amyloidosis on CMRI.

Other Diagnostic Tools

Positron emission tomography (PET) imaging helps in measuring disease activity and monitoring response to treatment particularly in cardiac sarcoidosis and other inflammatory conditions.

Holter monitoring helps in risk stratification for SCD in cardiomyopathies. Multiple or repetitive nonsustained VT in HCM is independent predictor of SCD. Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis is one of the major criteria for ARVC diagnosis.

TREATMENT

Treatment of acute HF is described in another chapter "acute HF" while *chronic HF drug therapy consists of diuretics, angiotensin-converting enzyme inhibitors (ACEI) β-blockers* and other drugs summarized in **Table 4** mainstay of treatment for HF with reduced EF (HFREF) or preserved EF (HFPEF).

Prevention of Sudden Cardiac Death

Implantable cardioverter defibrillator implantation for both primary preventions based on risk stratification and secondary prevention should be undertaken. For patients with recurrent ventricular tachycardia, epicardial catheter ablation may be effective in ARVC. *Mechanical circulatory support (MCS), e.g., left ventricular assist devices (LVAD)* can be considered in patients with intractable HF as destination therapy or as bridge to transplant. Patients with intractable HF may require cardiac transplantation.

TABLE 4: Drug therapy for cardiomyopathies with systolic and diastolic dysfunction.

Diuretics	*Furosemide* 20–40 mg once or twice up to total dose of 600 mg/day, *torsemide* 10–20 mg once up to total of 200 mg/day
β-blockers	*Carvedilol* 3.125 mg BD up to 25 mg BD, bisoprolol 1.25 mg BD up to 10 mg OD, and metoprolol succinate 12.5–25 mg OD target dose of 200 mg OD
Angiotensin-converting enzyme (ACE) inhibitors	*Enalapril* 2.5 mg daily up to max of 10 mg daily, *ramipril* 1.25–2.5 mg OD up to max 10 mg OD
Angiotensin II receptors blockers (ARBs)	*Valsartan* 40 mg BD up to 160 mg BD, losartan 12.5 mg to 50 mg OD
Mineralocorticoid receptor antagonists	*Spironolactone* 12.5–50 mg OD, eplerenone 25–50 mg OD
Angiotensin receptor neprilysin inhibitor (ARNI)	*Sacubitril/valsartan* 50 mg BD up to max of 200 mg BD has been shown to beneficial in patients with Heart failure with reduced ejection failure (HFREF)
Selected patients of dilated cardiomyopathy (DCM) with left bundle branch block (LBBB) may benefit from cardiac resynchronization therapy (CRT)	

Specific Treatment

- *Surgical myomectomy* is indicated in patients of HCM who remain symptomatic despite optimal medical management. Alcohol septal ablation can be considered in patients with prohibitive surgical risk. Novel pharmacotherapy with mavacamten, allosteric modulator of cardiac β-myosin, shows promise in relieving LVOT obstruction by causing reversible inhibition of actin myosin cross bridging.
- *Radiofrequency (RF) ablation* is a novel technique for septal reduction and can be used in patients with coronary anatomy unsuitable for alcohol septal ablation, but carries higher risk of complete heart block. Primary amyloidosis is treated with chemotherapy aimed at plasma cells. Familial amyloidosis is treated with liver transplantation and investigational therapies like tafamidis. Treatment of cardiac sarcoidosis includes glucocorticoids supplemented with other immunosuppressive agents (methotrexate, azathioprine, cyclophosphamide, and infliximab).

MECHANICAL CIRCULATORY SUPPORT

Mechanical circulatory support devices are mechanical pumps designed to assist or replace the function of either the left (LVAD) or the right ventricle, or both ventricles, of the heart. European Society of Cardiology 2016 Recommendations for implantation of MCS in patients with refractory HF *are as* bridge to

transplant, and as destination therapy. A preimplant creatinine clearance of <30 mL/min/m^2 is associated with a 22% 3-month mortality in recipients of a continuous-flow LVAD, and is a contraindication to durable LVAD implantation. The presence of portal hypertension with liver cirrhosis is a contraindication to initiating MCS support. High-fixed PVR (thresholds vary from 3 to 6 wood units) is a contraindication to heart transplantation and consequently to use of LVAD. Eligibility criteria for LVAD implantation are discussed in **Box 1**.

Design of the Ventricular Assist Device

Ventricular assist devices share a number of basic components **Figure 1**. All systems for left-sided support of an inflow cannula that drains blood from the heart (from the LV apex or from the left atrium via the right superior pulmonary vein or transseptal approach) to the pump and an outflow cannula that carries blood back to the arterial system by way of the aorta or femoral, axillary, or carotid artery. The power supply for implantable pumps is delivered through a percutaneous lead that traverses the skin and connects the external power system with the internal pump. The external components of an implantable system consist of a power source and a small, portable computer (controller) that controls device speed and monitors device function. Various devices are discussed in **Table 5**.

BOX 1: Eligibility criteria for implantation of left ventricular assist device (LVAD).

Patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following:

- LVEF < 25% and, if measured, peak VO_2 <12 mL/kg/min
- ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause
- Dependence on intravenous inotropic therapy
- Progressive end organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥ 20 mm Hg and SBP ≤ 80–90 mm Hg or CI ≤ 2 L/min/m^2)
- Absence of severe right ventricular dysfunction together with severe tricuspid regurgitation

(CI: cardiac index; HF: heart failure; LVEF: left ventricular ejection fraction; PCWP: pulmonary capillary wedge pressure; SBP: systolic blood pressure; VO_2: oxygen consumption)

Device Management and Complications

- *Measuring blood pressure*: Use of a Doppler and a peripheral blood pressure cuff is the most effective means to measure blood pressure. When compared to an automated blood pressure, palpation, and auscultation, Doppler was more highly correlated with the blood pressure obtained simultaneously from direct measurement with an arterial catheter. The narrow pulse pressure observed with continuous flow LVADs minimizes the distinction between systolic and diastolic pressure, often making them imperceptible. If the peripheral pulse is not detectable, the first sound detected with a Doppler can be considered the mean arterial pressure. Detection of a palpable pulse should prompt consideration for device malfunction or insufficient pump speed.
- *Managing hypotension in LVAD Patient*: For hemodynamically unstable (hypotension and features of hypoperfusion) LVAD patient, auscultate the precordium, "whirr" sound indicates functioning of LVADs while absence of any sound indicates mechanical failure of LVADs. Do not disconnect anything, search for cause, and check batteries. Small boluses of normal saline can be given followed by inotropes (dopamine or dobutamine), if conditions not improved. Perform basic electrocardiograph, laboratory tests, and bedside Doppler. Assessment for gastrointestinal (GI) bleed and over anticoagulation should be done. Once bleeding is ruled out, pulmonary embolism or device thrombosis can be treated by heparin or tissue plasminogen activator. Chest compression can dislodge

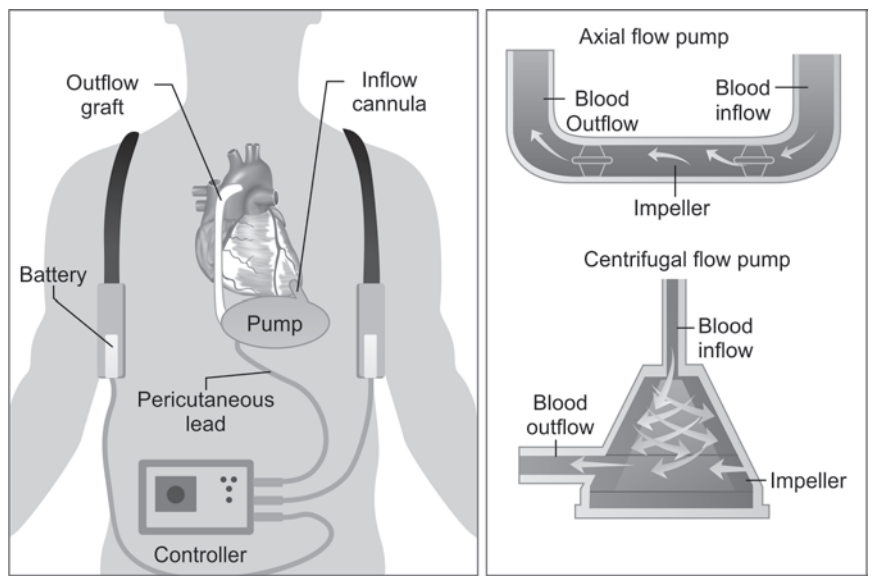

FIG. 1: Configuration of current era durable left ventricular assist devices (LVADs). Durable LVADs are implanted with the inflow cannula of the pump positioned at the left ventricular apex connected to either an axial flow or centrifugal flow device. The outflow graft is positioned in the aorta to provide flow via a continuous flow mechanism.

TABLE 5: Long-term durable mechanical circulatory support (MCS) devices.

Device	*Pump mechanism*	*Pump energy source*	*Ventricle supported*
HeartMate 3 (St Jude Medical, Minneapolis)	Continuous flow rotary pump with centrifugal design and magnetic levitation of internal impeller	• Electric motor • Power to pump delivered via percutaneous lead with external power source and computer controller	• Left ventricle • Implantable pump with intrapericardial placement
HeartMate II (St Jude Medical)	Continuous flow rotary pump with axial design with mechanical pivot support of internal impeller	• Electric motor • Power to pump delivered via percutaneous lead with external power source and computer controller	• Left ventricle • Implantable pump requiring preperitoneal pocket
HVAD (Medtronic, Minneapolis)	Continuous flow rotary pump with centrifugal design with magnetic and hydrodynamic levitation of internal impeller	• Electric motor • Power to pump delivered via percutaneous lead with external power source and computer controller	• Left ventricle • Implantable pump with intrapericardial placement • No preperitoneal pocket required
Syncardia TAH-t (SynCardia Systems, Tucson, Arizona)	Pulsatile, volume displacement (50-cc and 70-cc displacement devices)	• Pneumatic • Patient tethered to portable drive unit	Biventricular support orthotopic placement with removal of both ventricles

BOX 2: Complications of left ventricular assist device (LVAD).

- Intrinsic to the pump and its constituents:
  - Pump malfunction, controller faults, driveline faults, and short-shield malfunction
  - Related to the patient's native heart condition
  - Arrhythmias, valve insufficiency, and RV failure
- Pump-patient interface:
  - GI bleeding (acquired von Willebrand disease), infection, pump thrombosis, anemia (from bleeding or hemolysis due to erythrocyte destruction from pump, thromboembolism (stroke, pulmonary embolism, and mesenteric ischemia specially in suboptimal anticoagulation)
  - Treatment of infection is on lines of sepsis management with volume resuscitation and antibiotics. In general, LVAD-related bloodstream infections are difficult to eliminate and frequently require pump exchange or transplantation

the LVAD, and ventricular rupture and bleeding can occur. Clinical judgment should be used if chest compression is absolutely necessary and excessive deep compression should be avoided. Defibrillator pads should not be placed over LVADs drive line while using defibrillation/cardioversion as per advanced cardiac life support protocol. Complications of LVADs can be broadly divided as in **Box 2**.

- *Anticoagulation*: Contemporary LVADs are managed with both an anticoagulant (therapeutic INR 2–3) and an antiplatelet agent (aspirin).

SUMMARY

Cardiomyopathies are diverse group of conditions with varied presentations ranging from HF to SCD. Great deal of progress has been made in imaging and diagnosis of these conditions with understanding of genetics and pathophysiology. Patients presenting with cardiomyopathy need precise diagnosis utilizing the imaging modality available and risk stratification for further treatment.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Valvular Emergencies

Rahul Mehrotra, Mayank Gupta

INTRODUCTION

"If one can hear a heart murmur in the middle of a hectic emergency department, then, by definition the murmur is significant".

This popular dictum highlights the importance of picking a murmur in the busy emergency room (ER). There are several reasons why this over simplified approach has been recommended. Out of all the emergencies encountered in the ER, a cardiac lesion giving rise to a murmur is perhaps one of the less common ones and hence likely to be missed. Besides, it is quite difficult to listen to a murmur in the hustle and bustle of the busy and noisy ER, some of which are very soft and require quiet surroundings to be audible. All murmurs are not pathological and need to be classified before deciding the significance. Murmurs need to be classified in terms of the timing (systolic, diastolic, or continuous), duration, pitch, frequency, response to certain maneuvers, etc. All these are clearly not possible to elicit given the emergency scenario and also an ER physician is not expected to be conversant with all these details. Very often the intensity of the murmur is not proportional to the severity or criticality of the lesion. For example, a diastolic murmur of acute aortic regurgitation (AR) due to proximal aortic dissection involving the aortic valve can be very soft and quite easily be missed.

As such this simplistic approach of considering any murmur picked up in the ER to be significant, rather than dismissing it or analyzing it for significance, appears as a useful strategy. It ensures that no patient with an important cardiac lesion is missed out. Besides, it also captures the frustration emergency physicians feel when trying to diagnose or manage valvular pathologic conditions with familiar yet limited tools, such as the stethoscope, chest radiograph, bedside ultrasound, and electrocardiogram (ECG).

It should be remembered that, more often, a valvular pathologic condition is a chronic, sideline issue that, nevertheless, needs to be taken into account when managing patient's other pressing needs which brings him/her to the ER. Sometimes though, the emergency physician makes a first diagnosis of a problematic heart valve by noting a previously unmentioned murmur on physical examination. *At other times, patients present to the emergency department (ED) with a known valvular disease and the valvular pathologic conditions may be at the very root of the patient's chief complaint, for example, in aortic stenosis causing syncope or acute left-sided valve failure leading to hemodynamic collapse.*

It is thus important for the ER physicians to have a working knowledge of the various cardiac diseases which can present as murmur and the approach that one needs to follow for the different types of murmurs. We discuss these concepts along with four important and common conditions which may be encountered by the ER physicians.

GENERAL CONCEPTS OF A CARDIAC MURMUR

Murmurs are generally classified as systolic, diastolic, or continuous depending on their presence in the cardiac cycle. The gap between the first and second heart sound represents systole and that between second and the subsequent first sound represents diastole. Continuous murmurs pass through/overlap with the second heart sound starting from systole. Further the systolic and diastolic murmurs are graded as depicted in **Table 1**.

Although attention needs to be paid to all murmurs picked up in the ER without any background explanation, some degree of triage can be performed if the ER physician is experienced enough. Apart from auscultation, using stethoscope, echocardiography is of paramount value in this scenario and can rapidly help to resolve the etiology of the valvular lesion,

TABLE.1: Grading of systolic and diastolic murmurs.

Systolic murmurs	***Diastolic murmurs***
Grade 1/6: Barely audible	Grade 1/4: Barely audible
Grade 2/6: Faint, but immediately audible	Grade 2/4: Faint but immediately audible
Grade 3/6: Easily heard	Grade 3/4: Easily heard
Grade 4/6: Easily heard and associated with a palpable thrill	Grade 4/4: Very loud
Grade 5/6: Very loud, heard with a stethoscope lightly on the chest	
Grade 6/6: Audible without stethoscope directly on the chest wall	

the severity of lesion causing the murmur, and associated cardiac abnormalities. There are unique advantages offered by echocardiography which make it an indispensable tool in this scenario. It is extremely safe, versatile, portable (can be carried in the ER), and the results are available instantly. Apart from echocardiography, ECG and chest X-ray are useful adjuncts that should be utilized in most patients.

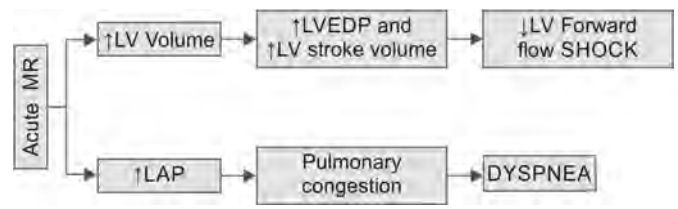
In case of chronic valvular heart diseases, the general teaching is that all symptomatic murmurs need to be evaluated further, usually by echocardiography, either immediately or at a later date. Similarly, no follow-up is needed if the murmur is midsystolic, grade II or softer, and thought to be innocent or functional by an experienced listener (**Flowchart 1**). On the contrary, an asymptomatic murmur that is diastolic, continuous, holosystolic, late systolic, and associated with ejection clicks, or that radiates to the neck or back needs to be evaluated by echocardiography.

In an emergency setting, however, this approach cannot be recommended and the decision has to be individualized based on the expertise in interpreting the murmur, availability of echocardiography facility, the history and hemodynamic status of the patient, etc. The best approach is usually to resolve any murmur heard in the ER before discharging the patient. *We discuss here four important lesions that can present in the ER with murmur.*

ACUTE MITRAL REGURGITATION

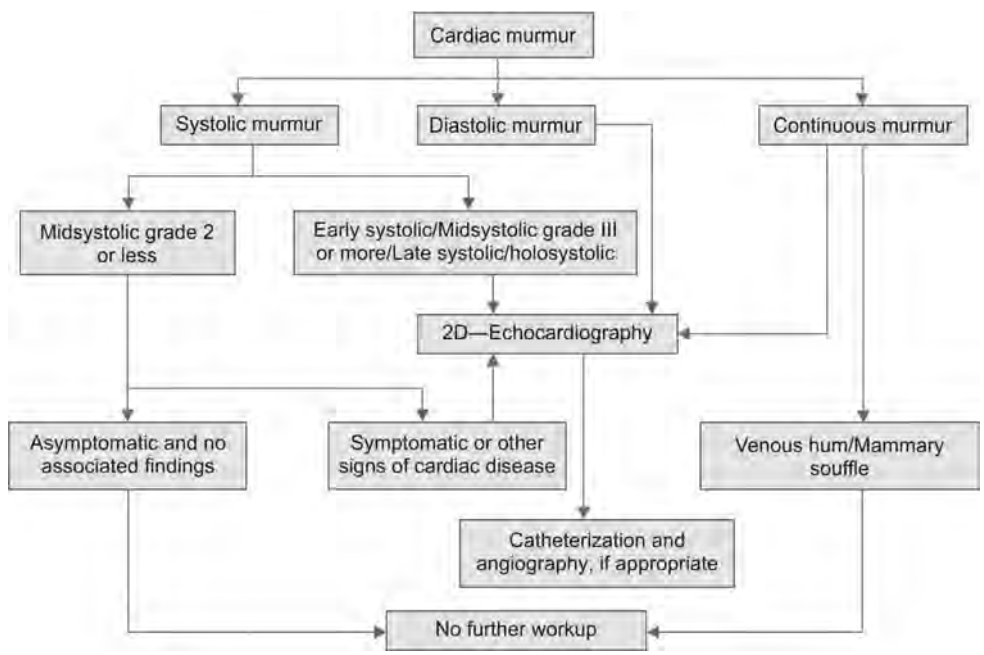
Acute mitral regurgitation (MR) is a medical and surgical emergency. Patients usually present to ED with acute severe decompensated heart failure due to the sudden pressure and volume over load imposed on a previously normal left atrium. In addition, there is an acute drop in the forward cardiac output because a major proportion of the blood pumped by the left ventricles regurgitates into the left atrium instead of flowing forward into the aorta (**Flowchart 2**). However, acute MR is often misdiagnosed as an acute pulmonary disease in the ED because of severe dyspnea, an abnormal chest radiograph and the absence of a clearly audible cardiac murmur. Acute MR typically can also be "silent," without any murmur, because of the equalization of left ventricular (LV) and left atrial pressure in midsystole.

Patients with acute MR generally present with complaints of sudden onset of severe shortness of breath with signs of congestive cardiac failure and cardiogenic shock. On examination, a hyperdynamic cardiac impulse can be palpated, along with a palpable S3, which represents a prominent LV filling wave. On auscultation, the first heart sound, S1 may be diminished while an S3 may be present as a result of increased blood flow across the mitral valve. As discussed earlier, a soft early systolic murmur that may diminish or disappear in late systole may be heard. *A systolic murmur may be entirely absent even with severe regurgitation in patients with* LV *systolic dysfunction or low systemic blood pressure*. However, in view of the clinical scenario, when the differential diagnosis includes acute MR, echocardiography can be used to confirm the diagnosis. Usually, a transthoracic echocardiogram (TTE) performed at the bedside may be sufficient to detect an acute severe MR on color Doppler but sometimes, in extremely eccentric or splayed jets, transesophageal echocardiography (TEE) will be required to detect the true severity of MR and also determine the possible etiology. The vena contracta width measurement and density of the continuous wave Doppler signal are the simplest techniques to quickly determine if significant MR is present. The continuous wave Doppler regurgitant flow velocity curve often shows the characteristic triangular (instead of rounded) shape due to a rapid decline



(LAP: left atrial pressure; LVEDP: left ventricular end diastolic pressure; LV: left ventricle)

FLOWCHART 2: Pathophysiology of acute mitral regurgitation.



FLOWCHART 1: Approach to cardiac murmurs.

in late systolic velocity reflecting the abrupt increase in left atrial pressure. There can be several etiologies responsible for causing an acute severe MR (**Table 2**). The specific features and the associated echocardiographic findings are highlighted in (**Table 3**). Acute ischemic MR is associated with a poor short-term and long-term prognosis even if the degree is only mild or moderate. Emergency coronary revascularization can reduce the magnitude of regurgitation. In patients with acute secondary MR or when the patient is too ill for immediate surgical intervention, pharmacological afterload reduction or use of mechanical circulatory support such as intra-aortic balloon pump (IABP), may be required as a bridge to recovery or to late surgical therapy, with an exception in cases of takotsubo cardiomyopathy and hypertrophic cardiomyopathy.

TABLE 2: Etiology of acute mitral regurgitation.

Acute ischemic MR	• Systolic leaflet tethering related to sudden onset severe LV dysfunction • Moderate MR progress to severe MR
Ischemic papillary muscle rupture	Associated with inferior wall MI often fatal
Infective endocarditis	Rapid valve destruction due to leaflet rupture or chordae rupture in known endocarditis
Iatrogenic	Balloon-induced trauma secondary to PTMC and TAVI/LVAD-induced trauma
Others	• Chest trauma (penetrating and nonpenetrating) • SLE • SAM in patient with takotsubo cardiomyopathy

(PTMC: percutaneous transvenous mitral commissurotomy; TAVI: transcatheter aortic valve implantation; LVAD: left ventricular assist device; SLE: systemic lupus erythematosus; SAM: systolic anterior motion of mitral leaflet)

TABLE 3: 2D echo finding of aortic regurgitation according to etiology.

Papillary muscle rupture	A ruptured muscle papillary head (observed as a triangular mass) swings back and forth between the left atrium and the left ventricle with the entire leaflet prolapsing into the left atrium in systole
Ischemic MR	Leaflet tethering along with a wall motion abnormality in the region of the culprit coronary artery and characteristics leaflet "tenting" due to papillary muscle displacement
Post TAVR	A pigtail catheter or a guidewire in the left ventricle may inadvertently hook the chordae, resulting in substantial MR
LVAD	Frequent echocardiographic evaluation of the position of the transaortic ventricular assist devices are recommended both for optimal positioning for flow and to ensure that they do not affect the mitral apparatus
Takotsubo cardiomyopathy	Apical ballooning and hyper dynamic LV basal wall induce abnormal mitral valve motion in the acute phase with the color Doppler echocardiograph showing turbulent flow due to outflow tract obstruction and the posteriorly directed by MR jet

ACUTE AORTIC REGURGITATION

Patients with acute AR, present with an abrupt onset of symptoms chiefly dyspnea, pulmonary edema, hypotension, or cardiogenic shock and may be confused with pulmonary disease as common with all acute left-sided regurgitant lesions. Acute AR may result from not just the pathology of the aortic valve, but also the aortic root, or both (**Box 1**). The pathophysiology behind symptoms related to acute AR is mainly the consequence of rise in left ventricular end diastolic pressure (LVEDP) secondary to acute AR causing signs and symptoms of cardiac failure (**Flowchart 3**).

So, a patient with acute AR will not have widened pulse pressure seen in chronic AR, because forward stroke volume (and therefore systolic blood pressure) is reduced which help us differentiating acute AR from chronic AR. One may hear a soft S1 with S3 along with brief soft diastolic murmur or a systolic flow murmur. There may be loud P2 if pulmonary hypertension sets in. One should always rule out aortic dissection if a patient present with severe chest pain along with acute AR.

Electrocardiogram shows sinus tachycardia with nonspecific ST-T wave changes but may show ischemic changes if the aortic dissection affects the coronary ostia.

Chest X Ray typically shows signs of pulmonary edema with normal heart size since the lesion is acute. However, if there is cardiomegaly, it strongly suggests chronic disease with acute worsening. Similarly, widened mediastinum on chest X-ray with acute AR usually suggests acute aortic Dissection.

Echocardiography is an important tool to evaluate acute AR with holodiastolic flow reversal in abdominal aorta and premature mitral valve closure being the hallmark of a severe lesion. Aortic dissection in echocardiography is characterized by a flap in the aorta. However, if a transthoracic study is not conclusive, TEE can reveal the mechanism and severity of the regurgitation.

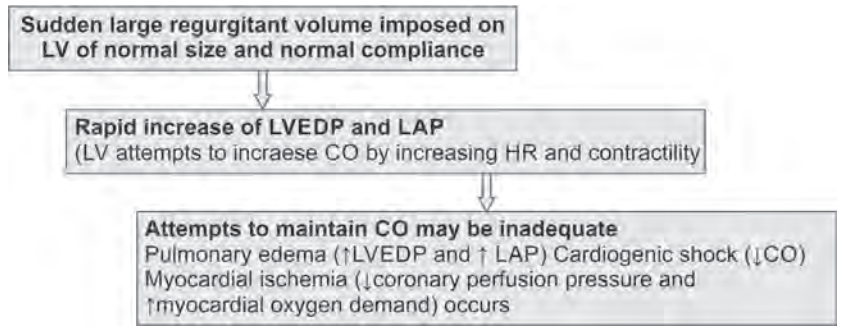
The treatment for acute AR is aortic valve repair or replacement. Medical therapy can stabilize the patient's condition before surgery, but it is not a substitute for surgery. Vasodilators such as sodium nitroprusside can be used to improve forward flow, and inotropic agents such as dobutamine can improve the patient's cardiac output. IABPs tend to be contraindicated in acute AR, because balloon inflation during diastole may impair LV hemodynamics. IABP use is specifically contraindicated in cases of aortic dissection.

PROSTHETIC HEART VALVE THROMBOSIS

Prosthetic heart valve (PVT) thrombosis (obstructive and nonobstructive) is a life-threatening complication that requires

BOX 1: Etiology for acute AR.

- Type A dissection
- Ruptured fenestration
- Blunt Trauma
- Endocarditis
- Prosthetic valve dysfunction
- Iatrogenic injury secondary to instrumentations


Sudden large regurgitant volume imposed on LV of normal size and normal compliance
Rapid increase of LVEDP and LAP
(LV attempts to incraese CO by increasing HR and contractility
Attempts to maintain CO may be inadequate
Pulmonary edema (↑LVEDP and ↑ LAP) Cardiogenic shock (↓CO)
Myocardial ischemia (↓coronary perfusion pressure and
↑myocardial oxygen demand) occurs

(LV: left ventricle; LVDP: left ventricle end diastolic pressure; LAP: left atrial pressure; CO: cardiac output)

FLOWCHART 3: Pathophysiology of acute AR.

immediate diagnosis and treatment. Despite advances in valve technology and improvements in anticoagulation therapy, the incidence of PVT ranges from 0.1% to almost 6% per patient-year for left-sided valves and up to 20% for tricuspid valves. PVT with or without prosthetic valve (PV) dysfunction is a complex *multifactorial phenomenon* which involves *three main factors involved in endovascular thrombus formation (1) surface factors, (2) hemostasis, and (3) hemodynamics-related factors* (**Table 4**).

Patients with a PV dysfunction with or without thrombosis may present with progressive dyspnea and signs of heart failure or systemic embolization**.** Normal caged valves, because of smaller orifice produce some degree of obstruction causing systolic ejection murmur, while tilting disk valves do not occlude their outflow tract completely when closed, allowing some back flow causing low intensity diastolic murmur along with metallic click. Therefore, presence of a diastolic murmur >2/4 grade or absence of metallic click is considered pathological (indicating valve thrombosis). Arterial thromboembolism (TE) after surgical or transcatheter heart valve replacement should be considered prosthesis-related until proven otherwise. Arterial TE manifests with signs and symptoms related to the arterial territory occluded by the embolism such as stroke or transient ischemic attack, acute peripheral ischemia, acute mesenteric ischemia, or acute ischemic kidney injury. PV dysfunction should be suspected in patients with symptoms of acute or subacute onset associated with an increase in transprosthetic gradient across the PHV compared with the last echocardiographic follow-up.

Transthoracic echocardiography is helpful for evaluating PV hemodynamics and valve motion (**Table 5**). However, TEE is superior to transthoracic echocardiography for evaluating PV dysfunction, regardless of the valve type (mechanical or tissue).

In patients with inconclusive transthoracic and TEE findings (which may be rather frequent), multidetector CT provides an accurate evaluation of the PV structure and functional status. Determination of the etiology of the PV dysfunction is the first step in defining subsequent treatment, i.e., surgery, thrombolytic therapy, and anticoagulation, since PV dysfunction can be a life-threatening situation.

The *management strategy (Surgery, thrombolytic therapy and/or anticoagulation)* depends on several factors. The recent European Society of Cardiology (ESC) guidelines recommend surgery on urgent or emergent basis in critically ill patient with no serious co morbidities as class I recommendation and a class II A recommendation in large >10 mm nonobstructive mechanical valve thrombosis. However, in places where surgery is not available or in high-risk patients or in thrombosis of right-sided prosthesis, *fibrinolysis with rTPA [10 mg bolus plus 90 mg over 90 minutes with unfractionated heparin (UFH)] or streptokinase (1,500,000 U in 60 minutes without UFH) should be considered (class II A recommendation).* Anticoagulation using vitamin K antagonist (VKA) or UFH has class I recommendation in patients with bioprosthetic heart valve (BHV) thrombosis and surgery should be considered when anticoagulation fails. However, reoperation has class I recommendation in patient whom there is significant increase in transprosthetic gradient across the BHV or there is significant regurgitation. Transcatheter valve-in-valve implantation in the aortic position should be considered by the heart team depending on the risk of reoperation and the type and size of prosthesis, has class II recommendation.

TABLE 4: Main causative factors for prosthetic valve thrombosis.

Surface factors	*Hemostatic factors*	*Hemodynamic factors*
• Incomplete prosthesis • Endothelialization • Leaflet damage • Stent fracture/ malposition	• HIT • Hypercoagulable state • Suboptimal anticoagulation	• Low cardiac output • Prosthesis hemodynamic profile • Hyper viscosity

(PVT: prosthetic valve thrombosis; HIT: heparin-induced thrombocytopenia)

TABLE 5: 2D echocardiography for PHV thrombosis.

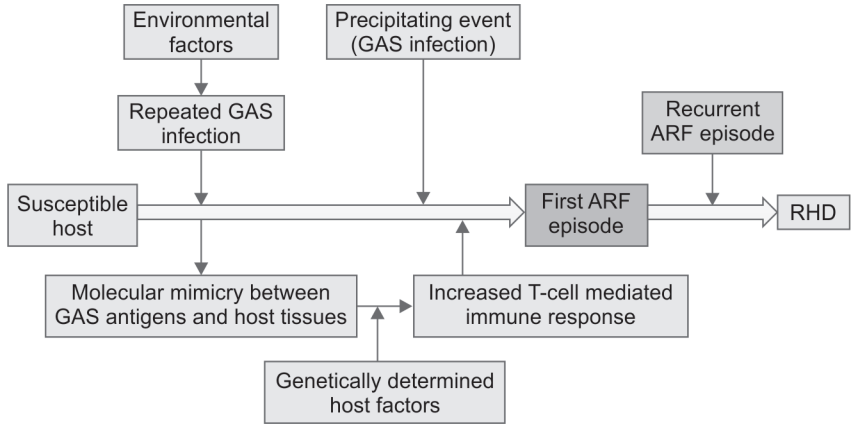
Predictors of MHV thrombosis	*Predictors of BHV thrombosis*
• Increased transvalvular gradient (aortic Pmax ≥ 50 mm Hg, Mitral Pmean ≥ 10 mm Hg) • Presence of occlusive mobile mass on prosthetic valve • An international normalized ration (INR) ≤ 2.5	• >50% increase in mean echo Doppler gradient from baseline within 5 years • Paroxysmal AF • Increased valve cusp thickness • Abnormal cusp mobility

(AF: atrial fibrillation; PHV: prosthetic heart valve)

ACUTE RHEUMATIC FEVER

Rheumatic fever is the leading cause of acquired heart disease in children and young adults worldwide. Initiated by a pharyngeal infection with *group A beta-hemolytic streptococci (GAS)* and following a latent period of approximately 2–3 weeks, the illness is characterized by acute inflammation of the heart, joints, skin, subcutaneous tissue, and central nervous system. Pathologically, the inflammatory process causes damage to collagen fibrils and connective tissue ground substance (i.e., fibrinoid degeneration), and thus rheumatic fever is classified as a connective tissue or collagen vascular disease (**Flowchart 4**). The incidence of rheumatic fever varies from 0.2 to 0.75/1,000/year schoolchildren 5–15 years of age.

A typical patient with an attack of acute rheumatic fever (ARF) is in the age group of 5–15 years and present to the ER with high-grade fever along with complaints of, migratory polyarthritis, often affecting the knees, ankles, and elbows, sparing the small joints of the hands, feet, and hips. Sydenham's chorea, although rare, may occur as an isolated manifestation of ARF. It is characterized by uncoordinated movements of the extremities and face. When it occurs after puberty, it is generally found in women. Carditis associated with murmurs from valvulitis usually is present within the first 3 weeks of ARF. The most common valvular lesion is MR causing an apical pansystolic murmur. AR is less common. Stenotic lesions are uncommon in the early stages of the disease, but a transient apical mid-diastolic murmur (Carey-Coombs) may occur in association with the murmur of MR. The patient may complain of chest discomfort from pericarditis, but isolated myocarditis or pericarditis without valvulitis is rarely seen in ARF. Subcutaneous nodules are often present over the extensor surfaces of joints of the elbows, knees, wrists, or ankles but may also appear on the Achilles tendon, occiput, and spinous processes and they may be associated with carditis. Erythema marginatum is a nonpruritic, annular rash most often found on the trunk and limbs, is usually asymptomatic and can progress to lesions with a raised border and central clearing. Although no specific test exists to confirm a diagnosis of rheumatic fever, the diagnosis is usually made using the clinical criteria first formulated in 1944 by T Duckett Jones. Since then the criteria have undergone multiple modifications, with the most recent revision by the American Heart Association (AHA) in 2015 (**Table 6**).



(GAS: group A streptococcal infection; RHD: rheumatic heart disease)

FLOWCHART 4: Pathogenesis of acute rheumatic fever.

TABLE 6: Ducket-Jones criteria.

	Low-risk population	*Moderate to high-risk population*
Major criteria	• Carditis • Arthritis (polyarthritis) • Chorea • Erythema marginatum • Subcutaneous nodule	• Carditis • Arthritis (monoarthritic, polyarthritis, and polyarthralgia) • Chorea • Erythema marginatum • Subcutaneous nodule
Minor criteria	• Polyarthralgias • Fever (≥38.5°C) • ESR > 60 mm and CRP ≥ 3.0 mg/dL • Prolonged PR interval	• Monoarthralgias • Fever (≥38.5°C) • ESR > 30 mm and CRP CRP ≥ 3.0 mg/dL • Prolonged PR interval

Joint manifestations are only considered in either the major or the minor category, but not in both categories in the same patient.

Annual acute rheumatic fever (ARF) incidence of ≤2 per 100,000 school-aged children or all-age rheumatic heart disease (RHD) prevalence of ≤1 per 1,000 people per year.

Polyarthralgia should only be considered as a major manifestation in moderate- and high-risk populations after exclusion of other causes.

C-reactive protein (CRP) value must be greater than the normal laboratory upper limit. In addition, because the erythrocyte sedimentation rate (ESR) might evolve during the course of ARF, peak ESR values should be used.

The aim of treatment of a proven attack of rheumatic fever is (1) to suppress the inflammatory response and thus minimize the effects of inflammation on the heart and joints, (2) to eradicate the GAS from the pharynx, (3) to provide symptomatic relief, and (4) to commence secondary prophylaxis. The choice of anti-inflammatory is among nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. The appropriate dosages of anti-inflammatory agents are aspirin, 100 mg/kg/day in four or five divided doses to 60–70 mg/kg /days after symptom resolution in mild arthritis +/- carditis, and in moderate-to-severe case prednisone, 2 mg/kg/day for 2 weeks followed by tapering 2.5–5 mg every 3rd day after erythrocyte sedimentation rate (ESR) normalizes with overlapping aspirin for 12 weeks. Chorea is generally self-limiting, administration of carbamazepine or valproic acid can be considered in patients whose symptoms interfere with activities of daily living. Primary prevention of ARF requires therapy for GAS pharyngitis. Patients with ARF are at risk of developing recurrent disease in response to future upper respiratory tract infections caused by GAS. These individuals require continuous antibiotic prophylaxis for secondary prevention (**Table 7**).

SUMMARY

Ninety percent of the valvular heart disease is chronic with delayed onset of symptoms because of adaptation by the heart in form of dilatation or hypertrophy. In contrast to more common chronic presentation, acute valvular heart diseases present with dramatic symptoms and are potentially lethal. Since emergency physicians are the first point of contact in this situation, prompt diagnosis and correct treatment are essential to prevent high mortality and morbidity. The presence of a murmur is often the first clue to the presence of underlying valvular cardiac disorder. These are otherwise not very common for an ER physician to suspect. The following chapter reviews the approach to murmur and common valvular emergencies including physical diagnosis, 2D Echo findings, initial medical therapy, and definitive management.

TABLE 7: Drug therapy for prevention of acute rheumatic fever.

Antibiotics	*Administration*	*Dose*
Drug therapy for primary prevention of acute rheumatic fever		
Benzathine benzylpenicillin	Single intramuscular injection	1.2 million units, if weight <30 kg, reduce the dose by 50%
Penicillin VK	Oral for 10 days	250–500 mg three times daily for 10 days
Erythromycin ethyl succinate	Oral for 10 days	Varies with formulation
Drug therapy for secondary prevention of acute rheumatic fever		
Benzathine benzylpenicillin	Single intramuscular injection every 3–4 weeks	1.2 million units, if weight <30 kg, reduce the dose by 50% (600,000 units)
Penicillin VK	Oral	250 mg twice daily
Sulfonamides	Oral	1gram per day in patient of >30 kg 500 mg in patient of <30 kg
Erythromycin	Oral	250 mg/day

MULTIPLE CHOICE QUESTIONS

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Cardiac Tamponade and Pericardiocentesis

71
CHAPTER

Laila Ali Hussein, Ayesha Almemari, Devendra Richhariya

OVERVIEW OF CARDIAC TAMPONADE

Cardiac tamponade is a complex situation in which accumulation of fluid occurs in pericardial space due to multifactorial cause. Symptoms ranging from minor to fatal situation and can be diagnosed on the basis of signs and symptoms in association with diagnostic imaging. It is very important to know if patient is in cardiac tamponade or not, so evaluate the patient of pericardial effusion for clinical manifestation of cardiac tamponade, take the help of echocardiographic imaging, and also ascertain the history if pericardial effusion developed rapidly or gradually. All these workups in patient of pericardial effusion to find out causes, which are helpful in preventing the cardiac arrest due to cardiac tamponade. Tamponade occurs when intrapericardial fluid accumulation appears more than ventricular diastolic pressure resulting in reduced myocardial compliance and intracardiac chambers. Thus, cardiac filling and cardiac output reduced. The main pathophysiology indicator of cardiac tamponade is equalization of diastolic pressures which can be confirmed by right heart catheterization.

ETIOLOGY

Various conditions can cause (**Box 1**) pericardial effusion followed by cardiac tamponade. Most commonly cause in which rapid progression occurs is traumatic while other medical cause of cardiac tamponade is gradual and more challenging to diagnose. Most common medical causes of cardiac tamponade includes malignancy, renal dysfunction, infection, connective tissue disorder, radiation, chemotherapy, or idiopathic source.

BOX 1: Causes of cardiac tamponade.

- Idiopathic
- Connective tissue disorder—systemic lupus erythematosus (SLE) and scleroderma
- Infection—viral, bacterial, fungal, and parasitic
- Malignancy
- Uremia
- Postmyocardial infarction
- Postoperative
- Radiation
- Traumatic

CLINICAL FEATURES

Apart from traumatic pericardial effusion, the signs and symptoms are neither specific nor sensitive for cardiac tamponade. A rapid deterioration and circulatory collapse should be anticipated if onset signs and symptoms are observed.

Beck triad—muffled heart sound, distended jugular vein, and hypotension pathognomonic for cardiac tamponade. This triad is more prominent in traumatic pericardial hemorrhage. Breathlessness is most common symptom followed by chest pain and palpitation. Tachycardia tachypnea distension of jugular venous pulses is common physical finding. Patient with tamponade may find exaggerated decrease in blood pressure with inspiration which is known as pulsus paradoxus but not pathognomonic of cardiac tamponade.

Findings on clinical examination which showed raised concern for deterioration are, agitation or altered mental status, worsening tachypnea (acidosis), decline in tachycardia (circulatory fatigue) poor extremities perfusion (cold and clammy), and pallor. Hypotension is late finding and not seen until impending cardiac arrest.

DIAGNOSTIC TESTING

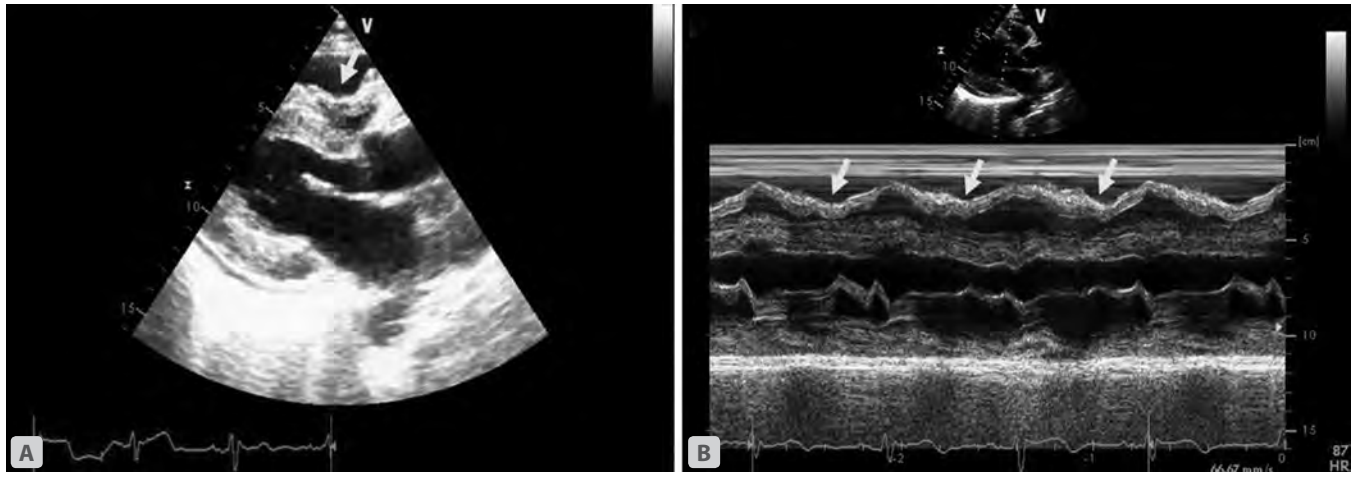
Every patient of chest pain and dyspnea should undergo basic testing of electrocardiogram (ECG), and chest radiograph. In ECG, common finding is tachycardia and low voltage. Electric alternans may present if large pericardial effusion. On chest X-ray *"water bottle heart sign"* enlarged cardiac silhouette is common findings (**Fig. 1**). Every patient of suspected pericardial effusion should be evaluated by echocardiography as per recommendation by American Society of Echocardiography,

FIG. 1: Chest X-ray "water bottle heart sign" enlarged cardiac silhouette.

American Heart Association, and American College of Cardiology. Advantages of echocardiography are its cost effectiveness, noninvasive, portable, and widely availability. For suspected cardiac tamponade, echocardiography is diagnostic modality of choice for evaluation. Bedside clinical finding and echocardiographic finding should be correlated well. Quantification by echocardiography alone might be unreliable.

Echocardiographic findings of cardiac tamponade are:

- Late diastolic RA collapse (**Figs. 2A** and **B**—2D image in apical four-chamber view, B- M-mode)
- Early diastolic RV collapse; (**Fig. 3**—2D image in PLAX view, B- M-mode)
- Significant respiratory variation in mitral inflow velocity (**Fig. 4**)
- Dilated, noncollapsing inferior vena cava (IVC) (**Figs. 5A** and **B**)



FIGS. 2A AND B: Late diastolic RA collapse; 2D image in apical four-chamber view, B- M-mode.

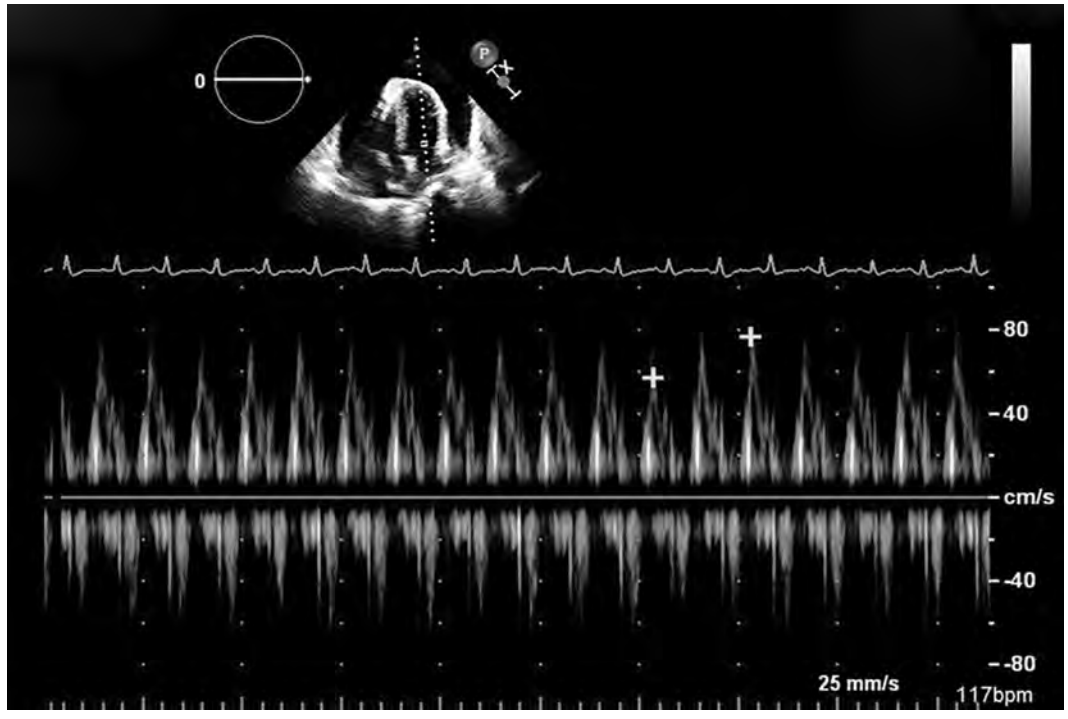


FIG. 3: Early diastolic RV collapse; 2D image in PLAX view, B- M-mode.

MANAGEMENT

Traumatic Cardiac Tamponade

Cardiac tamponade after blunt trauma chest often causes aortic dissection which is associated with high mortality. In this condition, time is very important for immediate interventions. Pericardiocentesis with controlled drainage can be attempted for stabilization. Another option is thoracotomy followed by evaluation of tamponade but it required lot of resources and trained specialist.

Hemodynamically Stable Cardiac Tamponade

Patient of cardiac tamponade, who has not yet suffered cardiovascular collapse, needs continuous cardiac monitoring, and requires resuscitation. These are temporary measure till the definitive therapy is instituted. Many patients are intravascularly hypovolemic. Initially volume challenge should be given with crystalloid fluid. Excessive amount of fluid should be avoided.

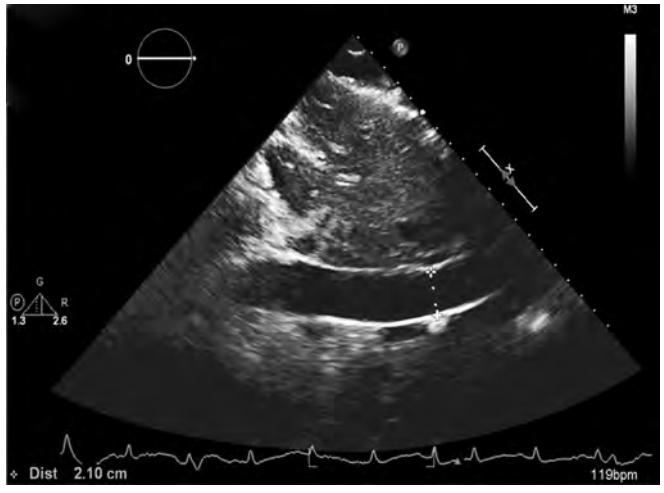


FIG. 4: Significant respiratory variation in mitral inflow velocity.

According to many studies, isoprenaline, dopamine, and dobutamine can be started so first-line agent to raise cardiac output. In case of cardiac tamponade, as no therapy is superior but mostly recommendation is initial use of dobutamine. Some researchers advocate vasopressors (e.g., norepinephrine) to improve blood pressure. The initiation of positive pressure ventilation may result catastrophic circulatory collapse due to increase of intrathoracic pressure and worsen venous return. So, mechanical ventilation may prove deadly in patient with cardiac tamponade.

Hemodynamically Unstable Cardiac Tamponade

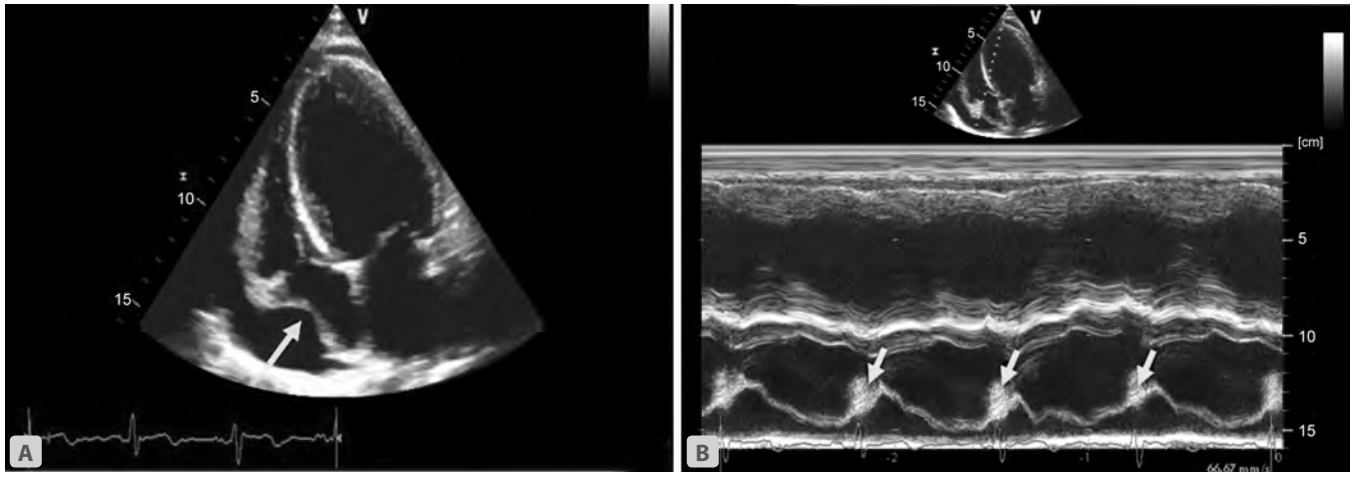
These patients can rapidly progressive to death, so these patients require urgent pericardiocentesis or operative repair. After evacuation of pericardial fluid, stability returns gradually. Evacuation of large amount of pericardial fluid is not advised. Large volume pericardial fluid leads to pulmonary edema and rapid respiratory compromise. In most causes, 50–100 mL of pericardial fluid is sufficient to restore hemodynamics.

PERICARDIOCENTESIS

For treating patient with cardiac tamponade, *three-step scoring system* (**Table 1**) has been developed by *European Society of Cardiology Working Group on Myocardial and Pericardial disease.* This scoring system is based on clinical signs and symptoms and echocardiographic findings**.** Scoring system can be used to identify the patient with immediate need of pericardiocentesis. Emergent pericardial drainage is required if score is 6 or above. Drainage can be postponed up to 48 hours if score is <6.

METHODS FOR REMOVAL OF PERICARDIAL FLUIDS

- Blind percutaneous drainage
- Ultrasound guided pericardial drainage



FIGS. 5A AND B: Dilated, noncollapsing inferior vena cava.

TABLE 1: Diagnosis of cardiac tamponade—three-step scoring system.

1. Score the etiology	*2. Score the clinical presentation*	*3. Score the imaging*
• Malignant disease 2 • Tuberculosis 2 • Recent radiotherapy 1 • Recent viral infection 1 • Recent PE history of pericardiocentesis 1 • Chronic end stage renal disease 1 • Immunosuppression 1 • Hypo- or hyperthyroidism 1 • Systemic autoimmune disease 1	• Breathlessness/tachypnea 1 • Orthopnea 3 • Hypotension 0.5 • Oliguria 1 • Pulsus paradoxus 2 • Pericardial chest pain/friction rub 0.5 each • Rapid worsening of symptoms 2 • Slow progression of disease wrire as 1	• Cardiomegaly on X-ray 1 • Electrical alternans 0.5 • Low voltage ECG 1 • Right atrial collapse 1 • Right ventricular collapse 1.5 • Inferior vena cava (IVC) plethora 1.5 • Respiratory flow variation of mitral valve1 • Swinging heart 1
Calculate the score of 1 + 2 + 3. If score is 6 or >6 perform immediate pericardiocentesis Urgent surgical management is required (irrespective of score) if type A aortic dissection, ventricular free wall rupture, uncontrolled iatrogenic hemopericardium, and severe recent chest trauma		

Source: Ristic D, Imazio M, Adler Y, Anastasakis A, Badano LP, Brucato A, et al. Triage strategy for urgent management of cardiac tamponade: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2014;35:2279-84.

- Percutaneous balloon pericardiotomy
- Surgical creation of pericardial window

Patient in emergency department who is hemodynamically unstable and crashing, first two methods are useful. Patient who is stable and whose tamponade is recurrent and gradual and procedure can be done as semielective with the help of cardiologist and cardiothoracic surgeon. Pericardiocentesis can be performed with a kit similar to central venous catheter kit which consists of 18-gauge spinal needle, 20 mL lock syringe and three-way stopcock. Complications are cardiac chamber perforation, coronary laceration, pneumothorax, intra-abdominal laceration, and hollow viscus injuries.

Blind Subxiphoid (Subcostal) Approach

If there is high clinical suspicion, patient rapidly deterioration, impending cardiac arrest or in pulseless electrical activity (PEA) and if ultrasonogram is not available, the safest approach in emergent situation is blind subxiphoid technique. Needle is inserted between xiphoid process and costal margin with a 30–45° angle towards left mid clavicle (**Fig. 6**).

As described earlier, central venous kit or pericardiocentesis kit if available can be used (**Fig. 7**). Initially, small amount of pericardial fluid should be aspirated so that hemodynamic can be improved and pigtail catheter can be placed which can allow further fluid removal if hemodynamic worsens.

Ultrasound-guided Approach

This is more accurate and safe method to remove pericardial fluid in cases of cardiac tamponade, if ultrasound is available (**Fig. 8**). With the help of ultrasound, largest fluid pocket is identified and aspiration is monitored in real-time throughout the entire procedure. In this process, experienced operator and good hand eye coordination is required. Ultrasound-guided approach is associated with less complications.

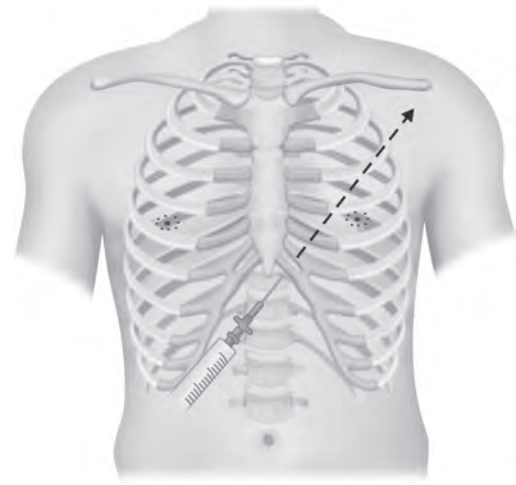


FIG. 6: Subxiphoid approach for pericardiocentesis.

FIG. 7: Emergency department pericardiocentesis kit.

SUMMARY

Traumatic cause of cardiac tamponade (rapidly developing accumulation) presents with hypotension and precipitates

FIG. 8: Ultrasound-guided pericardiocentesis.

death if not diagnosed in time, so in this special situation of cardiopulmonary resuscitation, high index of suspicion is needed. Signs and symptoms of the cardiac tamponade are found nonspecific. With the frequent use of point-of-care ultrasound, even new users can detect pericardial effusion very early and helpful during cardiopulmonary resuscitation. Right atrial and ventricular collapse, plethora of IVC swinging heart, and respiratory variation in mitral flow are highly suggestive of cardiac tamponade.

Once the cardiac tamponade is diagnosed, patient condition should be monitored very closely. Fluid challenge should be given very cautiously, appropriate medication should be given if needed. But lives can only be saved, if skilled team leader diagnoses the cardiac tamponade condition very early and performs immediate pericardiocentesis for stabilization of hemodynamics and patient gets definitive therapy.

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CHAPTER

Cardiac Temporary Pacing

Kartikeya Bhargava

INTRODUCTION

Temporary pacing refers to electrical stimulation of cardiac chambers (usually ventricle, occasionally atrium) as part of the treatment of bradyarrhythmia or tachyarrhythmia. The underlying arrhythmia may be transient, intermittent, or persistent and the temporary pacing aims to establish adequate hemodynamics till the arrhythmia resolves completely or definitive therapy usually in the form of permanent pacing is performed. Though, most commonly, temporary pacing is performed as a lifesaving emergency measures in a patient with symptomatic bradycardia till a permanent pacemaker is implanted; there are many more indications of temporary pacing that will be discussed below.

TYPES OF TEMPORARY PACING

Temporary pacing is performed most commonly in the *ventricles* in order to provide adequate ventricular rate in patients with symptomatic atrioventricular (AV) block; but can also be performed in the *atrium* in patients with symptomatic bradycardia due to sinus node dysfunction or in patients with intact AV conduction and frequent supraventricular or ventricular tachyarrhythmias so as to prevent occurrence of the arrhythmias (ventricular fibrillation or polymorphic ventricular tachycardia) or overdrive treat the arrhythmia (supraventricular tachycardia) if it occurs. *Dual-chamber AV sequential* temporary pacing is often performed through epicardial wires in postoperative patients, though it can be performed transvenously to improve hemodynamic performance in certain patients with AV block such as those with acute inferior and right ventricular myocardial infarction (MI).

Temporary pacing can also be classified according to the route of electrical stimulation as follows:

- *Transvenous pacing*: The pacing lead **(Fig. 1)** is inserted in the right ventricle (or atrium) through a transvenous route from access via either femoral, internal jugular, or subclavian vein. It can be fluoroscopically guided or performed blindly in the emergency or intensive care unit (ICU).
- *Transcutaneous external pacing*: The pacing is performed noninvasively via transcutaneous adhesive patches placed on the chest wall in anteroposterior or anterolateral configuration connected to an external defibrillator with pacing capability. This means of stimulation is painful and used only when transvenous pacing is not immediately available and can be instituted in the emergency often as a bridge to transvenous pacing.
- *Epicardial pacing*: The pacing is performed usually in the postoperative period through temporary epicardial fine pacing wire electrodes implanted during cardiac surgery. The wires are usually removed before discharge from the hospital and hence this means is not available to the emergency physician.
- *Transesophageal pacing*: The pacing is performed through a flexible pacing electrode placed in the midesophagus (for atrial pacing) or the fundus of the stomach (for ventricular pacing). This approach is better tolerated in a conscious patient than transcutaneous pacing as it is painless but is not frequently used clinically.

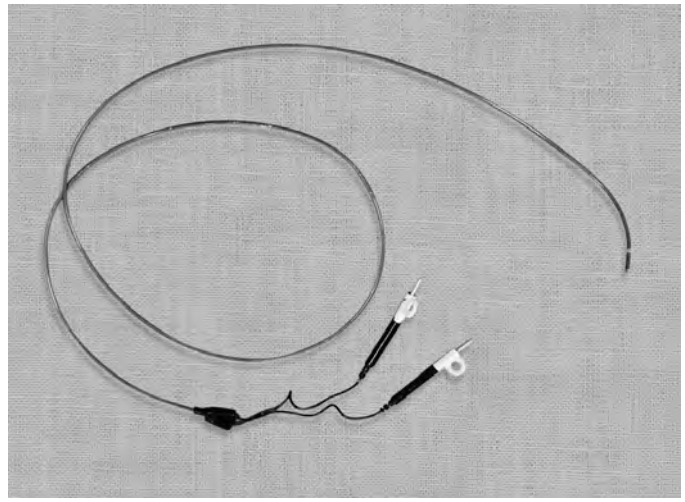

FIG. 1: *Transvenous temporary pacing lead*. The lead has two electrodes (distal tip and the proximal ring) at its tip and two connecting pins—distal and proximal at the other end where it connects with the pulse generator via a connecting cable.

INDICATIONS OF TEMPORARY PACING

Most commonly temporary pacing is performed as an emergency procedure in patients with symptomatic and/or life-threatening bradycardia, although many elective indications of temporary pacing also exist (**Box 1**). In general, emergency temporary pacing is reserved for patients with bradycardia who have recurrent syncope occurring at rest (mostly AV block), or hemodynamically instability or ventricular tachyarrhythmias due to bradycardia. The patients with sinus node dysfunction are usually not symptomatic at rest and if pacing is indicated, they can directly undergo permanent pacing. Temporary transvenous pacing poses the risks of not only infection but also damages to venous access sites that may potentially be needed for permanent pacing; and hence should be avoided if possible without compromising patient's safety.

Among patients with acute MI, one needs to be more proactive and aggressive with temporary pacing in those with anterior MI. Sinus bradycardia and AV block associated with acute inferior MI are usually hemodynamically well tolerated, responsive to drugs and fluids, not life-threatening and infrequently need temporary pacing. AV block in most patients with acute inferior MI recovers spontaneously with time and permanent pacing is only rarely necessary. On the other hand, bradyarrhythmias or new intraventricular conduction disturbances associated with acute anterior MI can result in unpredictable and sudden hemodynamic deterioration and warrant temporary pacing although, many of them may not require permanent pacing. Elective temporary pacing is usually required to cover for any pacing support in catheterization laboratories or surgical procedures in patients with high risk of AV block or bradycardia.

BOX 1: Indications of temporary cardiac pacing.

Emergency indications:

- Complete or second-degree (Mobitz II or advanced or high grade) atrioventricular block with recurrent syncope at rest as a bridge to permanent pacing
- Ventricular tachyarrhythmias related to bradycardia
- Bradyarrhythmias in acute myocardial infarction:
  - Ventricular asystole
  - Symptomatic or hemodynamically significant bradycardia unresponsive to atropine—sinus bradycardia or second-degree type 1 AV block
  - Complete AV block associated with hypotension, or wide QRS escape rhythm or ventricular arrhythmias
  - Mobitz type II AV block
  - Intraventricular conduction defects at high risk of unpredictable complete AV block or asystole even with absence of symptomatic bradycardia, e.g., new or indeterminate bifascicular block with prolonged PR interval, bilateral bundle branch block, and alternating bundle branch block
- Recurrent polymorphic ventricular tachycardia with or without QT prolongation not adequately controlled by drugs
- Recurrent monomorphic ventricular tachycardia or supraventricular tachycardia not controlled with drugs in order to overdrive treat the arrhythmia

Elective indications:

- Catheterization laboratory procedures with potential for requirement of temporary pacing support:
  - Pacemaker pulse generator replacement in patients with complete AV block or pacing dependence
  - Permanent pacemaker system explantation usually for infection
  - Immediately prior to permanent pacemaker or CRT device implantation in patients with AV block or left bundle branch block
  - Alcohol septal ablation for hypertrophic cardiomyopathy
  - Rota-ablation of coronary stenosis especially right coronary artery
  - Transcatheter aortic valve implantation
- Noncardiac surgery under general anesthesia in patients with high risk of AV block
- Cardiac surgery—epicardial pacing wires are routinely placed for any perioperative pacing requirement

TEMPORARY PACING PROCEDURE

Transvenous Pacing

The temporary pacing is best performed under fluoroscopic visualization in catheterization laboratory; however, it is often performed blindly at the bedside as an emergency procedure especially if catheterization laboratory facility is not available. Though, many routes of venous access, each with its advantages and disadvantages are available, the femoral vein (in catheterization laboratory) and the right internal jugular vein (bedside) are the most suitable and most commonly used approaches. In general, the subclavian veins especially the left should be avoided for temporary pacing since these may be needed in future for permanent pacemaker implantation.

The procedure entails placement of a venous sheath using Seldinger's technique taking all aseptic precautions in a sterile environment, positioning of the temporary pacing lead (**Fig. 1**) in the right ventricle (or atrium) preferably under fluoroscopy, connecting the lead to an external pulse generator **(Fig. 2)**, ensuring adequacy of electrical pacing parameters and finally securing the lead with sutures to the skin to avoid its displacement. Some experience is needed to negotiate the lead from the right atrium across the tricuspid valve in the right ventricle and echocardiography can sometimes be very useful in guiding the lead placement in absence of fluoroscopy at the bedside.

Transcutaneous Pacing

The external transcutaneous pacing can be easily performed without much learning curve using transcutaneous defibrillation patches (**Fig. 3**) and an external defibrillator (**Fig. 4**) with pacing capability. The patches can be placed preferably in anteroposterior configuration on the chest but an anterolateral configuration can be used in an emergency situation. Though, this means of pacing is painful and often requires the patient to be sedated; it can be very useful due to universal availability in emergency wards and coronary care units and ease of use. Moreover, this is often very useful to transfer a patient from a small nursing home to a facility with catheterization laboratory.

FIG. 2: *Temporary pacing pulse generator*. This is a single chamber pulse generator and has three knobs for adjusting pacing rate, output and sensitivity; light indicators for pace, sense, and low battery; switches to turn on or off; a port for connecting the cable and a battery that can be replaced. The model shown also has capability of delivering rapid pacing (beyond 180/min) mainly used for rapid atrial pacing to terminate supraventricular tachycardia or atrial flutter.

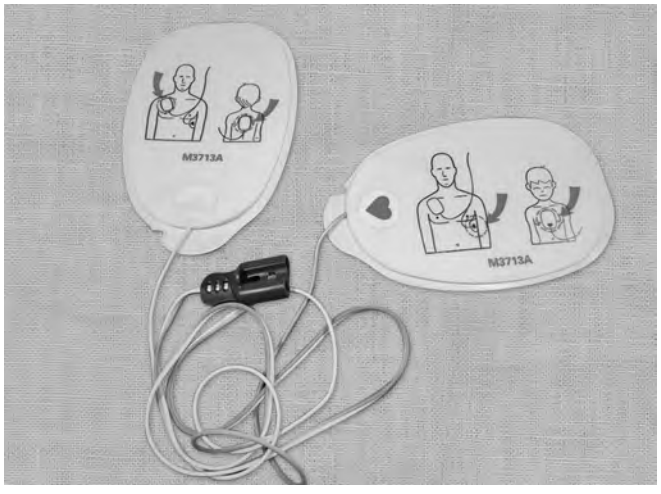

FIG. 3: *Transcutaneous patches for pacing and defibrillation*. The two patches are attached to the right anterior and left lateral (or posterior) chest wall as shown and are connected to the external defibrillator using the attached connecting cable.

FIG. 4: *External defibrillator*. The external defibrillator can deliver transcutaneous temporary pacing through patches shown in **Figure 3**. The rate and output of pacing can be adjusted as per the patients need, tolerability, and capture threshold.

BOX 2: Complications of temporary transvenous pacing.

- *Venous access-related complications*:
  - Hematoma and bleeding at puncture site, femoral pseudoaneurysm
  - Venous thrombosis and pulmonary embolism
  - Pneumothorax (internal jugular or subclavian puncture) or hemothorax
  - Infection at local puncture site
- *Lead placement related complications*:
  - Catheter knotting
  - Tricuspid valve injury
  - Myocardial perforation and cardiac tamponade
  - Air embolism
- *Pacing lead related and electrical issues*:
  - Lead dislodgement or disconnection
  - Cardiac perforation and tamponade
  - Extracardiac (phrenic nerve) stimulation
  - Increase pacing threshold
  - Ventricular arrhythmias—ectopics, and tachycardia due to mechanical effect of the lead or inappropriate pacing due to improper sensing

COMPLICATIONS OF TEMPORARY PACING

As with any invasive procedure, transvenous temporary pacing can also lead to complications in 14–20% of patients, the frequency of which increases with the duration of pacing. The complications may be related to the venous access, mechanical effects of the pacing lead or to the electrical issues (**Box 2**).

POSTPROCEDURE CARE

Care of the patient after temporary transvenous pacing in the emergency and ICUs is very important to prevent complications and recognize them promptly if they occur. *The salient points are mentioned below*:

- *Postprocedure and periodic chest X-ray and ECG*: A chest X-ray should be performed to ascertain the position of the pacing lead and also look for any pneumothorax or hemothorax. Similarly, an ECG should be performed postprocedure and repeated if needed to assess adequate sensing and pacing. If there are any doubts, an echocardiogram should be performed to look for lead position and presence of pericardial effusion.

- *Continuous ECG monitoring*: The patients with temporary pacemaker should have continuous ECG monitoring in order to promptly recognize any loss of pacing or occurrence of ventricular arrhythmias.
- *Checking electrical parameters,* system integrity and pulse-generator battery—at least once daily checking of sensing and pacing parameters, lead connections and need for battery change should be performed and adequacy of parameters programmed should be ensured. The pacing output should be programmed to at least three times the pacing threshold. The underlying rhythm should also be checked by gradually reducing the pacing rate to below intrinsic rate to assess the continued need for temporary pacing. Lack of pacing and asystole often occurs due to loose connections or rise in pacing threshold.
- *Care of the access site*: An occlusive dressing with antibiotic or antiseptic ointment should be performed at the site of puncture and sheath access to prevent infection. The dressing should be changed if soiled and once daily. If the sheath is in place, it should be flushed periodically with heparinized saline to prevent thrombosis.
- *Prevention of infection*: Prophylactic antibiotics that cover *Staphylococcus* should be used especially if a femoral route has been chosen for temporary pacing. If the temporary pacing is to be used for a prolonged period (>7 days) or any sign of local infection is seen, the pacing site and lead should be changed to prevent systemic infection.

SUMMARY

Temporary cardiac pacing involves electrical stimulation of the heart usually the ventricles in order to treat bradyarrhythmias and sometimes tachyarrhythmias and is commonly performed transvenously using a pacing lead and pulse generator. It should be used judiciously and only when necessary for an appropriate length of time in order to avoid its complications. Choice of the approach, the access site and the duration of pacing need to be individualized based on the patient's requirements and routine postprocedure care taken to prevent complications from this procedure.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Postcardiac Surgery Emergencies

Yatin Mehta, Devendra Richhariya

INTRODUCTION

Cardiac surgery is an evolving surgical specialty which had significant morbidity and mortality in past, but with streamlining of the specialty by protocols for every aspect of cardiac surgery, the morbidity and mortality both have come down significantly in the last few decades. Quality surgical as well as anesthetic care with utmost attention to every detail can further improve the outcomes (**Box 1**).

PARAVALVULAR AORTIC/MITRAL REGURGITATION

If this is diagnosed immediately after coming off cardiopulmonary bypass (CPB) by transesophageal echocardiography (TEE), It requires going back on CPB and placing the valve in appropriate manner as to treat the paravalvular aortic regurgitation/mitral regurgitation (AR/MR). However, if it happens to be a delayed complication (delayed diagnosis or delayed presentation), it can also be treated in cardiac Catheterization laboratory by device closure of the regurgitation. Late paravalvular AR or MR (paravalvular leaks) is hemodynamically insignificant. However large ones lead to heart failure, intravascular hemolysis, and increased risk of infectious endocarditis. Hemolysis is also common in small paravalvular leaks. RE-DO surgeries are associated with very high risk while transcatheter closure devices techniques are less invasive and of immense use in high-risk patients**.** Other *diagnostic clues* are continuing sign and symptoms of heart failure in postoperative period (or even later) with evidence of hemolysis such as falling hematocrit, rising bilirubin elevated lactate dehydrogenase activity (LDH), changed reticulocyte counts, etc. The diagnosis is confirmed by echocardiography.

BOX 1: Common postcardiac surgery emergencies.

- Paravalvular aortic or mitral regurgitation
- Bleeding (bleeding requiring reexploration)
- Arrhythmias (atrial fibrillation and other dysrhythmias)
- Acute coronary syndrome (ACS) following surgery
- *Early tamponade*: Collection of blood around heart requiring reexploration of the chest
- Tension pneumothorax
- Stroke
- Acute kidney injury (AKI)
- Acute decompensated heart failure (ADCHF)/low cardiac output syndrome (LCOS)
- Respiratory failure

Treatment

Either surgical or using the transcatheter closure devices. Reoperation is the choice of procedure when paravalvular leaks are associated with significant dysfunction or mechanical instability of the prosthetic valve or associated with infective endocarditis. Transcatheter device closure is reserved for small paravalvular leaks.

BLEEDING

Excessive Bleeding

Considering the complexity of cardiac surgery, the inflammatory cascade generated by CPB machine and circuit, bleeding remains an issue which requires due attention. But with the institutional protocols being in place for the kind of patients who will need to be re-explored for bleeding, the decision-making is not difficult.

What is Significant Bleeding?

Various criteria have been used to define excessive bleeding, as a rough guide, it is the chest tube and mediastinal tube drainage of >200 mL/h for 4 hours, >1,000 mL in total, or a sudden drainage of 400 mL. Any sudden and significant increase in drainage is considered as a genuine reason to reexplore the mediastinum and chest because it signifies a disruption of surgical anastomosis or a slippage of clips or bleeding from aortic cannulation site. In pediatric cardiac surgeries, it is significant if the chest tube drainage and mediastinal tube drainage are >10 mL/kg in the first hour after the surgery or a total of >20 mL/kg over the first 3 hours after surgery.

BOX 2: Measures to prevent/control postcardiac surgery bleeding.

- Stop platelet inhibiting drugs in advance if possible (especially clopidogrel for 5–7 days)
- Avoid hypertension after aortotomy
- Rule out surgical cause and achieve hemostasis with reasonable speed (delaying closure also increases propensity to bleed)
- *Chest radiograph*: To get an idea of collection
- *Neutralize heparin*: More protamine is suggested in a dose of 0.5–1 mg/kg, if ACT is >150 seconds or the aPTT is more than 1.5 times control
- Warm the patient to above 36° as hypothermia is known to increase bleeding tendencies
- *Apply PEEP*: 5–10 cm H_2O. Although it has *not a proven role,* but it is still used with the theoretical rationale of a tamponade effect on the bleeders and oozing
- Desmopressin in the dose of 0.2–0.4 µg/kg intravenously is suggested when bleeding time is prolonged with expected platelet defect
- Epsilon aminocaproic acid in a bolus dose of 50 mg/kg, followed by 25 mg/kg/h is used as *antifibrinolytic prophylaxis*
- Similarly, tranexamic acid in a bolus dose of 10 mg/kg, followed by 1 mg/kg/h can be used as *antifibrinolytic prophylaxis*
- Platelet transfusion in pediatric is weight guided as a dose of *1 U/10 kg* when platelet count is less than 100,000/mm^3. However, in adult, platelet transfusion is not weight guided
- Fresh frozen plasma in a dose of *15 mL/kg is transfused when the* PT or aPTT is more than 1.5 times control
- Cryoprecipitate in dose of *1 U/4 kg when the* fibrinogen levels are >1 g/L or 100 mg/dL
- Recombinant *factor VIIa* with a risk of graft occlusion in CABGs
- *Acceptable limit*: Bleeding below 50 mL/h for 2 hours is acceptable to consider the patient for extubation

(ACT: activated clotting time; aPTT: activated partial thromboplastin time; CABG: coronary artery bypass grafting; PEEP: positive end-expiratory pressure; PT: prothrombin time)

At times, postoperatively cardiac surgery patients bleed more. In such cases, early diagnosis and intervention helps in preventing impairment hemodynamic, anemia, and impairment of hemostasis, tamponade, and reduction of innate coagulation factors (**Box 2**).

Cardiac surgery, especially because it involves heparin and at times the use of thrombolytics in preoperative period as in emergency coronary artery bypass graftings (CABGs) may end up with deranged hemostasis and hence increased bleeding. Also, the use of CPB leads to platelet destruction, dilutional coagulopathy, and activation of inflammatory and coagulation cascades. However, these are not the only factors leading to increased bleeding after any cardiac surgery. Approach to postcardiac surgery bleeding is summarized in **Flowchart 1**.

ARRHYTHMIAS

Atrial Fibrillation

Arrhythmias are one of the most common complications in the postoperative period of cardiac surgery. Postsurgically, the most common arrhythmia seen is atrial fibrillation (AF), occurs in nearly 30–40 % of patients; while the cause is poorly understood, the factors linked to the occurrence of AF are age, male sex, prior episode of AF, surgeries related to mitral valve, and a history of heart failure. AF has a strong association with increased mortality and morbidity in terms of stroke and prolonged hospital stay. *Risk factors for postsurgery AF are* fluid and electrolyte imbalance associated with the use of diuretics, enlargement of left atrium/right atrium because of stenosis or regurgitation of atrioventricular valves, left atrium enlargement associated with diastolic dysfunction, hypoxia, pulmonary emboli, and myocardial infarction.

Prophylaxis and treatment modalities can be achieved by amiodarone, magnesium, and/or beta-blockers. Normally, amiodarone is given first as a slow bolus and followed by infusion. Commonly is stable AF, so does not require DC shock as an emergent maneuver. Management of AF is rate control and if possible, conversion of rhythm to sinus rhythm, or rate control with anticoagulants. Amiodarone is relatively less depressant to the heart than other antiarrhythmic drugs. It is used in the dose of 150–300 mg intravenously to manage acute postoperative AF. Its use is therefore justified in patients with poor left ventricular (LV) function than other antiarrhythmic drugs.

Regimen for Amiodarone

As an intravenous infusion, 150 mg in 10 minutes, followed by 1 mg/min for 6 hours, followed by 0.5 mg/min for 18 hours. AF longing >48 justifies the use of echocardiography, preferably TEE to rule out LA clots. TEE should be done before any intervention to revert the rhythm. Use of thromboembolic prophylaxis in such cases is warranted. In those with risk factors such as previous stroke, heart failure, diabetes mellitus (DM), and advanced age, warfarin is used with a target international normalized ratio (INR) between 2 and 3.

Ventricular Fibrillation

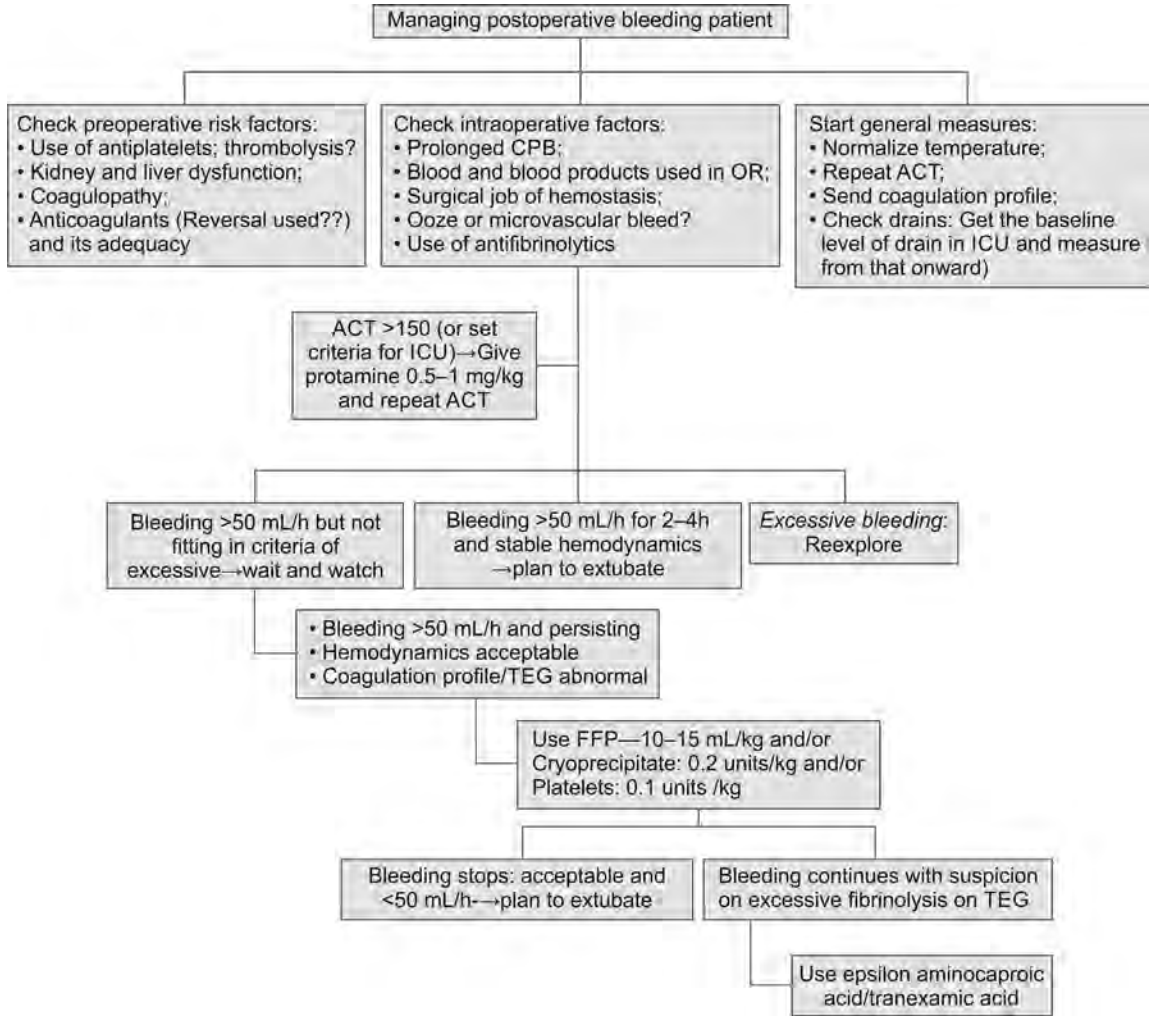
Ventricular fibrillation (VF) commonly occurs just while coming off CPB, which is acceptable at that moment (it is not a surprise at that moment). Defibrillation by internal cardiac defibrillation 10–20 j (1–4 j/kg in pediatrics) is sufficient. However, if it occurs late in the course like in postcardiac surgical ICU, it is treated as any witnessed arrest with a VF and treated on the same lines. The only difference is that there can be internal cardiac massage after opening the chest if the need so arises. The dose for external defibrillation is 150–200 j biphasic.

Ventricular Tachycardia

Stable or unstable ventricular tachycardia (VT); stable VT may be given a trial of medical treatment, however, if unstable, the treatment is defibrillation. Other arrhythmias are not very common in postcardiac surgery barring pediatric surgery where they may occur.

Prophylaxis for Arrhythmias

Though not proven with certainty to have a predictable antiarrhythmic, anti-ischemic effect, magnesium in the dose of 2 g slow intravenous dose and lignocaine 100 mg bolus followed by an infusion at the rate of 2 mg/min are used. A universal drug


Managing postoperative bleeding patient
Check preoperative risk factors:
• Use of antiplatelets; thrombolysis?
• Kidney and liver dysfunction;
• Coagulopathy;
• Anticoagulants (Reversal used??) and its adequacy
Check intraoperative factors:
• Prolonged CPB;
• Blood and blood products used in OR;
• Surgical job of hemostasis;
• Ooze or microvascular bleed?
• Use of antifibrinolytics
Start general measures:
• Normalize temperature;
• Repeat ACT;
• Send coagulation profile;
• Check drains: Get the baseline level of drain in ICU and measure from that onward)
ACT >150 (or set criteria for ICU)→Give protamine 0.5–1 mg/kg and repeat ACT
Bleeding >50 mL/h but not fitting in criteria of excessive→wait and watch
Bleeding >50 mL/h for 2–4h and stable hemodynamics →plan to extubate
Excessive bleeding: Reexplore
• Bleeding >50 mL/h and persisting
• Hemodynamics acceptable
• Coagulation profile/TEG abnormal
Use FFP—10–15 mL/kg and/or Cryoprecipitate: 0.2 units/kg and/or Platelets: 0.1 units /kg
Bleeding stops: acceptable and <50 mL/h-→plan to extubate
Bleeding continues with suspicion on excessive fibrinolysis on TEG
Use epsilon aminocaproic acid/tranexamic acid

(ACT: activated clotting time; ICU: intensive care unit; FFP: fresh frozen plasma; TEG: thromboelastography)

FLOWCHART 1: Algorithm for management of bleeding.

for all kind of arrhythmias is amiodarone—though there is no scientific evidence to support its use, magnesium in a dose of 2 g is frequently given prior to CABG in many institutes. The multidisciplinary team will have to come to a rationale-based use of such drugs as a prophylaxis.

Bradycardias

Bradycardias especially complete heart block (CHB) is most commonly seen either in aortic valve replacement (AVR) on adults or in ventricular septal repairs in children because of the unintended damage to the conduction system. For the same reason, the pacing wires are left in AVR for 72 hours and for nearly 48 hours in CABG or mitral valve replacement (MVR). At the completion of the open heart procedure/or CABG and before closing the chest, pacing wires are normally placed epicardially at the end of the surgery as a prophylactic measure, so that whenever the need arises, the wires can be attached to the external pacemaker to tide over the crisis. Later, if the patient is pacing dependent, the patient may be given a permanent pacemaker in the cardiac catheterization laboratory. The most common mode used in the postoperative period is DDD. A cautionary note here is never to leave the patient with DOO or VOO because it is just a sensing mode.

TENSION PNEUMOTHORAX

Normally in the immediate postsurgical time, this emergency is not seen because mediastinal and chest tubes are in place (unless the tubes are blocked with blood or kinked); however, it may occur on the side where the chest tube is not placed. It may also occur later in postoperative period when the chest tube is removed. Most of the times, if it is tension pneumothorax, it is diagnosed clinically and confirmed on CXR or while putting the chest drain on mere clinical suspicion. If the hemodynamics suddenly gets deranged, differential diagnosis of tension pneumothorax should be kept in mind along with other causes. Check the chest tube or any blockade with blood, or crimping. And if found so, then release the blockade or crimping. If it does not get resolved, then place wide-bore angiography catheter in the anterolateral part of chest above T4 level. Consider placing intercostal drain on ipsilateral side (with pneumothorax).

CARDIAC TAMPONADE

Cardiac tamponade is a common but largely unrecognized cause of the Low cardiac output syndrome (LCOS) after cardiac surgery. It happens when the heart gets compressed

by blood and/or clots and/or fluid accumulating in the mediastinum. Hemodynamic derangement due to tamponade is seen in nearly 3–6% of the patients requiring massive/multiple blood/blood products for bleeding after surgery. Postoperative cardiac tamponade is called acute when it is within 24 hours of surgery. Delayed pericardial tamponade on the contrary develops after 10–14 days after surgery. Delayed tamponade is known to occur in patients on preoperative anticoagulants.

Reduced filling of the heart because of tamponade causes hemodynamic collapse. As the collection or tamponade increases, pressure inside heart increases in order to compensate. However, if the pressure because of tamponade is more than pressure because of filling inside the heart, diastolic collapse of ventricle (right ventricle first) happens leading to severe deterioration of hemodynamic. Reduced venous return leads to reduced filling (lesser end diastolic volume) which in turn leads to reduced end systolic volume. This explains the LCOS in cardiac tamponade. Low cardiac out, reduced atrial natriuretic factor (because of decreased atrial size because of tamponade), and increased adrenergic discharge in turn lead to reduced urine output.

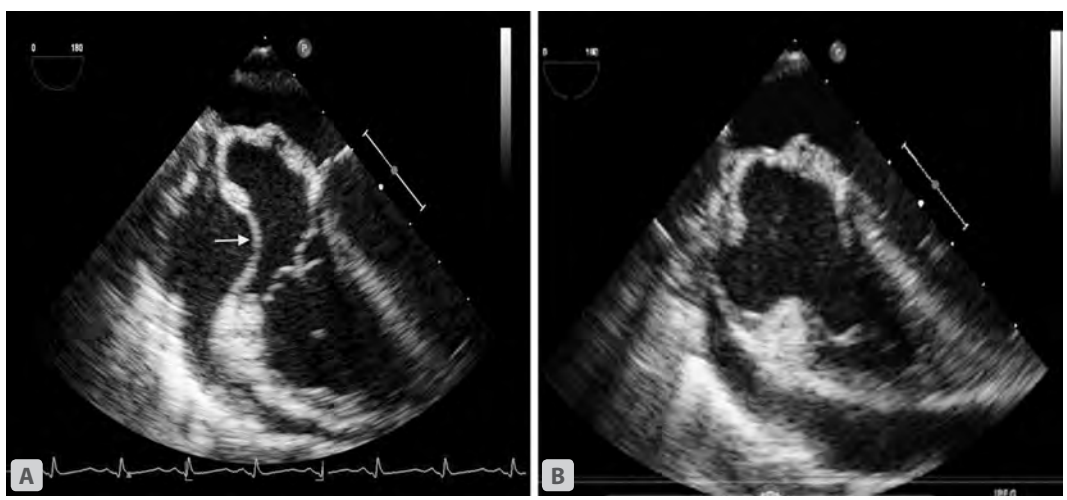
The tamponade that happens postoperatively is very different from tamponade arising of medical reasons (which happen slowly and is therefore well tolerated) because postoperative pericardial tamponade can be regional as well global, clotted and unclotted, pericardium open, and communicating with the pleural cavity. In a slowly increasing pericardial collection (especially medical), compensatory changes occurring over a period do not allow hemodynamic collapse even in presence of a major collection in the pericardial cavity (>1,000 mL). Many surgeons leave the pericardial cavity open and in communication with pleural cavity, so, at times it may be well tolerated even with large volumes.

A very high degree of suspicion should be kept for this diagnosis. If the hemodynamic suddenly deteriorates, it is advisable to open the chest and not wait for the diagnosis. Diagnosis of tamponade is considered in a postcardiac surgery patient whose hemodynamic deteriorate along with (or without) a classical triad of lower blood pressure, increased heart rate and increased filling pressures, and/or low cardiac output. However, it may also present as slowly increased requirement of inotropes and pressers. The classic findings of elevated central venous pressure or equalization of intracavity pressures (in all chambers of heart) may or may not occur. Similar clinical picture is seen in postoperative biventricular failure. invasive positive pressure ventilation (IPPV) deteriorates, it further because of excessive additional pressure on the heart leading to further reduction of filling. Increased pulse pressure variation and stroke volume variation with IPPV when seen with increased central venous pressure and reduced cardiac output should be sufficient to ring the bell toward tamponade.

With a widened cardiac shadow in chest X-ray (CXR), significant pericardial collection on echocardiography, reduced drainage, and deranged hemodynamics—the patient is a candidate for urgent exploration of the chest for relieving tamponade. Similarly, if you have a patient who is not maintaining hemodynamic despite two inotropes, and good amount of intravenous fluids, you must consider tamponade.

Echocardiographic features of tamponade (**Figs. 1** to **3**) include systolic collapse of right atrium and left atrium (atrial diastole) and diastolic collapse of RV (LV collapse does not occur, but occasionally it may occur) along with fluid all around the heart. However, these may not necessarily be seen in a postcardiac surgery patient. However, if the fluid is present all around the heart, more the fluid moves anterior, more is the severity.

Management includes intravenous fluids and inotropes but not those alone; the exploration of chest for removing clots and relieving tamponade is the definitive treatment. It may happen that the tamponade is acute and severe, in that case it may need to be explored as an emergency in postcardiac surgery unit only. If tamponade occurs later than 2 weeks, it is justified to proceed with pericardiocentesis. While the preparations are made to explore the chest, it is advisable to go liberal with intravenous fluids and increasing inotropic doses. Both these measures manage to improve cardiac output till definitive measures are taken. Ventilation should be managed with lowest tidal volume and positive end-expiratory pressure (PEEP) which allows acceptable gas exchange as the mechanical ventilation causes increased pressure on the already compromised heart and its venous return. Sedation should be used with utmost caution as the innate sympathetic discharge may be compromised which is required to maintain hemodynamic.



FIGS. 1A AND B: Systolic collapse of RA in pericardial tamponade; (B) Diastolic collapse of RV in pericardial tamponade.

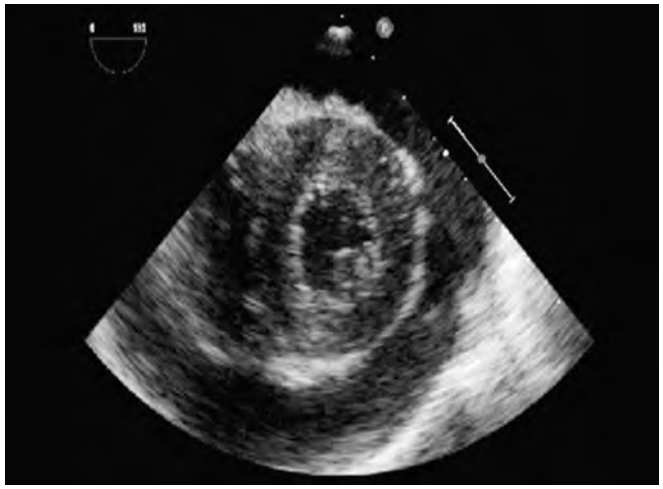


FIG. 2: Fluid all around the heart in pericardial tamponade (fluid is even around the anterior most part of heart indicating that it is severe).

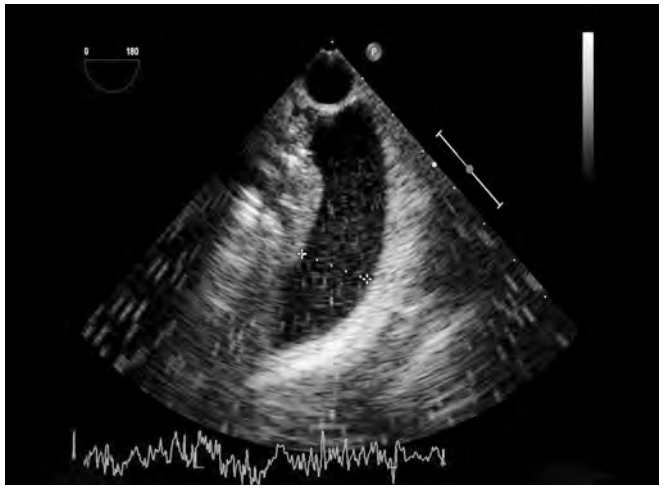


FIG. 3: Associated pleural collection in a c/o pericardial tamponade (tiger claw sign depicting the left pleural collection—claw tip on left side).

ACUTE CORONARY SYNDROME FOLLOWING CARDIAC SURGERY

Myocardial ischemia in postoperative period is not as uncommon as thought. It occurs in nearly 30–45% of patients who underwent CABG. It is detectable in the form of electrocardiogram (ECG) and echocardiographic changes in the form regional wall motion abnormalities (RWMAs). Significant RWMAs are associated with worse outcomes.

Causes

Though there is revascularization of the heart but during the procedure itself, plaques can rupture; later in postoperative period grafts can clot or the lie of the grafts may make them prone to kinking and occlusion, air bubbles (especially in the immediate postoperative period while coming off CPB), stunning, tachycardia, and excessive use of inotropes all can lead to acute myocardial infarction. During valvular repair, coronary artery may get occluded accidentally and may lead to fresh hemodynamic instability, most of the times immediately going back on CPB, if recognized then and correcting the cause. The notorious amongst these is the left circumflex artery getting included while doing MVR.

The handling of the tissues during cardiac surgery leads to troponin I levels getting elevated even without MI. The acceptable limit of troponin levels in postoperative period is 10 times the normal. However, if it exceeds 20 times the normal, it probably indicates ischemia and is associated with increased morbidity and mortality in postoperative period.

Postoperative ischemia is probably caused by the arterial grafts (left internal mammary artery graft and radial graft) or the native diseased vessels going in spasm. The reason for spasm is the endothelial dysfunction because of handling during surgery and preexisting atherosclerosis. Apart from the endothelial dysfunction, it can be the use of vasoconstrictors, calcium, preoperative withdrawal of calcium channel blockers, and probably thromboxane released by platelets causing the spasm. The treatment for the vasospasm of the arterial grafts and native vessels is the use of glyceryl trinitrate (GTN) and/or calcium channel blockers (diltiazem) and/or phosphodiesterase inhibitors.

Intra-aortic balloon pulsation (IABP) can be a great help in alleviating the crisis both by increasing flow to coronaries by diastolic pressure augmentation (inflation of balloon during diastole) and reduced afterload (deflation of balloon in systole), thereby reducing cardiac work and increasing oxygen supply to heart.

INTRACTABLE HYPOTENSION

Intractable hypotension is also commonly seen during postoperative period because of the CPB and because of the drugs such as angiotensin-converting enzyme (ACE) inhibitors being used in preoperative period. It requires vasoconstrictors and if not corrected with that, one may have to proceed with the use of methylene blue. It may not be amenable to even intravascular volume and vasoconstrictors such as selective alpha-agonists or vasopressin. Administration of vasoconstrictors must be guided by objective assessment of cardiac function on pulmonary artery catheters/echocardiography/other monitoring**,** because optimization of blood pressure by vasoconstrictors may make us miss a LCOS state.

GASTROINTESTINAL EMERGENCIES

Gastrointestinal (GI) emergencies that require emergent surgical or medical care are rare after cardiac surgery but these do occur in nearly 1% of patients undergoing cardiac surgery. The most common complication among these is *upper GI bleeding* from duodenal or gastric ulceration or varices. For this reason, the stress ulcer prophylaxis is important.

Mesenteric ischemia is another dreaded complication that has a very high mortality. It may occur because of hypoperfusion that may happen during CPB or because of embolization to the splanchnic vessels during aortic manipulation. The embolization can be treated in catheterization laboratory by interventional radiologist, if a removable thrombus is localized. Mortality remains high.

STROKE AND OTHER NEUROSURGICAL/ NEUROLOGICAL COMPLICATIONS

Neurosurgical Complications

The complications such as subdural hematoma (SDH)/extradural hematoma (EDH) may happen inside operation theatre and present in postoperative period. SDH may happen because of a heparinized patient (for putting in CPB) having poor venous drainage from brain (venous cannula malposition). EDH also happens partially because of heparinization (for CPB) having undiagnosed cerebral aneurysms or very high blood pressure during the perioperative period.

Not all patients with the SDH/EDH require neurosurgical intervention for drainage. Only those with significant midline shifts on CT scan need to be operated as emergency. Transferring these patients to CT suites itself is a very tedious and risky cause they may be on life support systems such as ventilatory and inotropic support, although with the advent of portable CT at bedside has become easier.

Neurological Complications

The treatment of perioperative stroke is actually preventive**.** The reason being that by the time it presents in the postoperative period as a deficit, the irreversible damage is already done. Neurologic events happening in the postoperative period have a strong association with increased mortality, increased length of stay in ICU and hospital, and reduced life span. Neurological complication not only includes stroke but cognitive dysfunction, visual deficits, coma as well. In fact, cognitive dysfunction has an incidence of nearly 80% in the perioperative period. All these lead to a poor quality of life, even though the cardiac issue may be resolved.

The incidence of these neurological emergencies postcardiac surgery is not very high but its occurrence is ominous. With the improved preventive and therapeutic techniques, there is improved survival rate and lifespan. Still therapies are tried with mixed benefits both in digital subtraction angiography (DSA) catheterization laboratories and as a neurosurgical procedure.

Because of rising population in general and geriatric population surviving more, the requirement of cardiac surgeries is increasing. Once cerebral injury is diagnosed, the main measures to be taken in the ICU are:

- Glucose control
- Prevention of hypertension
- Prevention of seizures
- Maintenance of normal oxygenation and normocarbia
- Prevention of raised intracranial pressure (ICP)

Neurological injuries are more common after heart surgery in the geriatric age group. Though the mortality rate because of cardiac surgeries has gone down, but the rate of neurological complications has remained nearly the same. The neurological injuries in the perioperative period leads to nearly 20% increased mortality in comparison to those without neurological dysfunction. The morbidity also increases in the population with neurological deficits in the perioperative period. The mechanism of neurological injuries is cerebral embolism, hypoperfusion because of low perfusion pressure, inflammatory mediators because of CPB, and preexisting neurological deficits/problems.

CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY

Cardiac surgery associated acute kidney injury (CSA-AKI) as the name indicates is AKI associated with cardiac surgery. It has a huge impact on the quality of life in perioperative period and even in later life after surgery. The etiology of this complication is governed by multiple factors especially related to perioperative management and use of pharmacological agents. Significant implications for short- and long-term outcomes are:

- Increased infections
- Increased stay in hospital and increased ICU stay
- Later, dependency on dialysis
- Greater mortality

Risk Factors of CSA-AKI

Advanced age, female gender, severe left ventricle dysfunction congestive heart failure (CHF), DM, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), valve surgery emergency surgery, prolonged CPB time excessive and prolonged hemodilution on CPB, combined procedures and severe LV dysfunction, use of IABP, and preoperatively elevated serum creatinine.

It is seen in up to 30% of subjects after CPB. Fortunately, only up to 5% require dialysis, but in that 5%, the mortality rate is very high AKI is the strongest independent risk factor for death after CPB. The risk is least in CABG alone, but increases exponentially for valve replacement and is greatest after combined procedures. Unfortunately, this complication and its effect on mortality have not reduced despite better understanding of pathophysiology, pharmacotherapeutics, and the advances in renal replacement therapy (RRT).

Diagnosis

Acute kidney injury is a complex diagnosis. Many diagnostic criteria have been applied for the AKI (example, percentage change in serum creatinine and requirement for hemodialysis).

There are two classifications, which need special mention—(1) the *RIFLE* (GFR, creatinine and urine output) and (2) *AKIN classification* (creatinine and urine output). Even these well-validated criteria-based classifications are not completely reliable as these do not guide about the actual site of kidney injury whether tubular or glomerular. Also, both these depend more on change in serum creatinine. *Society of Thoracic Surgeons (STS) bedside risk tool* and many other such models are used to predict the kidney dysfunction or need for dialysis in advance. Newer biomarkers are also being studies to help in the early detection of AKI. Early detection of AKI leads to early institution of RRT and better outcomes.

Serum Creatinine

It is not sensitive and not consistent in diagnosis. It has a significant time lag in the diagnosis of AKI as well as its recovery. Multiple factors apart from AKI govern the increase and decrease of serum creatinine. Also, it does not guide about the nature of kidney injury whether ischemic or prerenal. The risk of AKI requiring dialysis—10–20% with baseline creatinine of 2.0–4.0 mg/dL and 25% if >4.0 mg/dL. Other newer markers,

which were found to have a better association with AKI, are *NGAL, KIM-1, IL-18, and L-FABP.*

What Fluids to Use ?

A good preload is important for prevention of AKI, but we are unclear as to what fluids are better for kidney. Recent studies have shown that balanced solution is better than saline in reducing the risk of AKI in perioperative period. The chloride restriction reduces AKI as well as the need for RRT. The chloride is detrimental because of its thromboxane release, renal vasoconstrictive effect, and decreased GFR. Dexmedetomidine also may be beneficial.

Ultrafiltration (UF) has been studies a lot for its benefit for AKI. It is safe and reduces perioperative morbidity. The optimal use of UF is combined use of conventional UF and modified UF. More studies in larger trials are required for using UF in a better way. There is still no consensus on best timing of initiation of RRT.

Measures to prevent and managing the CSA-AKI are summarized in **Box 3** and **Flowchart 2**.

ACUTE DECOMPENSATED HEART FAILURE

In postcardiac surgery decompensated heart failure may be encountered pretty often.

The causes may be preoperative LV dysfunction, poor myocardial protection during CPB, prolonged CPB, and cross clamp time; chronic regurgitant lesions with LV dysfunction, graft failure, and involvement of coronaries in valve surgery. It is one of the most common conditions requiring active management in the perioperative period. Postoperatively, decompensated heart failure is seen as an early occurrence of classical signs and symptoms of heart failure secondary to suboptimal heart function, often in those with preexisting heart failure. However, it does not mean that the acute decompensated heart failure (ADCHF) is an entity not seen in previously healthy subjects. It means that the clinicians should have a high index of suspicion for this condition in the perioperative period and the required skill in managing it.

Management of ADCHF in the perioperative period is very demanding and requires the in-depth knowledge of the pathophysiology behind ADCHF in perioperative period. The myocardial stunning causes injury to heart which happens during CPB and it sometimes takes quite a long time to recover. During this time of recovery, we need to support heart by pharmacological means and support devices.

Pharmacological Therapy

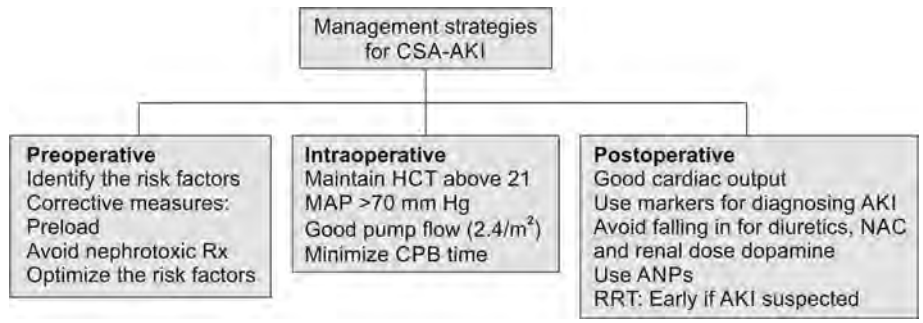
The intended purpose behind the pharmacological means is to support or improve the contractility while reducing the afterload/systemic vascular resistance (SVR) at the same time.

The choice between the inotropes rests between drugs such as adrenaline (0.05–0.2 μg/kg/min), milrinone (0.3–0.7 μg/kg/min), and dopamine (5–20 μg/kg/min) (not much preferred because of the arrhythmogenic nature and the unwanted tachycardia), dobutamine (5–20 μg/kg/min). While all these drugs increase the contractility, *only milrinone and dobutamine decrease the SVR as well and that way seem more suitable.* The disadvantage with milrinone is that it cannot be used for a longer period produces thrombocytopenia, and that it reduces the SVR exponentially, at times so severe as to require a vasopressor to counter the effect and hence nullifying the purpose.

BOX 3: Measure to prevent or treat the CSA-AKI.

- To maintain and replete intravascular volume
- Optimizing cardiac output/treating LV failure
- Avoid nephrotoxic agents whenever possible
- Discontinue of ACE inhibitors/ARB's though its benefit is doubtful; in fact, in diabetic nephropathy it has been shown to be beneficial
- Maintaining adequate tissue perfusion primary goal
- Reasonable glycemic control and outcomes (<180 mg/dL, avoid fluctuations)
- Nesiritide/recombinant atrial natriuretic peptide has shown good results but larger trials are needed
- Avoid anemia (especially on CPB) but at the same time avoid excessive transfusion, because anemia decreases the renal DO_2, increases oxidative stress, and impaired hemostasis and transfused stored RBCs decrease tissue DO_2, is proinflammatory, increases oxidative stress, and activates leukocytes and coagulation cascade
- Fenoldopam (D1 receptor agonist) also has shown positive results in smaller trials. Preoperative RRT as a prophylaxis in preoperative period for optimization is another option
- Be meticulous in closing and hemostasis as any reexploration is an added insult and the combination of insults including associated anemia and blood transfusion contribute to AKI

(ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; CPB: cardiopulmonary bypass; CSA-AKI: cardiac surgery associated acute kidney injury; RRT: renal replacement therapy)



(ANP: atrial natriuretic peptide; CPB: cardiopulmonary bypass; CSA-AKI: cardiac surgery associated acute kidney injury; HCT: haematocrit; MAP: mean arterial pressure; NAC: N-acetylcysteine; RRT: renal replacement therapy)

FLOWCHART 2: Strategies for prevention and treatment of CSA-AKI.

The devices that help the heart tide over the crisis are suitably called assist devices. The most common amongst these is the intra-aortic balloon counterpulsation which improves the coronary flow during diastole by getting inflated during diastole and reducing the afterload in systole by getting deflated during systole. Use of the intra-aortic balloon counterpulsation has been discussed earlier.

PERIOPERATIVE RESPIRATORY FAILURE

Postcardiac surgery respiratory failure is seen as ventilator dependency and may or may not be a direct complication of the cardiac surgery. The reason being, it may be a preexisting COPD/asthma leading to a type 2 respiratory failure, i.e., lack of drive leading to CO_2 retention and accompanying hypoxemia. In this case, however, the hypoxemia is very responsive to simple measures such as increasing FiO_2 by a minimal proportion. As a direct complication of the cardiac surgery, it occurs as type 1 respiratory failure which means a failure of exchange of gases, because of decompensated ADCHF or preexisting/new onset chest infection may not even respond to a FiO_2 of 100%, if not accompanied by other measures. So, type 1 respiratory failure requires not just raising the FiO_2 but also raising the PEEP, antibiotics, chest physiotherapy, frequent suctioning, and other supportive measures. Both these two classic types of RF have distinctly different abnormalities in the mechanics of breathing, but they share the mechanisms finally leading to respiratory muscle dysfunction, fatigue, and hence ventilator dependence.

Treatment of any type of respiratory failure includes these key elements other than the chest supportive measures:

- Improvement of cardiac function
- Achieving improved oxygen carrying capacity by improving hemoglobin
- Improving arterial saturation
- Reducing oxygen requirement

The endpoint of each therapy is individualized. Early freedom from ventilator dependency is done by prompt identification and correction of multiple factors which had been the cause of increased work load and/or compromised neuromuscular functions.

Aggressive early resuscitation is very important to avoid the vicious cycle of ventilator dependence. Acute management such patients follow airway, breathing, and circulation (ABC) of resuscitation and not CAB of the recent guidelines of CPCR, because here the concern is respiratory failure. This means these patients need airway, ventilator management, and optimal management of circulation. However, at the same time, open-minded approach is kept for prompt diagnosis and treatment plan for the cause of such condition early in course. It is guided by not just by the clinical examination and laboratory evaluation but also supplemented by the results of focused intensive care interventions.

It is very optimistic to know and say that amongst all other surgical fields, the outcomes of cardiac surgery have become excellent, reason being it is driven by very strict protocols. Also, the postcardiac surgical emergencies are getting rarer because of *precardiac surgery evaluation and advanced monitoring of vital parameters*. In the coming times, point-of-care monitoring for excessive bleeding and the liberal use of TEE for any hemodynamic instability in postoperative period will actually reduce the two common complications, i.e., bleeding and tamponade apart from other complications getting diagnosed early like paravalvular regurgitation.

PREVENTION OF POSTCARDIAC SURGERY COMPLICATIONS

Precardiac Surgery Evaluation

Cardiac surgical patients are one of the most extensively investigated. However, evidence from studies using intraoperative TEE suggests that as many as 5% of patients have additional undocumented pathology (e.g., valvular heart disease and patent foramen ovale). Therefore, thorough preoperative evaluation is essential to identify the risk factors, asses the risk of surgery, optimize medical condition if necessary and take written informed consent, is necessary.

History

In majority of cases, the diagnosis would have already been established. So, preoperative assessment invariably begins with a review of the patient's medical record. The presence of risk factors known to be associated with increased perioperative mortality and morbidity like age >60 years, arterial and pulmonary hypertension, BMI <20 or >35, CHF, peripheral vascular disease, DM, renal insufficiency, acute coronary syndromes, chronic pulmonary obstructive disease, neurological disease, and previous cardiac surgery should be sought. Drug history is very important.

Patient on medications such as steroids, bronchodilators, antihypertensive, anticoagulants, antiplatelet, antibiotics, antidiabetics, immunosuppressants, etc., should be noted. Some medication may need discontinuation before cardiac surgery such as anticoagulant, potent antiplatelets, oral antidiabetics, ACE inhibitors, etc. If the patient is on anticoagulation warfarin should be stopped 3–7 days before surgery and INR should be generally <1.5 for surgery. Heparin should be discontinued 6 hours before cardiac surgery.

History of allergy to any drug or food should be noted, especially fish allergy as there are higher chances of protamine reaction in these patients. Signs and symptoms of cardiorespiratory disease [e.g., angina, dyspnea, orthopnea, impaired exercise tolerance, and (pre)syncope] should be actively looked for. The severity of symptoms and effort tolerance should be documented using conventional indices; for example, the Canadian Cardiovascular Society angina score, the New York Heart Association (NYHA) classification of functional capacity and the Duke activity status index. A short systematic examination should be conducted to exclude any gastrointestinal, renal, hepatic, neurological, metabolic, or hematological disease. A symptom suggestive of gastroesophageal reflux necessitates the use of strategies to reduce the risk of regurgitation and pulmonary aspiration during anesthesia. Furthermore, a history suggestive of upper gastrointestinal tract pathology, such as hiatus hernia, may contraindicate the use of TEE intraoperatively.

Physical Examination

Physical examination should be focused on the cardiovascular and respiratory systems. Examination should include heart rate, blood pressure measurement in supine and sitting

position, respiratory rate; characterization of the heart rhythm, gentle palpation of the carotid, femoral and peripheral arteries, and auscultation of the precordium, carotid arteries, and lung fields. Allen's test although not specific but should be performed to confirm the presence of an adequate collateral (ulnar) circulation in patient who are likely to undergo radial artery cannulation. Assessment of dentition, mouth opening, and cervical mobility should be done to predict difficult airway.

Investigations

A blood count, coagulation profile, blood group, serum electrolytes, urea, creatinine and liver function test, a 12-lead ECG, and a left heart catheter should be regarded as routine preoperative investigations in virtually all cardiac surgical patients. A plain posteroanterior CXR provides information about heart size, pulmonary vasculature, lungs size of trachea sings of cardiac failure, and bony cage of the chest. Left heart catheterization typically comprises coronary angiography (useful in coronary artery patients), aortography, left ventriculography (ventricular function), and manometry. This provides information about the sites and severity of coronary artery stenoses, mitral and aortic valve function, and LV morphology and function. ECG is done to detect arrhythmias, conduction changes, myocardial injury, and myocardial infarction. Exercise stress testing is a noninvasive test. It is useful in patient with chest pain of unknown etiology, and for quantification and prognosis in patients with known coronary artery disease (CAD). Currently many treadmill protocols are available of which Bruce protocol is most familiar. Pharmacological stress testing, e.g., dobutamine stress echocardiography is suitable for patient who are unable to exercise adequately. Transthoracic echocardiography is frequently used to define cardiac anatomy and assess ventricular and valvular function. Regional wall motion abnormality can be seen and it is helpful in deciding optimum preoperative management and perioperative monitoring and care. Additional investigations such as respiratory function tests, arterial blood gas analysis, carotid ultrasonography and angiography, creatinine clearance, and evaluation of a permanent pacemaker or cardiodefibrillator should be conducted, as appropriate.

Risk Assessment and Stratification

Cardiac surgeries still have a certain risk of death and serious complications despite advances in surgical techniques, anesthesia and critical cardiac care. It is essential that the cardiac anesthesiologist understands how risk is assessed and that the patient and his/her relatives are adequately informed about the risk of surgery. In the late 1980s, Parsonnet and colleagues identified 14 independent risk factors for death after cardiac surgery. The so-called Parsonnet score was adopted by many centers worldwide and is still in use today. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was developed in the late 1990s, across 128 centers in eight European states in 19,030 patients undergoing cardiac surgery. Based on the EuroSCORE, the patients were categorized as, patients with low risk (EuroSCORE 0-2), moderate risk (EuroSCORE 3–5), and high risk (EuroSCORE >6) of in-hospital mortality following cardiac surgery. The model has not been validated till date in India and Australia. The study involved assessment of 17 risk factors identified in EuroSCORE model. The additive EuroSCORE can be satisfactorily applied to low- and moderate-risk Indian patients but is less accurate for high-risk Indian patients undergoing cardiac surgery. For high-risk patients, the logistic EuroSCORE[10] provides a more accurate prediction than the simple additive score.

SUMMARY

In patient undergoing cardiac surgery extensive cardiac evaluation, preoperative cardiac risk assessment and stratification is a part of routine workup. The main goal is to provide risk adjusted mortality rates for the preoperative patient and adequate patient and family counseling. Various complex or simplified models are available and can serve as a tool for risk assessment and stratification for perioperative mortality and morbidity.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Systemic Hypertension

Au Kin Heng Constantine, Quintin Kwok

INTRODUCTION

Systemic hypertension, or simply "hypertension", is a common condition affecting about 1.5 billion adults in the world. Untreated hypertension leads to cardiovascular diseases such as heart attacks and strokes.

Hypertension does not traditionally belong to the realm of emergency medicine. It is, by and large, a chronic condition managed by general practitioners. It does, however, cross paths with emergency physicians in several ways. First of all, as all patients have their vital signs checked at the emergency department (ED), many previously undiagnosed cases are identified. Secondly, patients who are taking antihypertensive drugs may attend ED when their blood pressures (BPs) are not well controlled or due to the side effects of the antihypertensives. Last but not least, hypertension can sometimes be life-threatening. Such instances are called hypertensive emergencies. They are not common but are truly medical emergencies. There are different categories, treatment protocols, and even definitions for systemic hypertension. This manuscript serves as a general reference. Please refer to your local guidelines.

DEFINITION CLASSIFICATION GRADING

In adults, hypertension is defined as a systolic blood pressure (BP) equal to or over 140 mm Hg, or a diastolic BP equal to or over 90 mm Hg according to European, Indian, and UK standards. The American Heart Association uses a definition of BP > 130/80 mm Hg instead (**Table 1**).

ETIOLOGY AND PATHOPHYSIOLOGY

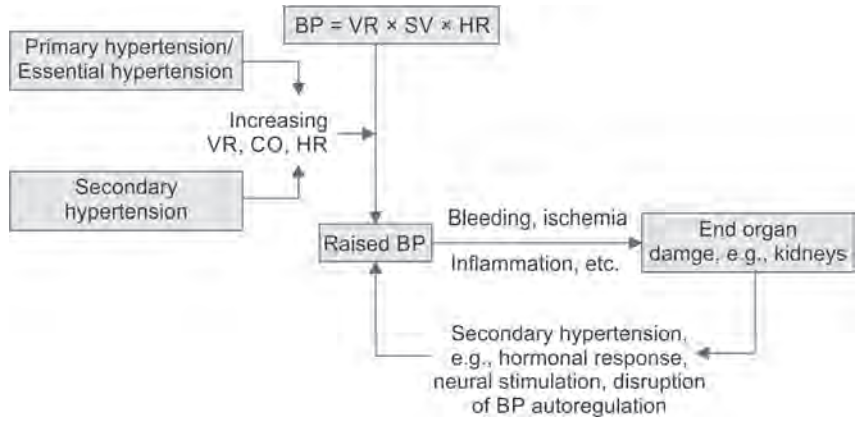
A majority (90%) of adult patients with high BP have primary hypertension (also called essential hypertension), which means the condition is not caused by another disease. Genetic and environmental factors such as diet and lifestyle are believed to be the underlying causative factors. Secondary hypertension is high BP caused by certain underlying, often undiagnosed diseases or drugs (**Table 2**). Some of these diseases are rare. Emergency physicians must have a high index of suspicion to diagnose these conditions. **Flowchart 1** summarizes the

TABLE 1: Grading of hypertension in adults.

Grading	*Systolic (mm Hg)*		*Diastolic (mm Hg)*
Mild	140–159	and/or	90–99
Moderate	160–179	and/or	100–109
Severe	≥180	and/or	≥110
Hypertensive urgency	Severe hypertension without acute organ failure		
Hypertensive emergency	Severe hypertension with evidence of acute target organ failure		
For a child, refer to standardized tables of blood pressure for diagnosis			

TABLE 2: Secondary causes of systemic hypertension.

Secondary cause	*Features suggesting*
Acromegaly	Enlargement of forehead, jaw, and nose
Drugs/food/herbs	Oral contraceptives, amphetamine, ephedra, and poor antihypertensive drugs compliance
Coarctation of aorta	Radiofemoral delay, murmur
Cushing syndrome	Cushingoid features
Genetic causes	Rare (e.g., Geller syndrome)
Hyperaldosteronism	Hypokalemia, metabolic alkalosis
Hyperparathyroidism	Hypercalcemia and hypophosphatemia
Obstructive sleep apnea	Snoring, daytime somnolence
Pheochromocytoma	Episodic attacks: Flushing, headache, and palpitation
Primary aldosteronism	Muscle weakness
Renal artery stenosis	Renal bruit, kidneys of unequal size on ultrasound (the smaller one on the side with the stenosed renal artery)
Renal parenchyma	Raised creatinine, proteinuria
Hyper-/hypothyroidism	Goiter, abnormal thyroid tests



(BP: blood pressure; HR: heart rate; SV: stroke volume; VR: vascular resistance)

FLOWCHART 1: Etiology and pathophysiology of hypertension.

etiology and pathophysiology of hypertension. A patient may have both primary and secondary hypertension together.

CLINICAL PRESENTATION

Patients with essential hypertension may have no symptoms at all. Some may complain of mild headache or dizziness only. In secondary hypertension, there may be features of the underlying diseases noted on history taking, physical examination, or basic investigation. One should be alert if the patient is young (<40), or the BP is very high or difficult to control with medications.

In hypertensive emergencies, the BP will be in the severe range; patients may have signs and symptoms of acute target organ failure (**Table 3**). The organs affected most often are the brain, eyes, heart, and kidneys. Added to this list is preeclampsia in pregnancy. These target organs may, in turn, raise the BP via hormonal, neuronal response, or disruption of autoregulation.

Red flags (concerning features) look for the features of hypertensive emergencies and secondary hypertension as summarized in **Tables 1** to **3**. Hypertension itself and antihypertensive drugs may complicate the patient's presentation in a trauma setting. Beware of the Cushing's triad in trauma patients. With regards to treatment, lowering the BP too rapidly may be harmful. Drug history such as amphetamine or missing antihypertensive drugs must be checked.

TABLE 3: Acute target organs damaged involved in severe hypertension.

Target organs	*Pathophysiology*	*Features*
Brain	• Ischemia • Bleeding	Confusion due to hypertensive encephalopathy or intracerebral hemorrhage
Eyes	• Retinal hemorrhages • Microaneurysms • Papilledema	Papilledema on fundoscopy
Heart/chest	Overloading of the left ventricles	Arrhythmia, acute coronary syndrome, aortic dissection, and pulmonary edema
Kidneys	Endothelial dysfunction and damage	Hematuria, proteinuria, and raised creatinine/potassium/acidosis
Lungs	Increased hydrostatic pressure in lungs, or increased permeability	Pulmonary edema
Preeclampsia	Abnormal vascular changes	Proteinuria, peripheral edema, and hyperreflexia

Measurement of Blood Pressure in Emergency Department

Blood pressure is a dynamic physiological parameter which fluctuates over the course of the day and is affected by a wide range of factors from pain to emotion. Common presentation at the A and E is headache or vertigo. Their BPs may be very high at presentation, but once the symptoms are palliated, the BP returns to normal. These patients may be misdiagnosed as having hypertension. ED is not the ideal place to diagnose hypertension because of white-coat hypertension (raised BP at emergency but normal in the community) and masked hypertension (normal BP emergency but raised in the community). There are many factors affecting the BP measurement and some tips are used during measurement of the accurate BP (**Table 4**).

Ideally, hypertension should be diagnosed in the community when the patient is not acutely unwell, is relaxed and the reading is repeated on different days. Only if the BP is persistently high under these circumstances should one commit to the diagnosis. Home BP monitoring (HBPM) or 24-hour ambulatory BP monitoring (ABPM) may be helpful in uncertain cases.

For all these reasons, unless a hypertensive emergency with acute organ failure occurs, the emergency physician often refers patients with high BPs to their colleagues in the community for follow-up. Two important aspects of managing essential hypertension are risk factor identification and modification of lifestyle. These do not affect the immediate well-being of patients and should not be added to the workload of emergency.

TABLE 4: Factors affecting the blood pressure measurement and some tips for measurement.

Tip	*Remarks*
Environment	Relaxed
Position	Ideally, BP is measured with patient sitting on a chair with back support and upper arm positioned at the level of the heart
Cuff bladder size	• The length should be about 80–100% of the girth of the mid-arm; a bladder too short will overestimate the BP • The width should be about 40% of the girth of the mid arm
If irregular pulse	Use a manual sphygmomanometer
If BP different between left and right arms	• If difference is persistently >20 mm Hg systolic or 10 mm Hg diastolic, consider investigation of underlying cause • For documentation purposes, use the higher reading
Repeat and confirm	Never diagnose hypertension with one abnormal reading; consider HBPM or ABPM

(ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring)

EVALUATION OF HYPERTENSION

In the Acute Setting

Follow the adage of "ABCD" (airway, breathing, circulation, and disability). If the BP is in the severe range, ensure airway and breathing are adequate. The emergency physician should then determine whether a hypertensive emergency exists—are there any features of acute target organ failure as in **Table 3**? If so, a rapid reduction of the BP by 20–25% is suggested, together with treatments for the corresponding organ failures. This is usually accomplished by repeated doses of intravenous labetalol or nicardipine in adults. Reducing the BP too quickly or too much may cause ischemia and do more harm than good. Disability means acute organ failure.

The *choice of investigation* depends on which organ failure is suspected. Heart and brain failure may be obvious when the patient presents with acute coronary syndrome, acute pulmonary edema, or is confused or comatose. Consider 12-lead electrocardiogram, chest X-ray, echocardiogram, troponin I test, CT-angiogram, and CT-brain. Involvement of the eye and the kidneys, however, may be subtle. Fundoscopy, urine analysis for blood and protein, blood tests for creatinine, potassium, and bicarbonate must be done in this kind of patients. Thoracic CT (for aortic dissection) or drug/toxicology screening may be needed. Admit patients with hypertensive emergency after stabilization.

In hypertensive urgency where there is no acute target organ failure, BP should be lowered within 24 hours using oral antihypertensive agents such as an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), calcium channel blockers (CCBs), or beta-blockers. Patients should be admitted or have a follow-up within a week with an internal medicine specialist.

In the Chronic Setting

In the longer term, for patients with essential hypertension and for those who have recovered from their acute crises, managing hypertension is not only BP reduction. It includes cardiovascular risk assessments and modifications, patient education, lifestyle changes, drug treatment and long-term monitoring of BP control, and target organs' status. The ultimate aim is to reduce the risk of heart attacks, strokes, and other end organ damage.

Chronic Target Organ Damage Assessment

The organs affected acutely by hypertensive emergencies can also be damaged slowly by a chronically elevated BP. The well-being of these organs should be assessed regularly. If organ damage is suspected, further evaluations and treatments by relevant specialists should be instituted.

Risk Factor Identification and Modification

There are risk assessment tools such as Systematic Coronary Risk Evaluation (SCORE) to estimate the risk of cardiovascular events. There are many risk factors for cardiovascular diseases. Some of these are modifiable are given in **Table 5**.

STEPWISE APPROACH TO SYSTEMIC HYPERTENSION

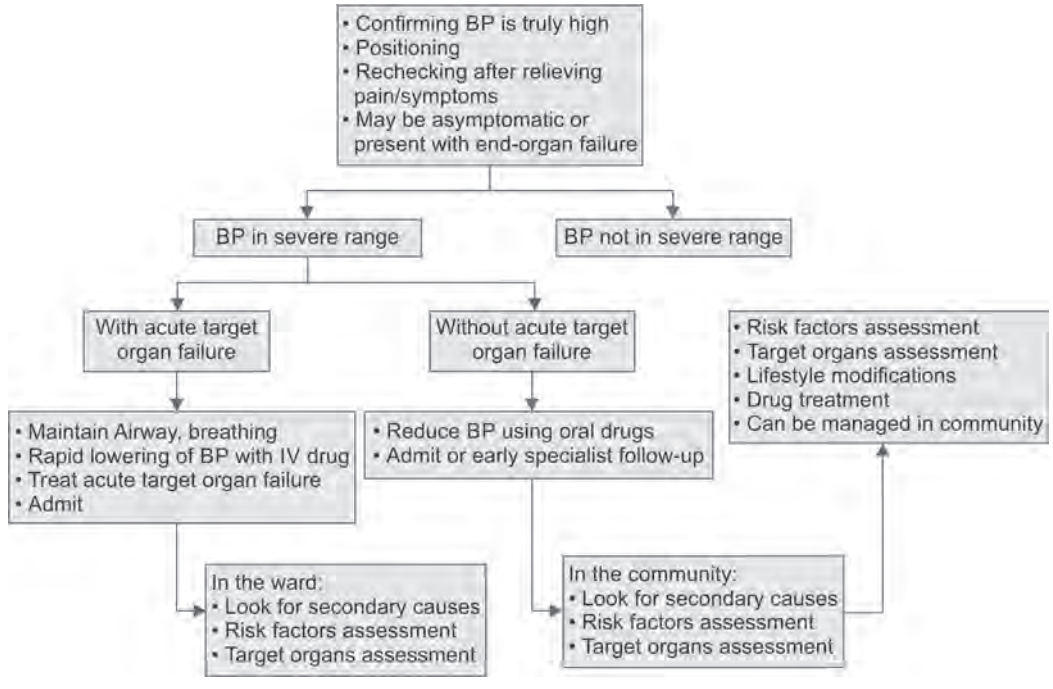
There are well-established evidence-based guidelines for choosing oral antihypertensive agents. The rule of thumb is to keep BP < 130/80 mm Hg. Other target BPs may be applied in subgroup patients. Always check for drug compliance and adverse drug reactions. Stepwise approach is considered while managing the hypertension and also selecting the appropriate antihypertensive agents (**Table 6**). Monitoring the BP at the observation ward may be needed before starting or changing the antihypertensive drugs. With newly diagnosed mild or moderate hypertension, an antihypertensive may be better started by a community physician after detailed assessment and lifestyle modification. Among the elderly, treatment target may be more relaxed so as to avoid the side effects of antihypertensives such as postural hypotension. **Flowchart 2** will helpful emergency physician in managing the systemic hypertension.

TABLE 5: Risk factors for cardiovascular diseases.

Nonmodifiable	*Modifiable*
• Early onset of menopause • Family history of cardiovascular disease • Increasing age • Male gender	• Diabetes mellitus (DM) • Diet • Drug-iatrogenic symptoms, drug abuse or missing dosages • Exercise • Hyperlipidemia • Hypertension • Obesity • Psychosocial factors • Smoking

TABLE 6: Drug choice in systemic hypertension.		
Step 0	Lifestyle modification such as weight loss, low-salt diet, exercise, avoidance of smoking and excessive alcohol	
	All ages with diabetes mellitus (DM)	No DM and > 55 years old
Step 1	ACE inhibitor or ARB	Calcium channel blocker (CCB)
	Check drug compliance	
Step 2	Add a thiazide diuretic or a CCB	Prefer adding an ACE inhibitor or ARB rather than a thiazide (not much synergy between thiazide diuretics and CCBs)
	Check drug compliance	
Step 3	ACE inhibitor or ARB plus a thiazide diuretic plus a CCB	
	Check drug compliance	
Step 4	• Known as resistant hypertension • Consider beta-blocker • Look for secondary causes • Refer to a specialist	
Choice of antihypertensives: • ACE inhibitor and ARB are preferred in diabetes and heart failure • β-blockers are preferred choice for Ischemic heart disease and heart failure • CCBs and diuretics are preferred in elderly • Pregnancy always demands special consideration; consider labetalol and hydralazine		
Remarks: • ACE inhibitors are contraindicated in hyperkalemia, bilateral renal artery stenosis produces cough • ARBs are contraindicated in hyperkalemia, bilateral renal artery stenosis • β-blockers are contraindicated asthma/COPD, pheochromocytoma 2° and 3° heart blocks • CCBs are contraindicated in 2° and 3° heart blocks • Renin–angiotensin levels are lower in patients >55; ACE inhibitors/ARBs are less effective on them • ACE inhibitors and ARBs are not usually used together		

(ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker)


• Confirming BP is truly high
• Positioning
• Rechecking after relieving pain/symptoms
• May be asymptomatic or present with end-organ failure
BP in severe range
BP not in severe range
With acute target organ failure
Without acute target organ failure
• Risk factors assessment
• Target organs assessment
• Lifestyle modifications
• Drug treatment
• Can be managed in community
• Maintain Airway, breathing
• Rapid lowering of BP with IV drug
• Treat acute target organ failure
• Admit
• Reduce BP using oral drugs
• Admit or early specialist follow-up
In the ward:
• Look for secondary causes
• Risk factors assessment
• Target organs assessment
In the community:
• Look for secondary causes
• Risk factors assessment
• Target organs assessment

FLOWCHART 2: Approach to systemic hypertension in emergency department.

THERAPEUTIC APPROACH TO HYPERTENSIVE EMERGENCIES AND URGENCIES

Clinical presentation of hypertensive emergencies in ED is associated with different diseases and they manifest in various form such as pulmonary edema myocardial ischemia, aortic dissection, and preeclampsia hypertensive encephalopathy. So, in each subset of presentation, the choice of antihypertensive agent is different (**Table 7**). The target BP goals in hypertensive emergencies of varied etiology are also different (**Table 8**). Controlled BP reduction to target goals should be achieved in order to prevent organ damage. Care should be taken to not lower BP rapidly and to normal levels. The therapeutic approach should be to refrain from a rapid reduction in BP as this approach has been found to be associated with considerable morbidity. Clinical presentation guides the choice of antihypertensive agents in hypertensive emergencies. In patients presenting with *hypertensive urgencies, oral medications* are used to gradually lower the BP over a period of 24–48 hours (**Table 9**).

TABLE 7: Choice of pharmacological agent in hypertensive emergency according to presentation.

Condition	*Preferred drugs*	*Drugs to avoid*
Acute pulmonary edema/ heart failure	Fenoldopam/nitroprusside + nitroglycerin (up to 60 µg/min) + loop diuretic	Hydralazine and β-blockers
Myocardial ischemia and infarction	Labetalol/esmolol + nitroglycerin (up to 200 µg/min) +/- nicardipine/fenoldopam if BP uncontrolled or poorly controlled	Hydralazine, minoxidil, diazoxide, and nitroprusside
Hypertensive encephalopathy	Labetalol/nicardipine/fenoldopam	β-blockers, methyldopa, clonidine, diazoxide, hydralazine, and nitroglycerin
Acute aortic dissection	Labetalol or nicardipine + esmolol or nitroprusside + esmolol/ IV metoprolol	Hydralazine, minoxidil
Preeclampsia and eclampsia	Labetalol/nicardipine	Diuretics and ACE inhibitors
Acute renal failure, Microangiopathic anemia	Fenoldopam/nicardipine	
Intracerebral hemorrhage	Nimodipine (oral)/nicardipine/labetalol/nitroprusside/ enalaprilat	β-blockers, methyldopa, clonidine, diazoxide, hydralazine, and nitroglycerin
Hyperadrenergic states/ Sympathetic overdrive	Phentolamine/nitroprusside/labetalol/nicardipine/verapamil. Alternatively, Fenoldopam +/– a benzodiazepine (in cocaine overdose)	β-blockers (in cocaine overdose)

TABLE 8: Target blood pressure (BP) goals for specific emergencies.

Conditions	*Target BP Goal*
Hypertensive encephalopathy	MAP lowered by maximum 20% or to DBP 100–110 mm Hg within 1st hour then gradual reduction in BP to normal range over 48–72 h
Ischemic stroke	MAP lowered no >15–20%, DBP not <100–110 mm Hg in first 24 h (thrombolytic protocols in stroke may allow slightly more aggressive management)
Intracerebral hemorrhage	MAP lowered by 20–25%
Hypertensive retinopathy	MAP lowered by 20–25%
Left ventricular failure	MAP to 60–100 mm Hg
Aortic dissection	SBP 100–120 mm Hg
Acute renal insufficiency	MAP lowered by 20–25%
Pregnancy-induced hypertension	SBP 130–150 mm Hg, DBP 80–100 mm Hg

(MAP: mean arterial pressure; SBP: systolic blood pressure)

TABLE 9: Oral antihypertensive agents for hypertensive urgencies.

Agent	*Dose*	*Onset of action*	*Duration of action*	*Precautions*
Captopril	25 mg	15–30 min	2–6 h	Can cause renal failure in bilateral renal artery stenosis
Clonidine	0.1–0.2 mg, can be repeated hourly to a total dose of 0.6 mg	30–60 min	8–16 h	Drowsiness and dry mouth
Labetalol	200–400 mg, repeated every 2–3 h	0.5–2 h	2–12 h	Bronchoconstriction, heart block, and orthostatic hypotension
Prazosin	1–2 mg, repeated hourly as needed	1–2 h	8–12 h	First dose syncope, palpitation, and orthostatic hypotension

SUMMARY

Systemic hypertension is common. The incidence and prevalence of people living with hypertension are growing in India every day. As a result, the number of hospital visits in our country due to hypertensive emergencies also is on the rise. It is imperative for the emergency physicians and other medical personnel working in the ED to have a proper understanding of the pathophysiology and presentation of hypertensive crisis and distinguish urgency from an emergency. Prompt treatment based on correct diagnosis can prevent severe end-organ morbidity. As such, the treating physicians should also know the various treatments available and their dosing including adverse effects. Various *antihypertensive drugs used in hypertensive emergencies* are summarized in **Table 10** for the benefit of the reader. Many medications are available to treat hypertensive emergencies but none is universally recognized as being superior to the others. The appropriate therapeutic approach is specific to patients depending on their clinical presentation. With appropriate identification and management, hypertensive crisis can be halted and reversed.

ACKNOWLEDGMENT

The authors wish to thank Dr Chan Wai Kwong, Dr Chan Tsan Fai, and Dr Risa Ozaki for their valuable advice.

TABLE 10: Pharmacological agents used in hypertensive emergencies.

Drug	*Dose*	*Onset of action*	*Duration of action*	*Adverse effects*	*Indications*
Sodium nitroprusside	0.25–10 µg/kg/min IV infusion	Few seconds	1–2 min	Nausea, vomiting, and cyanide toxicity	Most hypertensive emergencies; use cautiously in patients with high intracranial pressure or azotemia
Nitroglycerine	5–100 µg/min IV infusion	1–5 min	5–30 min	Headache vomiting, methemoglobinemia caution in right ventricular infarct	Cardiac ischemia, flash pulmonary edema; use cautiously in right ventricular infarction or with recent use of phosphodiesterase inhibitors
Nicardipine	5–15 mg/h IV infusion	5–10 min	15–30 min, may last several hours	Tachycardia, headache, flushing, and local phlebitis	Most hypertensive emergencies; caution—causes coronary steal in cardiac ischemia
Fenoldopam	0.1–0.3 µg/kg/min IV infusion	5–10 min	30 min	Tachycardia, headache, nausea, and flushing	Best for renal hypertensive emergencies
Enalaprilat	1.25–5 mg IV every 6 h	15–30 min	6–12 h	Significant fall in BP in high renin states	Acute left ventricular failure, flash pulmonary edema; avoid in acute MI
Hydralazine	10–20 mg 10–40 mg IM	10–20 min IV 20–30 min IM	1–4 h IV 4–6 h IM	Tachycardia, flushing, headache, vomiting, and worsening angina	Eclampsia; caution—gives erratic response
Clevidipine	1–2 mg/h then titrate to maximum 16 mg/h IV infusion	2–4 min	5–15 min	Headache, nausea, vomiting, hypotension, rebound hypertension, and reflex tachycardia	Postoperative hypertension, hypertensive emergency in renal dysfunction, or acute heart failure
Esmolol	250–500 µg/kg/min IV bolus, then 50–100 µg/kg/min IV infusion; repeat bolus after 5 min or increase infusion to 300 µg/kg/min	1–2 min	10–30 min	Nausea, hypotension, bronchoconstriction, heart failure, and first-degree heart block	Aortic dissection and perioperative hypertension
Labetalol	20–80 mg IV bolus every 10 min; or 0.5-2 mg/min IV infusion	5–10 min	3–6 h	Vomiting, dizziness, nausea, orthostatic hypotension, bronchoconstriction, and heart block	Most hypertensive emergencies, ideal for preeclampsia; caution—with acute heart failure
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, and headache	Pheochromocytoma and other conditions with catecholamine excess

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Pulmonary Hypertension

Asaad S Shujaa, Marah Alatrash, Noor Bamohammed

INTRODUCTION

Pulmonary hypertension (PH), defined as a mean pulmonary arterial pressure >25 mm Hg at rest or >30 mm Hg during exercise, is often characterized by a progressive and sustained increase in pulmonary vascular resistance (PVR) that eventually may lead to right ventricular (RV) failure. The hemodynamic-based definition of pulmonary arterial hypertension (PAH) includes mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg, pulmonary capillary wedge pressure (PCWP) < 15 mm Hg, and PVR ≥ 3 wood units. The incidence is estimated to be 2.5–7.1 cases/million and with a prevalence ranging from 5–52/million in studies from Scotland and France. The mean age ranged from 45 to 65 years. There is a female predominance noted with a female to male ratio ranging from 1.7:1 to 4.8:1 among different registries. The racial distribution reported by REVEAL (the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) registry shows |PAH most prevalent among Caucasian (72.8%) followed by African American (12.2%) then Hispanics (8.9%)]. It can be a life-threatening condition if untreated. Therapy for PH is targeted at the underlying cause and its effects on the cardiovascular system, with success rates varying according to the etiology. Novel therapeutic agents, such as prostacyclin and others undergoing clinical trials, have led to the possibility of specific therapies for these once untreatable disorders.

CLASSIFICATION

The World Health Organization (WHO) has divided PH into five groups on the basis of similarities in pathophysiology, clinical presentation, and therapeutic options (**Table 1**). The groups 1 and group 5 are further divided into subgroups also.

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis have been designated as 1' to reflect the fact that although related, they are clinico-pathologically and therapeutically distinct entities from PAH of note, while persistent PH of the newborn was previously classified under group 1 PAH, the 2013 classification schema removed this from group 1 to better reflect the differences

TABLE 1: Classification of pulmonary hypertension (WHO).

Group 1	Pulmonary arterial hypertension (PAH)
	Subgroup 1: Idiopathic PAH (IPAH)
	Subgroup 2: Heritable PAH, including those with BMPR2 and *ALK2* gene mutations
	Subgroup 3: Drug- and toxin-induced PAH (aminorex, fenfluramine derivatives, and toxic rapeseed oil have been identified as definite risk factors for PAH. Other drugs implicated as possible risk factors for PAH include amphetamine and amphetamine derivatives, cocaine, L-tryptophan, phenylpropanolamine, St John's wort, leflunomide, phentermine, mazindol, dasatinib, and interferon)
	Subgroup 4: Conditions with known localization of lesions in the small pulmonary arterioles, which include: (1) Collagen-vascular disease (scleroderma/CREST syndrome), (2) Congenital left-to-right shunts, (3) Portopulmonary hypertension, (4) HIV-associated pulmonary hypertension, and (5) Schistosomiasis
Group 2	Pulmonary hypertension due to left-sided heart disease
Group 3	Pulmonary hypertension due to lung diseases and/or hypoxia
Group 4	Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5	Pulmonary hypertension with unclear or multifactorial etiologies including: *Subgroup 1*—hematologic disorders (e.g., myeloproliferative disorders), *Subgroup 2*—Systemic disorders (e.g., sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, and vasculitis), *Subgroup 3*—metabolic disorders (e.g., glycogen storage disease, Gaucher disease, and thyroid disorders), and *Subgroup 4*—miscellaneous conditions (e.g., tumor obstruction, mediastinal fibrosis, and chronic renal failure on dialysis)

between this and other PAH subgroups. The updated schema also moved chronic hemolytic anemia from group 1 to group 5 PH.

On the basis of information adapted from the executive summary of the world symposium on primary PH in Evian, France, in 1998, PH may be divided into the following functional classes:

- *Class I*: These are patients with PH but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near-syncope.
- *Class II*: These are patients with pulmonary hypertension resulting in slight limitation of physical activity; they are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
- *Class III*: These are patients with PH resulting in marked limitation of physical activity; they are comfortable at rest, but even less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
- *Class IV*: These are patients with PH who are unable to perform any physical activity without symptoms; these patients manifest signs of right-sided heart failure; dyspnea or fatigue may even be present at rest, and discomfort is increased by any physical activity.

PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION

Pulmonary hypertension is a result of an increase in resting mean mPAP ≥ 25 mm Hg as measured with right heart catheterization. This low pressure is due to low resistance which results in a large cross-sectional area of the pulmonary circulation. This can happen due to several etiologies or due to anatomical site and function. Regardless the etiology, anything increase the resistant will cause an increase PH.

The pathological pathway consistent of enhanced pulmonary arteriole contractility, endothelial dysfunction, remodeling and proliferation of both endothelial and smooth muscle cells, and in situ thrombi. The physiological outcome of these disturbances is the partial occlusion of small pulmonary arteries, eventuating in increased PVR leading to RV hypertrophy with eventual cor pulmonale. There are three mechanisms of chemical disturbance (signaling pathways) that happen in the pulmonary trunk that's lead to smooth muscle hypertrophy of pulmonary arteries, and intimal fibrosis these are:

1. *Nitric oxide (NO) pathway*: NO is produced in endothelial cells and follows sequence of reaction that results of pulmonary vasodilation. Additionally, NO inhibits pulmonary vascular smooth muscle cells proliferation, platelet aggregation and thrombosis, and collectively maintaining normal healthy pulmonary vasculature. In PH, there is decreased bioavailability of NO, causing vasoconstriction and increased smooth muscle cell proliferation, inflammation, and thrombosis.
2. *Prostacyclin-thromboxane A2 pathway*: Prostacyclin, produced in endothelial cells prostaglandin I2 (PGI2), binds to specific receptors in smooth muscle cells which leads to smooth muscle relaxation and subsequent vasodilation. Prostacyclin inhibits platelet aggregation, attenuates smooth muscle proliferation, and produces anti-inflammatory and antithrombotic effects. In PH, the pathway shifts toward an alternative product, thromboxane A2, leading to platelet aggregation, vasoconstriction, and proliferation.
3. *Endothelin-1 (ET-1) pathway*: ET-1 is a peptide that acts as a potent vasoconstrictor. ET-1 is produced on endothelial cell membranes from the precursor peptide big-ET-1 by endothelin-converting enzymes. ET-1 activates endothelin receptor A (ETA) and endothelin receptor A (ETB)—two G-protein coupled receptors. ETA is found on vascular smooth muscle cells, and promotes vasoconstriction, hypertrophy, proliferation, cell migration, and fibrosis when activated. ETB is located on both vascular smooth muscle and endothelial cell surfaces. On smooth muscle, activation of ETB causes vasoconstriction whilst on endothelial surfaces, ETB activates NO and prostacyclin production, causing vasodilation and anti-proliferation. In PH, there is an increase in expression of ETA and smooth muscle ETB, but reduced expression of endothelial ETB. In addition, patients exhibit increased ET-1 concentrations in their plasma and pulmonary vascular endothelial cells.

CLINICAL PRESENTATION

The clinical manifestations of PAH are frequently masked by the underlying disease entities. The PH presenting in ED setting is complex because of nature of disease and nonspecific symptoms because the majority of symptoms are subtle except is started worsening and presented clinical evidence of RV failure and the only way you can evaluate by looking for full symptoms and signs as in **Table 2**. Most of emergency presentation is going with worsening RV failure such as dyspnea on exertion and eventually at rest, fatigue, syncope at exertion anginal chest pain, and hemoptysis. There is no clear red flag for PH because the symptoms are subtle and nonspecific especially in emergency settings, however, the only important red flags are worsening short breath with known cases of PH and clinical evidence of RV failure can raise suspicion for PH and need further work-up and investigation of *nonspecific symptoms* secondary to PH. These may include the following—dyspnea upon exertion fatigue lethargy syncope with exertion, chest pain, anorexia, and right upper quadrant pain. *Less common symptoms* include—cough hemoptysis hoarseness (due to compression of the recurrent laryngeal nerve by the distended).

TABLE 2: Symptoms and signs of pulmonary hypertension.

Symptoms	***Signs***
Dyspnea on exertion	Jugular vein distention
Fatigue	Prominent right ventricular impulse
Syncope	Accentuated pulmonic valve component (P2)
Anginal chest pain	Right-sided third heart sound (S3)
Hemoptysis	Tricuspid insufficiency murmur
Raynaud's phenomenon	• Hepatomegaly • Peripheral edema

EVALUATION

Obtaining a careful history may help differentiate PAH from groups 2–5 PH. Important clues to a specific cause include the following:

- History of heart murmur
- Deep venous thrombosis (DVT) or pulmonary embolism (PE)
- Raynaud phenomenon
- Arthritis or arthralgias
- Rash
- Heavy alcohol consumption
- Hepatitis
- Heavy snoring
- Daytime hypersomnolence
- Morning headaches
- Morbid obesity
- Family history of PH
- Drug use, in particularly diet drugs and illicit drugs
- Medications

INVESTIGATIONS AND INTERPRETATION

The diagnosis of PH requires a clinical suspicion based on symptoms and physical examination and reviews of a comprehensive set of investigations to confirm that hemodynamic criteria are met and to describe the etiology and the functional and hemodynamic severity of the condition. The interpretation of these investigations requires, at the very least, expertise in cardiology, and imaging and respiratory medicine and may best be discussed at a multidisciplinary team meeting. Tests for PH may include:

- *Blood tests*: Blood tests determine the cause of PH or look for signs of complications.
- *Chest X-ray* is inferior to the electrocardiogram (ECG) in detecting PH, but it may show evidence of underlying lung disease.
- *Electrocardiogram* is may demonstrate signs of RV hypertrophy, such as tall right precordial R waves, right axis deviation, and RV strain.
- *Echocardiogram* is the most useful imaging modality for detecting PH.
- *Right heart catheterization* should be performed in patients with unexplained PH, and remains the gold standard for its diagnosis and quantification. Catheterization is particularly useful in diagnosing occult shunts, congenital heart disease, and distal pulmonary artery stenosis. Various heart pressures are measured (pressure inside the pulmonary arteries, coming from the left side of the heart), the rate at which the heart is able to pump blood, and finds any leaks between the right and left sides of the heart (**Fig. 1**).

TREATMENTS FOR PULMONARY HYPERTENSION

Treatment for PH is based on three parameters: (1) To correct the underlying cause, (2) Therapy to decrease the PVR; and (3) Measures to increase the cardiac output.

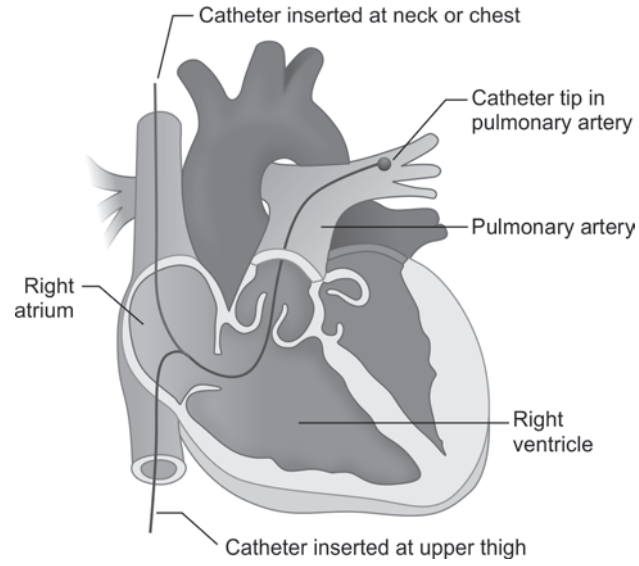

FIG. 1: Right heart catheterization.

Medical Therapy

Correct Underlying Cause

- Surgical treatment of mitral stenosis, left to right shunt, or accessible chronic thromboembolism.
- Afterload reduction, digoxin (Lanoxin), and diuretics for left ventricular dysfunction.
- Prevention and treatment of respiratory infection
- Avoidance of anorectic agents.

Decrease Pulmonary Vascular Resistance

- Vasodilators
- Oxygen
- Calcium channel blockers such as diltiazem (Cardizem) or nifedipine (Procardia)
- Nitric oxide (investigational)
- Anticoagulants for primary PH and chronic thromboembolism.
- Sildenafil and tadalafil relax pulmonary smooth muscle cells, which lead to dilation of the pulmonary arteries.
- Endothelin-receptor antagonists—bosentan and ambrisentan help block the action of endothelin, a substance that causes narrowing of lung blood vessels. These medications require monthly lab work to monitor liver function.

Increase Cardiac Output

- Short-term parenteral inotropes
- Digoxin
- Reduce volume overload
- Low-salt diet
- Diuretic

Surgical Therapies

- *Pulmonary thromboendarterectomy*: If present, a large clot in the pulmonary artery may be surgically removed to improve blood flow and lung function.

- *Lung transplantation*: Currently, this is the only cure for primary PH. Transplantation is reserved for advanced PH that is not responsive to medical therapy. The right side of the heart will generally return to normal after the lung/lungs have been transplanted.
- *Heart/lung transplantation*: This type of double organ transplant is very rare but is necessary for all patients who have combined lung and left heart failure.

DISPOSITION

Majority of above treatment will be started with specialized doctor as outpatient clinic, except if patient presented in pulmonary edema or instability in ED will treated according advanced cardiac life support (ACLS) protocol and to be consulted and admitted to the hospital.

SUMMARY

Pulmonary hypertension is a chronic, complex and challenging disease. Advances in treatment are for the subset of patients with pulmonary arterial hypertension. PH is classified into five groups based on WHO classification. Echocardiography remains the initial test of choice, and careful assessment of the right heart system aids in the diagnosis and prognosis of the disease. Right heart catheterization remains the gold standard of diagnosis and key guidance of treatment. Multidisciplinary approach is recommended for the care of patients with PH. Treatment selection is based on individual risk stratification of patients, and early referral to specialized centres improves outcomes of patients. Treating PH is complex and is best carried out in higher centres and with multidisciplinary approach. Early diagnosis and referral to those centres are key not to delay treatment.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

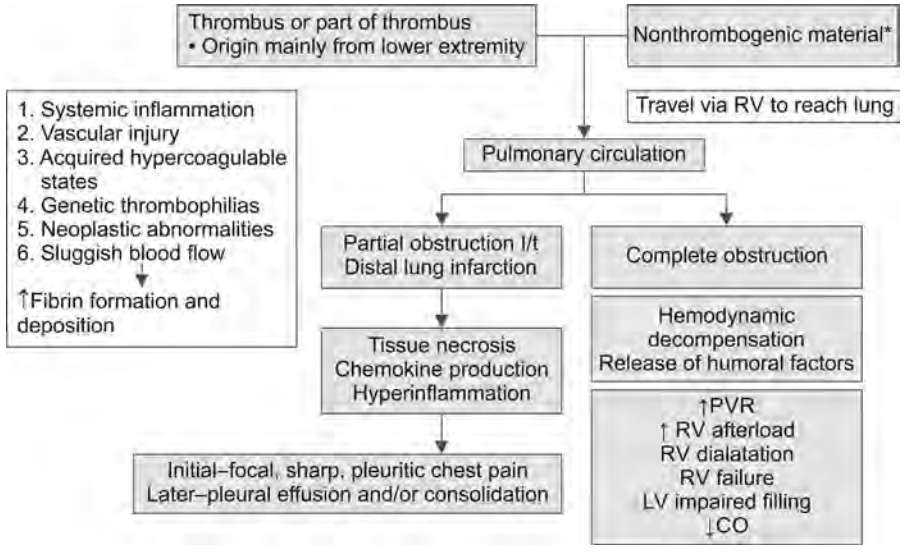
Pulmonary Embolism

Ashima Sharma

INTRODUCTION

Pulmonary embolism (PE) is a common emergency presenting to Indian emergency departments which frequently goes undiagnosed or misdiagnosed. PE is a condition when blood clots enter in to the pulmonary arterial circulation. Deep vein thrombosis (DVT) of the legs, arm pelvis jugular, or inferior vena cava is the common cause. PE and DVT are collectively known as *venous thromboembolism*. The symptomology can overlap with various cardiorespiratory illnesses such as acute coronary syndrome, pneumonias, chronic obstructive pulmonary disease (COPD) exacerbations, pericardial effusions, etc. It is a potentially life-threatening diagnosis that is seen in patients with dyspnea and/or chest pain, but can span the entire clinical spectrum of medical presentations from asymptomatic to cardiovascular collapse. It does not have any particular historical feature, physical examination finding, laboratory test, or diagnostic modality that can independently and confidently excludes its possibility.

The role of the emergency physician is to identify potentially life-threatened patients, who would benefit from early intervention and treatment, and to stabilize and treat accordingly. Although the treatment of PE is straightforward and algorithmic, the diagnostic approach is subject to significant debate and variability. Incidence in India, Overall, the annual incidence of PE ranges between 23 and 69 cases per 100,000 population, with an average case fatality rate within 2 weeks of diagnosis of approximately 11% roughly accounting for at least 100,000 deaths each year. **Flowchart 1** shall illustrate the pathophysiology of the disease. In severe cases, the disease



*Adipocytes, hematopoietic, amniotic, trophoblatic, or tumor cells, bacteria, fungi, parasites, foreign material (e.g., central venous catheters), or gas.

(PVR: pulmonary vascular resistance; RV: right ventricular)

FLOWCHART 1: Pathophysiology of pulmonary embolism.

progresses to pulmonary hypertension and post-thrombotic syndrome to cause significant morbidity.

RISK FACTORS

- Trauma to lower extremity and pelvis during the past 3 months
- Travel ≥4 hours in the past month, air travel for 3,000 miles for ≥6 hours
- Originally, the increased risk was attributed to the high estrogen content of the early oral contraceptive pill (OCP); however, low estrogen plus progesterone OCP has also been associated with thrombogenicity.
- Surgery within the last 3 months—neurosurgical, oncologic, and orthopedic are high-risk procedures. 15% of postoperative deaths are due to PE.
- Pancreatic carcinoma has the highest incidence, whereas bladder tumors have the lowest incidence. Patients with lung, brain, or ovarian tumors are also particularly prone to the development of DVT and PE.
- Sickness like congestive heart failure (CHF), stroke, sepsis/infection, hyperviscosity syndromes—polycythemia, multiple myeloma, nephrotic syndrome, human immunodeficiency virus, and Behçet's disease. Classic and inherited risk factors of PE are summarized in **Table 1**.

CLINICAL PRESENTATION

The combination of classic findings of chest pain, dyspnea, and hemoptysis is present in less than 20% of patients. Any complaints related to pain, shortness of breath, nonspecific malaise or functional deterioration, extremity discomfort, weakness, dizziness, or syncope could be a presentation of PE. One should always keep a high degree of suspicion for PE, if a patient presents with rapid onset of symptoms, which can be a combination of any of the ones listed above. The elderly patients are known to present atypically. 20% of patients will have no identifiable risk factors at the time of ED presentation. Varicose veins are prone to develop clots, the smaller ones, however, seldom embolize. *Symptoms according to the descending order of appearance are*: dyspnea—90%, pleuritic chest pain—75%, tachycardia—<50%, nonpleuritic chest pain—20%, hemoptysis—<20%, and reproducible chest pain—<20% but we should know that even MI pain can be reproducible, uncommon symptoms are <5%—low grade fever, change in pattern of breathing, altered mental status, syncope, vomiting, abdominal pain, back pain, atrial fibrillation, syncope, hiccoughs, and reactive airways disease. No symptoms—<3%.

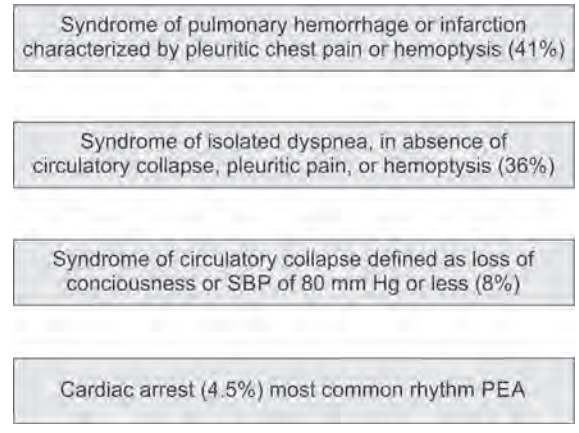
No physical examination finding is sensitive or specific for PE. Physical examination may fail to reveal any clues in 28–58% of patients. However, it may help to rule out other causes of dyspnea like presence of pallor (acute decompensated anemia), raised jugular venous pressure (JVP) (pericardial tamponade), Kussmaul breathing (metabolic acidosis) third heart sound and/or a new onset murmur (acute coronary event) and wheeze, and crepitations (acute COPD exacerbation and pneumonia). A systolic blood pressure (SBP) <90 mm Hg, tachycardia (>94/min), or sometimes bradycardia in patients on AV nodal blockers or beta-blockers and a low SpO_2 (<95%) are most commonly found. A shock index of >1.0, unilateral leg swelling, RR > 24/min, and fever >100.4°F are the classical physical findings but rare. **Figure 1** illustrates the different presentation syndromes. It is important to understand these because the pretest possibility of the disease is strongly associated with a clinical gestalt judgment by an experienced physician. However, it is argued that increased clinical experience may result in reduced comfort clinically excluding PE.

TABLE 1: Classic risk factors for PE can be memorized by a mnemonic "THROMBOSIS".

T	Trauma/travel
H	Hypercoagulable states/hormonal replacement therapy
R	Recreational drug use
O	Older
M	Malignancy
B	Birth control
O	Obesity/obstetrical (risk highest from second week of pregnancy to first 6 weeks postpartum)
S	Surgery
I	Immobilization
S	Sickness
Inherited risk factors: Factor V Leiden mutation, antiphospholipid antibody syndrome, antithrombin III deficiency, protein C deficiency, protein S deficiency, prothrombin gene mutation, Increased factor VIII activity, activated protein C (APC) resistance, and dysfibrinogenemia hyperhomocysteinemia	

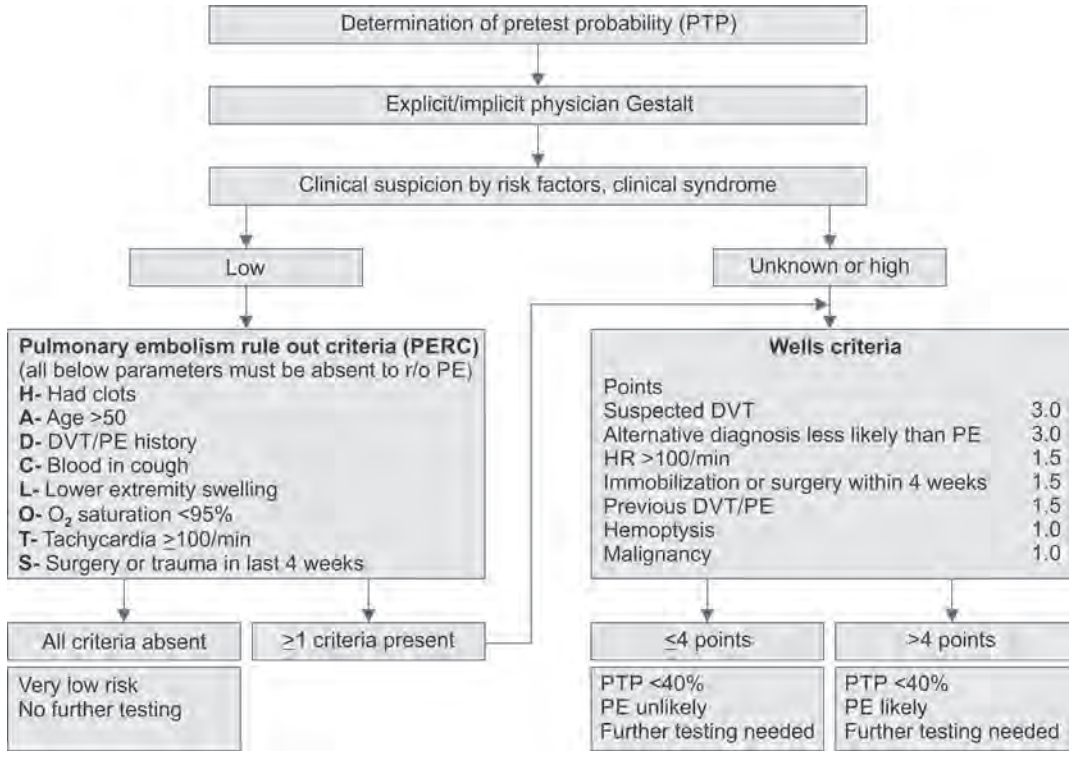
PRETEST PROBABILITY, SCORING SYSTEM AND PERC

Determining the pretest probability (PTP) identifies high-risk patients who may benefit from treatment prior to the completion of investigation, and low-risk patients in whom few, if any, investigations are required (**Flowchart 2**). Explicit assessment of PTP relies on the use of evidence-based clinical decision rules or scoring systems to categorize the PTP. *Three scoring systems have been prospectively tested* and validated in large clinical trials: (1) *The Wells score (**Table 2**), (2) the Geneva*


Syndrome of pulmonary hemorrhage or infarction characterized by pleuritic chest pain or hemoptysis (41%)
Syndrome of isolated dyspnea, in absence of circulatory collapse, pleuritic pain, or hemoptysis (36%)
Syndrome of circulatory collapse defined as loss of conciousness or SBP of 80 mm Hg or less (8%)
Cardiac arrest (4.5%) most common rhythm PEA

(PEA: pulseless electrical activity)

FIG. 1: Different presenting syndrome of pulmonary embolism.



(DVT: deep vein thrombosis; PE: pulmonary embolism)

FLOWCHART 2: Determining pretest probability.

TABLE 2: Assessing probability Of PE and DVT using Well's score.

Well's score for pulmonary embolism (PE)		***Well's score for deep vein thrombosis (DVT)***	
Factor	Points	Factors	Points
Suspected DVT	3	Active malignancy	1
Alternative diagnosis is less likely	3	Immobilization (paralysis and fracture)	1
Heart rate	1.5	Bedridden within 12 weeks for >3 days	1
Previous PE/DVT	1.5	Whole leg swelling	1
Surgery/immobilization last 1 month	1.5	Tenderness along deep vein distribution	1
Active malignancy	1	Calf swelling unilateral	1
Hemoptysis	1	Superficial vein collaterals	1
Interpretation of risk score: Probability of PE <2 points—low risk, 2–6 points—moderate risk, >6 points—high risk		Alternative diagnosis is more likely	–2
		H/O PE or DVT	1
		Interpretation of risk score: Probability of DVT ≥3 score high risk, 1–2 points moderate risk, <1 point low risk	

(DVT: deep vein thrombosis; PE: pulmonary embolism)

*score (**Table 3**), and (3) the Pisa score. The Pisa score is more appropriately used for hospitalized patients, whereas the Wells and Geneva scores were developed for use in the emergency department.*

Pulmonary Embolism Rule out Criteria (PERC) rule (**Box 1**) should be applied only in population with very low prevalence of PE. There are few more contraindications to apply the *PERC* rule. These are as follows—concurrent β-blocker use (may blunt tachycardia), transient tachycardia, thrombophilia, strong family history of thrombosis, patients with amputations, massively obese patients (may be difficult to clinical assess leg swelling), and patients with baseline hypoxemia.

DIAGNOSTIC WORKUP

Most routine investigations, including basic blood work, chest radiograph, ECG, cardiac troponins, brain natriuretic peptide (BNP), and arterial blood gas (ABG), are of limited value.

TABLE 3: Revised Geneva score for assessing probability of pulmonary embolism.

Clinical variables	*Points*
>65 years of age	1
h/o venous thromboembolism	1
Lower limb fracture (in previous month) or surgery requiring anesthesia	1
Malignancy (active)	1
Leg pain (unilateral)	1
Hemoptysis	1
Unilateral limb edema or pain	1
Heart rate >95	1
Interpretation of score 0–3 indicates low probability, 4–10 moderate probability, >10 high probability of PE	

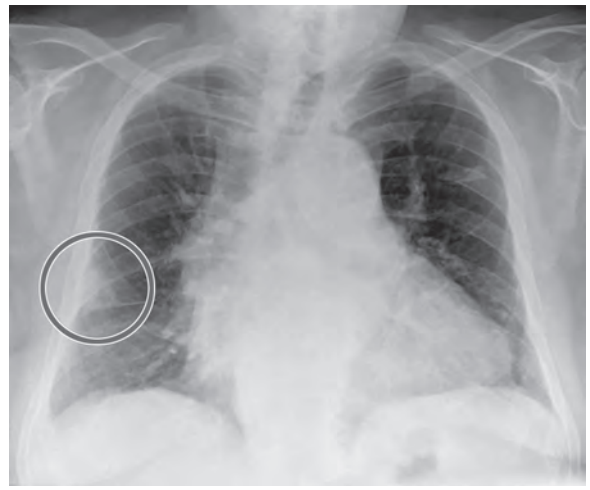


FIG. 2: Chest X-ray showing Hampton hump.

BOX 1: Pulmonary Embolism Rule out Criteria (PERC).

- Age <50 years
- Pulse <100 bpm
- Oxygen saturation >94%
- No hemoptysis
- No history of PE/DVT
- No surgery/trauma (no requirement of endotracheal intubation and anesthesia)
- No unilateral limb swelling, tenderness
- No h/o hormone replacement (estrogen) therapy
- Low clinical probability (<15% by Gestalt assessment)
- All clinical factors must be present to rule out pulmonary embolism

(DVT: deep vein thrombosis; PE: pulmonary embolism)

Electrocardiograph

It is neither sensitive nor specific. A normal ECG can be seen in 30% of patients with PE, whereas the classic S1Q3T3 occurs in only 20% of patients with angiographically proven PE, and has a sensitivity and specificity of 54% and 62%, respectively. The most common ECG change is T-wave inversion in the precordial leads, found in 68% of patients with PE. T-wave inversions may mimic an ischemic event, which is seen in 11% of patients without prior history of cardiopulmonary disease. Sinus tachycardia is the most frequent rhythm seen in patients with PE, occurring in 36%. Other ECG findings include changes suggestive for acute cor pulmonale—right bundle branch block, P-wave pulmonale, right axis deviation, and new-onset atrial fibrillation.

Chest Radiograph

It is typically nonspecific and nondiagnostic. It is reported to be normal in 12–24% of patients. Cardiomegaly, elevated hemidiaphragm, atelectasis, pleural effusion, parenchymal infiltrates, and PA enlargement are among the most common abnormalities. Patients without cardiopulmonary disease had only blunting of the costophrenic angles, and none had an effusion more than one-third of the hemithorax. The flip side of chest infiltrates is that those which are not fitting in clinical diagnosis of pneumonia, these patients can be having PE.

Hampton hump (**Fig. 2**) is a wedge-shaped, pleural-based, apex central pulmonary opacity that is uncommon and has a sensitivity and specificity of 22% and 82%. *Westermark* sign (**Fig. 3**) is relative oligemia usually in the presence of an ipsilateral dilated PA. It is also uncommon and has a sensitivity and specificity of 12% and 97%.

Arterial Blood Gas

In patients with normal lungs, a PCO_2 >36 mm Hg and normal alveolar arterial oxygen (A-a) gradient had a 98% negative predictive value for PE. The unexplained presence of hypoxemia or any sudden change in the A-a gradient increases the likelihood of PE. An elevated lactate generally reflects aerobic hyperlactatemia due to endogenous epinephrine production. This reveals that the patient is under occult hemodynamic stress, and is trying to compensate for that stress through increased sympathetic outflow.

Neutrophil/Lymphocyte Ratio

It is affected by occult physiologic stress (because endogenous cortisol will increase the neutrophil count and reduce the lymphocyte count, thereby increasing the ratio). Neutrophil/lymphocyte ratio (NLR) may be interpreted in the context of acute PE as follows—NLR <5.5 suggests low mortality risk (~2.7%), NLR 5.5–9.2 is a gray zone (NLR in this range is nonspecific and adds no useful information) and NLR >9.2 suggests high mortality risk (~26%).

Troponin and Brain Natriuretic Peptide

Troponin value may be helpful to clinicians in risk stratification of those patients found to have acute PE. Troponin can be increased in patients with massive acute PE and may be related to acute right ventricular strain or failure. BNP is not specific for PE and may be increased secondary to acute right ventricular strain with CHF, or other causes of pulmonary hypertension.

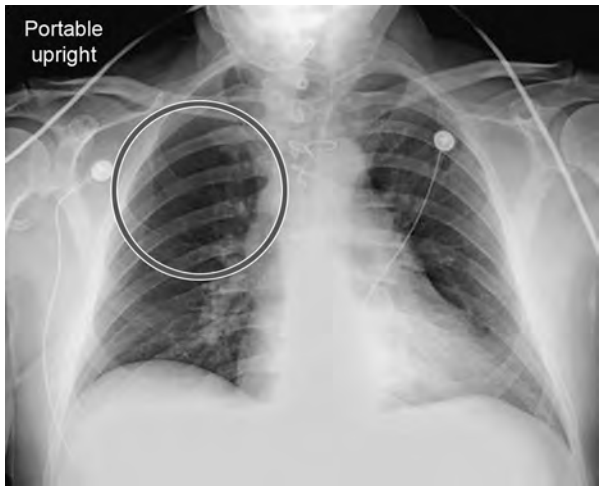
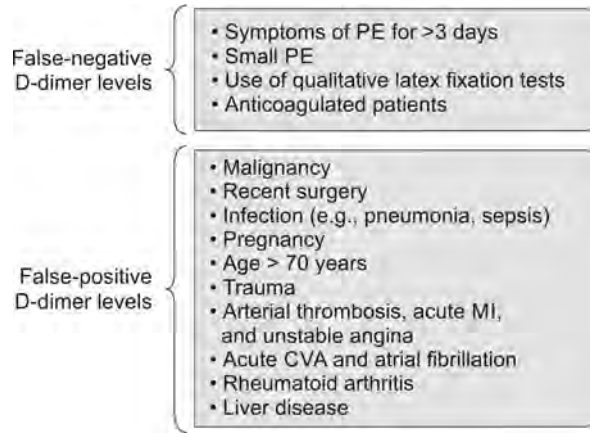


FIG. 3: Chest X-ray showing Westermark signs.


False-negative D-dimer levels
• Symptoms of PE for >3 days
• Small PE
• Use of qualitative latex fixation tests
• Anticoagulated patients
False-positive D-dimer levels
• Malignancy
• Recent surgery
• Infection (e.g., pneumonia, sepsis)
• Pregnancy
• Age > 70 years
• Trauma
• Arterial thrombosis, acute MI, and unstable angina
• Acute CVA and atrial fibrillation
• Rheumatoid arthritis
• Liver disease

(MI: myocardial infarction; PE: pulmonary embolism)

FIG. 4: Clinical conditions affecting the D-dimer level from expected values.

D-dimer

It is a fibrin degradation product that indicates the presence of intravascular fibrin deposition and is usually increased in thromboembolic disease. It was initially applied to patients already scheduled for imaging in an effort to reduce the number of pulmonary angiograms performed. With increasing use, the D-dimer became applied to manage patients even prior to the decision to perform diagnostic imaging. *The tips for using the D-dimer test wisely are* (1) Use a high sensitivity assay, (2) test low-risk patients, (3) test if you expect a negative result, and (4) Do not test if you have already scheduled the patient for computed tomography pulmonary angiography (CTPA). The quantitative D-dimer assays, ELISA and turbidimetric tests, have reported sensitivities of >93% and specificities of 39–55% (at a cutoff of 500 ng/mL; varies by institution) and are thus recommended for use to rule out the possibility of PE. It is important to learn how to decipher D-dimer result especially in elderly where normal D dimer level = Age in years × 10. Pregnant females increase their level by two times in second trimester and three times in third trimester, increase starting from end of first trimester. There is always a possibility to get normal value of D-dimer in presence of clinical PE and vice versa. In **Figure 4,** causes of false negative and false positive D-dimer value are given.

Echocardiographic

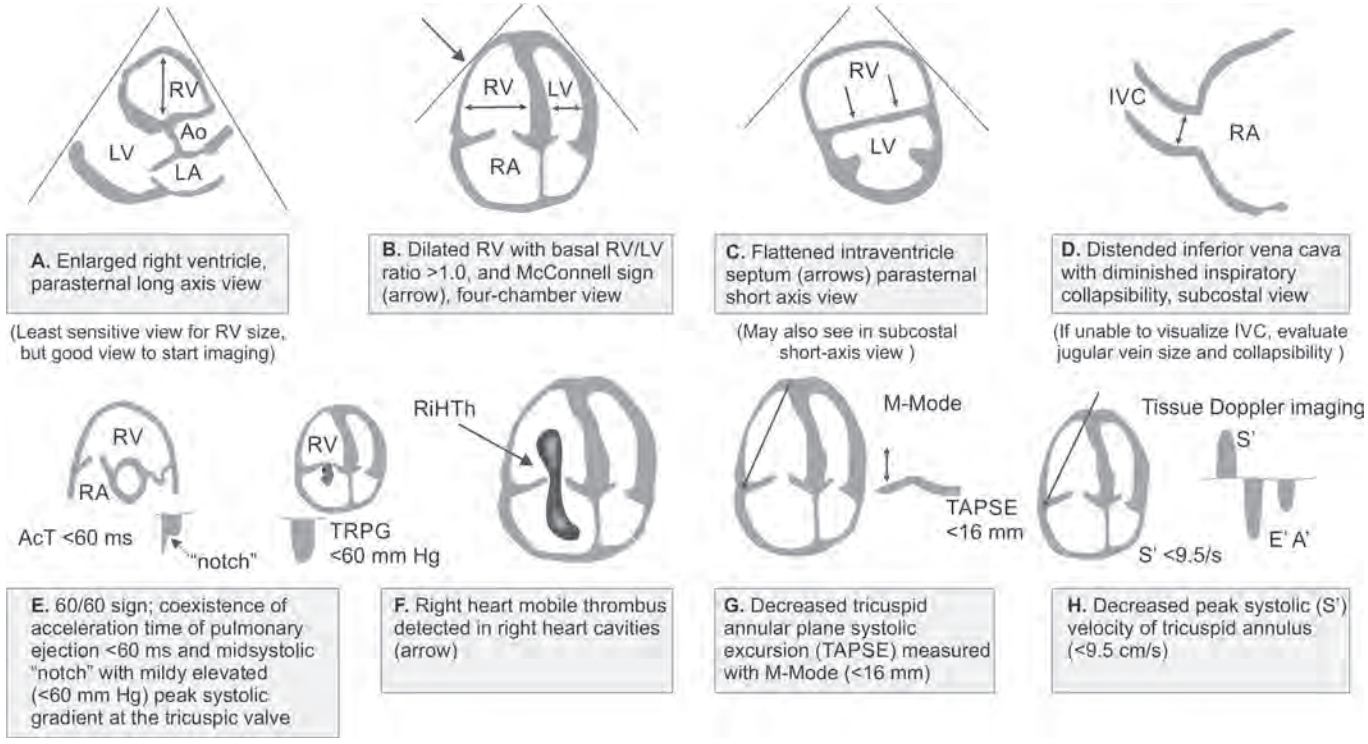
These abnormalities are present in approximately 30–40% of patients with PE. Transthoracic echocardiography (TTE) is noninvasive and rapidly available at the bedside, but lacks the sensitivity of TEE. Transesophageal echocardiogram (TEE) has greater sensitivity and diagnostic ability than TTE, but is invasive, of limited availability, often requires procedural sedation, and is unable to accurately detect peripheral PE. Echocardiography is most useful in patients with contraindications to other imaging modalities, hemodynamically unstable patients who cannot be transported outside the ED, or in patients with suspected massive PE to justify thrombolytics. Echocardiographic findings of PE are shown in **Figures 5A** to **H**.

Computed Tomography Pulmonary Angiography and V/Q Scan

- *The rule for computed tomography angiography (CTA)*—sensitivity for central clots is 100% and 90% for peripheral clots. It is 91% specific. If the PTP is high, but the CTA is negative, still one should order Doppler USG legs to look for VTE. The only good point here is that one can wait for initiating anticoagulation. The subsegmental PEs are more often recognized these days with advancement in CT scanners. 3–30% scans have isolated subsegmental clots with unclear clinical importance.
- *The rule for V/Q scan*—a young patient with no known lung disease [normal chest X-ray (CXR)] and normal V/Q scan, PE can be ruled out with very high predictive value. A normal V/Q scan essentially rules out PE with an NPV of 97%. A high-probability scan has a positive predictive value of 85–90% with a sensitivity and specificity of 41% and 97%, respectively. A low-probability interpretation is controversial, and many investigators advocate for additional testing. Indeterminate rates are more common among patients with significant cardiopulmonary disease, including acute and chronic airway disease, patients with abnormal chest radiography, and the elderly. A comparative analysis of both modalities is presented in tabular form in **Table 4**.

Other Modalities such as Compression Ultrasonography, MRI, and Pulmonary Angiography

- *Compression ultrasonography (CUS)* can be used at various points in the investigation of PE—(1) as an initial imaging modality; (2) after a negative or inconclusive CTPA; or (3) after a nondiagnostic V/Q scan. In patients with suspected PE, CUS as an initial investigation only detects 10% of DVTs. Two negative CUS examinations following a nondiagnostic or indeterminate V/Q scan result in a 3-month risk of PE of >1%. Early studies with single-slice or four-slice multidetector CTPA showed that CUS


RV
Ao
LV
LA
A. Enlarged right ventricle, parasternal long axis view
(Least sensitive view for RV size, but good view to start imaging)
RV
LV
RA
B. Dilated RV with basal RV/LV ratio >1.0, and McConnell sign (arrow), four-chamber view
RV
LV
C. Flattened intraventricle septum (arrows) parasternal short axis view
(May also see in subcostal short-axis view)
IVC
RA
D. Distended inferior vena cava with diminished inspiratory collapsibility, subcostal view
(If unable to visualize IVC, evaluate jugular vein size and collapsibility)
RV
RA
AcT <60 ms
"notch"
E. 60/60 sign; coexistence of acceleration time of pulmonary ejection <60 ms and midsystolic "notch" with mildy elevated (<60 mm Hg) peak systolic gradient at the tricuspic valve
RV
TRPG
<60 mm Hg
RiHTh
F. Right heart mobile thrombus detected in right heart cavities (arrow)
M-Mode
TAPSE
<16 mm
G. Decreased tricuspid annular plane systolic excursion (TAPSE) measured with M-Mode (<16 mm)
Tissue Doppler imaging
S'
E' A'
S' <9.5/s
H. Decreased peak systolic (S') velocity of tricuspid annulus (<9.5 cm/s)

FIGS. 5A TO H: Echocardiographic assessment of right ventricle in pulmonary embolism—whenever feasible evaluate right ventricles in several views A to D.

TABLE 4: Comparative analysis of computed tomography pulmonary angiography (CTPA) and V/Q scan.

CT pulmonary angiography	*V/Q scan*
Advantages: • Readily available at most centers • Short acquisition time • Ability to detect alternative diagnosis • Retrospective reconstruction • High sensitivity/specificity • Dichotomous interpretation • Sole diagnostic test (multidetector CT) • Age does not influence result *Disadvantages*: • High maternal breast radiation dose • Reader expertise required • Expensive • Nephrotoxic iodinated contrast injection • Not portable • Physiological changes in pregnancy may cause non diagnostic result • Contraindicated in patients with contrast allergy and renal insufficiency	*Advantages*: • Radionuclide poses minimal risk and is safe in pregnancy • Safe in patients with contrast allergy and renal insufficiency • Low maternal breast radiation (0.28–0.9 mSv) • Dose can be further decreased by perfusion only scan *Disadvantages*: • Inability to provide alternative diagnosis • Long acquisition time • Potentially significant rate of nondiagnostic results • Limited access and availability

diagnosed an additional 3.1–6% of DVTs in patients with negative CT.

- *Magnetic resonance angiography (MRA)* advantages include safer contrast material, the absence of ionizing radiation, and similar sensitivity and specificity to CTPA. The combination of MRA and magnetic resonance (MR) venography had a sensitivity and specificity of 92% and 96%, respectively. MRI should only be considered in centers in which it is routinely performed.
- *Pulmonary angiography* has long been considered the gold standard for the diagnosis of PE. It is less helpful in visualization of subsegmental pulmonary arteries and greater interobserver disagreement.

TREATMENT

Systemic anticoagulation is the mainstay of the treatment for venous thromboembolism (DVT + PE). Unfractionated heparin and low molecular weight heparin (LMWH) are the two most common options. LMWH is preferred over unfractionated heparin as per recent data. Early administration of heparin is recommended but no study found morbidity or mortality benefit if heparin administers early and prior to imaging. Other measures such as placing the affected limb at neutral level, removal of tight clothing, dressing, and cast are equally important. Vascular consultation and catheter-directed thrombolysis should be arranged. Systemic thrombolysis is another option with Alteplase 50–100 mg infusion over 4 hours. The management of PE will be dealt under following headings. The initial management starts with resuscitation of PE patient (**Box 2**).

Anticoagulation

The treatment of acute PE is systemic anticoagulation with or without thrombolysis. Anticoagulation halts clot progression and allows endogenous fibrinolysis to occur. Clot resolution occurs over weeks to months, and may be incomplete in some individuals. Typically, an initial short-term therapy using unfractionated heparin, LMWH (e.g., enoxaparin and dalteparin), or fondaparinux is used and bridges the transition to the vitamin K antagonist warfarin.

Initial anticoagulation should be administered for 5 days and until the INR is in the therapeutic range of 2–3 for 2 days. In patients with a high clinical probability of PE, this treatment should begin before diagnostic imaging. In patients with low clinical PTP, it is considered safe to await confirmatory tests before initiating systemic anticoagulation. In general, empiric treatment confers more benefit than harm when, PTP exceeds 30%, imaging would delay anticoagulation for >24 hours, and the patient has no major contraindications. Available choices and the indications are discussed below (**Table 5**).

Thrombolysis in Pulmonary Embolism

Thrombolysis of a massive PE reduces the risk of cardiovascular collapse.

- Thrombolysis with alteplase is safer than is usually thought, available studies are underpowered to clearly define the risk of intracranial hemorrhage, but it seems to be low (1%) for reduced-dose regimens of alteplase (e.g., 50 mg). There is no need of complete resolution of clot. The goal should be to normalize the pulmonary pressures, but rather merely to cut back pressure sufficiently to prevent sudden cardiac death. Hence, a small dose 12–50 mg of alteplase can be recommended with lower risk of hemorrhage, thereby

BOX 2: Important points to remember during resuscitation of pulmonary embolism patient.

- Use high-flow nasal cannula for hypoxemic failure
- Add inhaled pulmonary vasodilators, whenever possible
- First thrombolytics, then intubation
- Define criteria of intubation—depressed mental status or respiratory exhaustion
- Intubation pearls:
  - Before intubation, try to increase the SBP = 130–140 mm Hg, usually with an epinephrine infusion
  - Be prepared with push-dose epinephrine to support the blood pressure after intubation. Have a low threshold for using this for hypotension or worsening bradycardia
  - Consider getting inhaled pulmonary vasopressors at the bedside and ready to be given through the ventilator circuit as soon as the patient is intubated. Administration of a milrinone dose through the endotracheal tube may also be utilized, if this is available.
  - Use meticulous preoxygenation and apneic oxygenation, paired with intubation by the most experienced operator present
  - Use sedatives that are hemodynamically stable (e.g., ketamine)
  - Avoid overvigorous bag ventilation, which will cause excessive intrathoracic pressures
  - Pay extreme attention to the patient's hemodynamics and oxygenation in the first 10 minutes after intubation, as this is when they are most likely to arrest
- Epinephrine due to its beta-agonist action is the first-line vasopressor. Helps in pulmonary vasodilatations as well. Vasopressin as second-line drug—systemic vasoconstriction with pulmonary vasodilatation
- Nitric oxide and epoprostenol—comparable results. High FiO_2 is a poor man's pulmonary vasodilator
- Try to limit ABG punctures. These may be the sites of bleeding when urgent thrombolysis is done
- Similar caution has to be taken for central venous cannulation—single puncture, experienced physician
- Intubation and positive pressure ventilation increases peripheral vascular resistance. Avoid or delay intubation
- Fluid boluses—very small, guided by US massive PE is not a fluid depleted state. Expect the IVC to be full. If not, suspect another diagnosis

(ABG: arterial blood gas; FiO_2: fraction of inspired oxygen; IVC: inferior vena cava; PE: pulmonary embolism; SBP: systolic blood pressure)

TABLE 5: Antithrombotic agents for pulmonary embolism (PE) and deep vein thrombosis

Drugs	*Indications and doses*	*Comments*
Heparin	Submassive PE bolus dose of 5,000 IU or 80 IU/kg, followed by a continuous 18 IU/kg/h nomogram-adjusted infusion to an APTT of 1.5–2.5 times the normal value	It can be stopped if any indication of bleeding. It can be paused or down-titrated in anticipation of thrombolysis or procedures
Low molecular weight heparin (LMWH)	Dalteparin is dosed at 200 U/kg once daily Enoxaparin administered at 1 mg/kg twice daily Tinzaparin is given at 175 U/kg once daily Fondaparinux patients weighing <50 kg, 50–100 kg, and >100 kg = doses of 5 mg, 7.5 mg, and 10 mg, s/c per day, respectively	The LMWHs and fondaparinux are preferable to unfractionated heparin because they are easier to administer, do not require intravenous infusions, and do not require monitoring of INR or Xa levels

TABLE 6: Identifying risk of Intracranial hemorrhage with thrombolysis by PECH score.

	Criteria	*Points*
P	Peripheral vascular disease	1
E	Elderly age >65 years	1
C	Prior CVA with residual deficit	5
H	Heart—prior myocardial infarction	1
Risk = 0 points = 1.2%, 1 point = 2.9%, 2 points = 3.4%, 5 points or more = 18%		

improving the overall risk/benefit ratio. *PECH score* can help to predetermine the risk of ICH with thrombolysis (**Table 6**).

- Ideally, heparin will be stopped and allowed to clear from the patient prior to systemic thrombolysis. This may be possible for hemodynamically stable patients with submassive PE, but not for patients with massive PE. On the other hand, a patient who is anticoagulated (e.g., with enoxaparin) and develops hemodynamic instability can receive thrombolysis.
- It is equally important to know when to resume heparin. The traditional approach is to resume heparin (without a bolus) when the PTT is below 1.5–2 times normal. The newer approach is to avoid resumption until fibrinogen is over approximately 100–150 mg/dL.
- Tenecteplase is a bit easier to reconstitute, so it is possible that tenecteplase might have an advantage in PE-induced cardiac arrest if it were quicker to access.
- The most common dose of tPA for catheter-based thrombolysis (both PA cannulated) has been 0.5–1 mg/h per catheter for a total dose of 12–24 mg delivered over a 24-hour period.

Percutaneous Mechanical Thrombectomy by Interventional Radiology

Potential indications are: (1) Patients with high-risk submassive or massive PE with contraindication to thrombolysis; and (2) Patients in whom thrombolysis has failed to be effective. The devices used are Angiojet, Angiovac, Penumbra Indigo embolectomy system, etc.

Surgical Thrombectomy

Indications are: (1) Clot-in-transit which is lying across a patent foramen ovale. This situation carries a risk of immediate stroke if the clot breaks up and parts of it enter the systemic circulation. (2) Massive PE in a patient with absolute contraindication to thrombolysis. (3) Massive PE with failure of other interventions—10% of clots which have become chronic and have organized will not respond to thrombolysis.

Venous Arterial Extracorporeal Membrane Oxygenation

Potential indications in emergency department are (1) Massive PE in a patient with absolute contraindication to thrombolysis. (2) Stabilization of a patient with massive PE prior to intubation, and (3) patient with massive PE and persistent instability despite thrombolysis. Potential roles for venous arterial extracorporeal membrane oxygenation (VA-ECMO) may include bridge to anticoagulation efficacy, controlled thrombolysis—ECMO could be used to support a patient while undergoing gradual thrombolysis and intervention, e.g., catheter-directed thrombolysis or cardiothoracic surgery.

Inferior Vena Cava Filter

The role of placing IVC filter has been debated to do more harm than good. On one hand, it might intercept clots traveling to the lungs (thereby avoiding PE) and on the other hand, stasis of blood increases in lower extremity, veins get thrombosed and there is a major risk of procedural complications like IVC tear, filter embolization or bleeding. Inability to receive anticoagulation, (sub)massive PE with a low hemodynamic reserve and known DVT with large clot burden (especially large, free-floating, and proximal DVT) are the indications for IVC filter.

SUMMARY

The presentation of PE ranges from incidentally discovered asymptomatic emboli to massive embolism causing an immediate threat to life. The EP job is to recognize, resuscitate, investigate, and refer the patient to cardiologist, interventional radiologist, or cardiac surgeon. The introduction of PERT (pulmonary embolism response teams) including members from every department involved in the treatment of PE shall be a good move in future. Approach to treatment of PE is summarized in **Box 3**.

BOX 3: Summary of approach to pulmonary embolism

- Step 1—keep a high degree of suspicion of the disease
- Step 2—make an implicit and/or explicit determination of pretest probability (PTP)
- Step 3—decide on doing D dimer and CTPA or perfusion scan
- Step 4—categorize pulmonary embolism into:
  - *Low-risk PE*: Patients at the lowest risk of dying. Some may be able to be discharged home.
  - *Low-risk submassive PE*: Patients with RV dilation, but who are at low risk of dying and do not require intensive care
  - *High-risk submassive PE*: Hemodynamically stable patients who nonetheless have elevated mortality. They merit ICU admission and consideration for advanced therapies
  - *Noncrashing massive PE*: Patients with hypotension who stabilize well on low-dose vasopressor. These patients need ICU admission and advanced therapies
  - *Crashing massive PE*: Patients with hypotension and persistent features of instability, who are at the greatest risk for immediate death
- Step 5—start treatment

(CTPA: computed tomography pulmonary angiography; ICU: intensive care unit; PE: pulmonary embolism)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Acute Aortic Dissection

Devendra Richhariya

INTRODUCTION

Acute aortic dissection (AAD) is one of the catastrophic diseases seen in emergency department (ED), which is rare, difficult to diagnose, and also carries high mortality even if diagnosed early and properly. Delay in diagnosing the AAD in ED can be devastating for patient and also stressful for the emergency physician. AAD is responsible for 40% of the immediate death and 20% of the perioperative death. Although 50–70% survival rate is reported after initial surgery depending upon patient age and cause of the AAD.

EPIDEMIOLOGY

Acute aortic dissection can be instantly fatal in prehospital setting (cause of death may be attributed to other cause) so true incidence is difficult to define. Also missed diagnosis or delay in diagnosis leads to misclassification of disease. According to various studies prevalence ranges between 2.5 and 3 cases (United States) per 100,000 person/year to 16 cases (Sweden) per 100,000 person/year. Higher incidence (>60%) is noted in men with increasing age group. AADs have 75% mortality rate within 2 weeks if left untreated while in surgically repaired AAD 5-year survival rate is about 75% and 10-year survival rate is 40–60%.

Missed diagnosis of the AAD attracts the significant medicolegal issues also. Canadian Medical Protection Agency (CMPA) reviewed the litigations related to AAD and found complete lack of typical and atypical findings in these patients and about 56% of cases were dismissed. CMPA also cautioned the physician to consider the diagnosis in case of sudden severe chest pain with visceral symptoms such as nausea, vomiting pallor, diaphoresis, normal, or minimal changes of electrocardiography (ECG) findings. It is also suggested to avoid too much reliance on classic features like tearing chest pain, blood pressure/pulse discrepancies, new cardiac murmurs, mediastinal widening on chest radiograph, as these are potentially misleading.

PATHOGENESIS AND RISK FACTORS OF AORTIC DISSECTION

The aortic wall is consisting of three layers: (1) Intima the inner most layer, (2) media (made up of elastic connective tissue and smooth muscle), and (3) adventitia the outer most layer.

Normally, cardiac contractions give swinging movement of the heart within pericardium and give slight flexion movement of ascending and descending part of aorta. This multiple swinging movement (37 million beats/year) of the heart put stresses on the aortic layers. Prolonged hypertension is also hemodynamic stressors to aortic wall. Disease like Ehlers–Danlos syndrome where aortic walls are inherently weakened and laminar flow toward aortic wall is also altered in bicuspid aortic valve. So degenerative changes during normal aging process or any other pathological process and pulsatile blood flow create tear in the aortic intima resulting in the separation between the aortic intima and aortic media (**Fig. 1**). Blood travels into this false lumen and resulting in various clinical presentations. False lumen can extent distally or proximally and can lead to obstruction of other arterial origins from the aortic trunk, rupture back into the true vascular lumen, or into the pericardial sac or pleural cavity. Most aortic dissections occur with an initial transverse tear along the greater curvature of the aorta. The next most common site is the descending thoracic aorta immediately distal to the origin of the left subclavian artery.

Risk Factors

There are various reported risk factors (described in **Table 1**) that affect and weaken the aortic wall layers and create false lumen. Common risk factors are uncontrolled hypertension, history of cardiac surgery, or catheterization. Congenital and connective tissues disorder also risk factors for aortic dissection. Cocaine and other stimulant use are also associated with the aortic dissection. Positive family history is also associated with aortic dissection even in absence of any genetic syndrome.

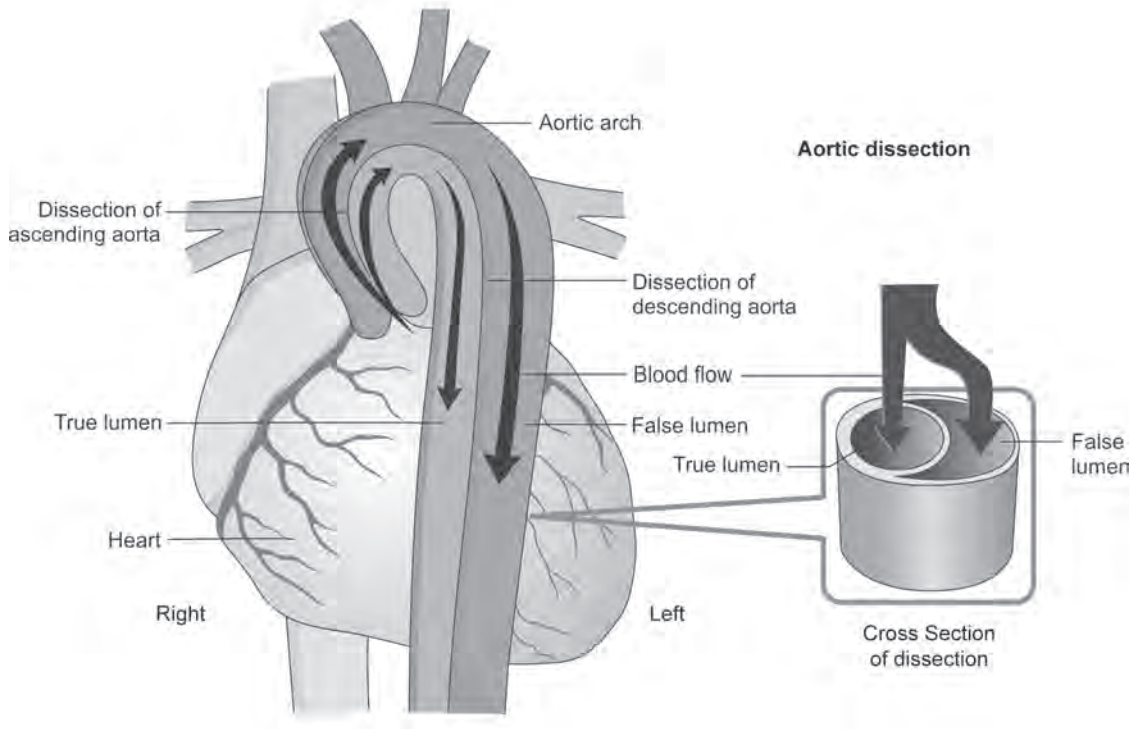


FIG. 1: Pathophysiology of aortic dissection (false lumen between intima and media due to various disease process).

TABLE 1: Risk factors for acute aortic dissection.

Disorders	***Impact***
Uncontrolled hypertension Pheochromocytoma Cocaine use Valsalva situation (weight lifting) Blunt trauma Coarctation of aorta	Aortic wall stressors
Genetic disorders: Ehlers–Danlos syndrome, congenital bicuspid aortic valve *Inflammatory vasculitis*: Takayasu, giant cell granulomatous arteritis	Affecting medial layers
Cardiac or valvular surgery intra-aortic balloon pump (IABP) insertion	Iatrogenic
Male: • Age > 50 years • Pregnancy • Polycystic kidney disease • Immunocompromised state	Other

Aortic dissection is also reported in pregnancy and certain infectious disease such as tuberculous aortitis.

CLASSIFICATION OF ACUTE AORTIC DISSECTION

Classification of AAD is based on anatomical location. This is very important to recognize the location of the dissection to ascertain the prognosis and treatment (**Fig. 2**). The Stanford (type A and type B) and DeBakey (type I, II, and III), two different anatomical classifications are commonly used described in **Table 2**.

As far as emergency physician is concern classification is may not be very useful as compare to vascular surgeons for surgical management planning. Aortic dissection is categorized in another way as acute (if diagnosis within 2 weeks of pain onset) subacute (2–6 weeks) and chronic (>6 weeks after onset of pain).

CLINICAL PRESENTATION OF ACUTE AORTIC DISSECTION

Diagnosing the AAD in ED is always challenging due to its catastrophic nature. Sudden onset chest pain, excruciating, severe at onset (sharp, tearing, in nature), is usually typical feature of aortic dissection. But aortic dissection may not present always with this typical feature. Sometime it is possible to localize the origin of dissection on the basis of pain, anteriorly situated pain (ascending aorta), neck or jaw (arch of aorta), interscapular pain (descending aorta), and intensity of pain may decrease over the time depending upon extension of dissection or involvement of other organ system. Chest pain is the prominent symptoms for type A dissection while back pain for type B dissection. Typical symptoms may accompany with visceral symptoms such as nausea, vomiting, diaphoresis apprehension, and light-headedness. Painless presentation of aortic dissection may be noted in patient of older age group, chronic steroid user, and Marfan's syndrome. These groups may present with syncope stroke or congestive heart failure.

Physical findings are usually absent but unreliable. We may get important clues by examination of upper extremities pulses

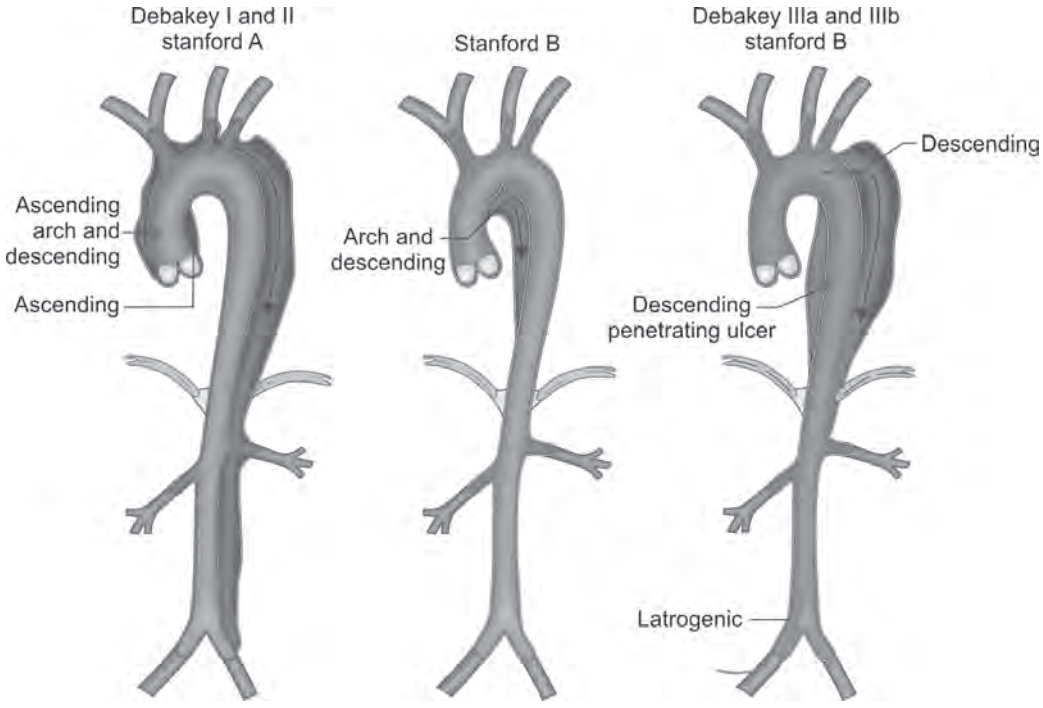


FIG. 2: Anatomical classification of aortic dissection (Stanford and DeBakey).

TABLE 2: Classification of acute aortic dissection (AAD).

Stanford classification of AAD		***DeBakey classification of AAD***		
Type A	**Type B**	**Type I**	**Type II**	**Type III**
Any dissection involving the ascending aorta (proximal to brachiocephalic artery)	Only descending aorta is involved (distal to subclavian artery)	Intimal tear originates from ascending aorta, involving arch and then extend even beyond descending aorta	Only ascending aorta is involved	Only descending aorta is involved

and blood pressure differential (in one study 20–30 mm Hg blood pressure differential reported as significant in cases of AD), while other study revealed that 20% of normal patient may have pulse differential. Newly developed aortic regurgitation is present in about 30–70% patient. Aortic regurgitation may present with severe complications such as life-threatening congestive heart failure or cardiogenic shock. Aortic dissection may give rise to mass effect on adjacent structure presenting with superior vena cava syndrome, Horner syndrome, hoarseness (recurrent laryngeal nerve), dyspnea (pressure on tracheobronchial tree), and dysphagia (pressure on esophagus).

Wide variety of presentation of AAD is noted ranging from painless presentation to life-threatening complications such as congestive heart failure and cardiogenic shock. Diagnosing the AAD remains a challenge for the emergency physician in this situation. Hence during triaging and initial assessment the triaging nursing staff/emergency physician should be aware of *"Red flags"* (**Table 3**). Clinical presentation helps them in implementing the lifesaving interventions in early stage. Apart from these presentations, AAD presents with symptoms of end organ damage described in **Table 4** (Complications of AAD).

DIAGNOSTIC STRATEGIES FOR ACUTE AORTIC DISSECTION IN THE EMERGENCY DEPARTMENT

Emergency physician must make the proper diagnosis if possibility of aortic dissection is considered. Routine initial test such as electrocardiogram chest radiograph, laboratory markers are available in every ED with variable reliability and thus further advanced imaging modalities are also required (**Box 1**).

TREATMENT

Early lifesaving management in AAD starts with high index of suspicion with targeted history, physical examination, and timely diagnosis. Once diagnosis is established, medical management is instituted as soon as possible to aggressively control the blood pressure and heart rate (target systolic blood pressure is 100–120 mm Hg and heart rate 60 beats/min. Several classes of drugs are used to achieve these goals. By controlling the BP and heart rate, the stressors which are acting on aorta (described in pathophysiology section) are diminished.

TABLE 3: Red flags (concerning features) for acute aortic dissection.

On the basis of history	*On the basis of pain*	*On the basis of examination*
• Family history	• Sudden onset	• Peripheral pulse difference
• Known aortic valve disease	• Excruciating	• Blood pressure difference
• Known aortic aneurysm	• Tearing	• Syncope
• Known Marfan's or other connective tissue disease	• Interscapular pain	• New aortic regurgitation murmur
• History of cardiac surgery		• Hypotension and shock

Alert for aortic dissection if patient presentation is chest pain + abnormal pulse or low blood pressure, or high blood pressure, or neuronal symptoms or chest pain poorly responds to medications

TABLE 4: Complications of acute aortic dissection (AAD).

Cardiovascular complications	• Aortic regurgitation • Pulse deficit • Blood pressure differential • Syncope (as a result of acute cardiac dysfunction, vascular outflow obstruction, and vasovagal pain response) • Myocardial infarction • Congestive heart failure • Shock
Neurological complications	• Focal neurological deficit (can be due to hypotension, decreased perfusion, thromboembolism, or nerve compression from mass effect) • Intracranial or brainstem involvement, e.g., cerebral ischemia and stroke syndrome (proximal arch dissection) • Spinal cord and lower extremities involvements (distal arch dissection) • Sudden coma (basilar artery occlusion) • Transient locked in syndrome described in painless AAD
Respiratory complications	• Dyspnea (mass effect) • Hemorrhage into lung tissues and pleural space pleural effusion
GI complications	• Mesenteric ischemia (type B) • Catastrophic GI bleed (rare)
Ear/Nose/Throat complications	Dyspnea, stridor, dysphagia, hoarseness of voice, and ipsilateral Horner syndrome
Atypical presentations	Chronic aortic dissection may present with fever of unknown origin, mesenteric ischemia, and renal colic

BOX 1: Diagnostic tests for acute aortic dissection.

Basic routine tests:

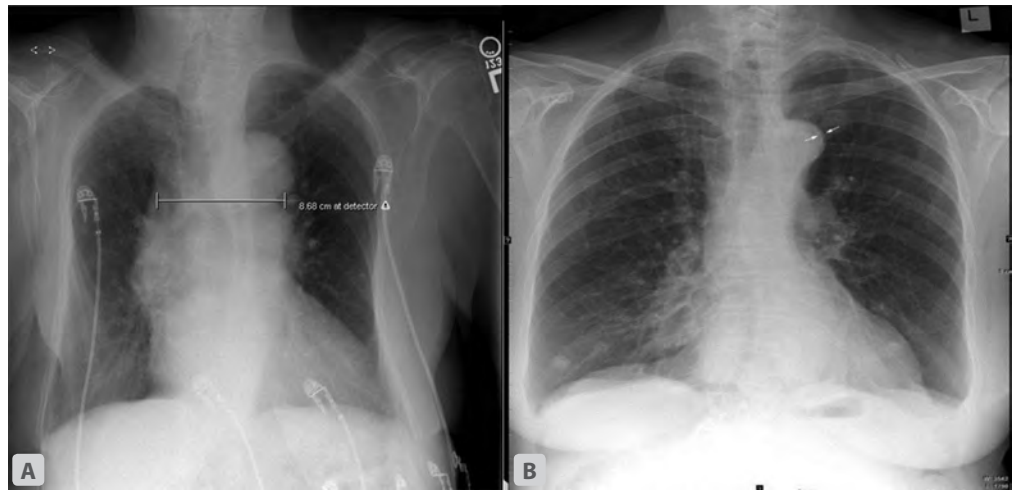
- *Electrocardiography (ECG)*:
  - Normal or nonspecific while left ventricular hypertrophy seen in hypertensive patients
  - ECG is primarily useful to rule out alternative diagnosis
- *Chest radiography*: 90% of patients with aortic dissection have abnormal aortic contour and mediastinal widening on chest radiograph (**Fig. 3A**). Other radiographic changes are displaced aortic calcification especially in elderly (**Fig. 3B**), pleural effusion, and abnormalities of aortic arch displacement of trachea. Normal chest X-ray narrows down the differential diagnosis
- *Laboratory markers*: (D-dimers and other biomarkers) Initial studies showed D-dimer as a highly useful marker (sensitivity 94–99%). In spite of that not recommended for screening and diagnosis because lack of large prospective studies. Similarly, further investigations are required for other biomarkers such as serum smooth muscle myosin heavy chain and calponin (smooth muscle troponin such as protein)

Advanced imaging modalities:

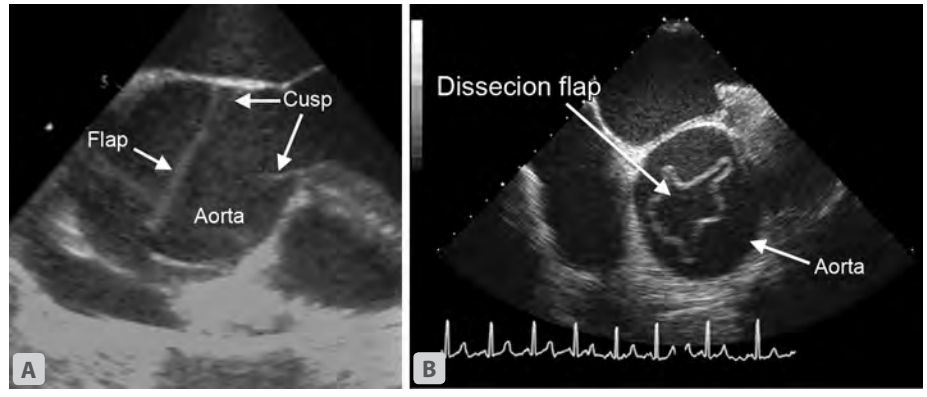
- *Transesophageal echocardiography (TEE)*: Important role in diagnosing the AAD rapidly noninvasively particularly in hemodynamically unstable patient (**Figs. 4A** and **B**). TEE also able to diagnose aortic regurgitation and pericardial effusion
- *Transthoracic echocardiography (TTE)*: TTE able to visualize aortic dissection but should not be used as isolated test to diagnose AAD. TTE can be used with TEE as there is a blind spot in the distal portion of the aortic arch on TEE
- *Computed tomography imaging (CT)*: CT with angiography is now imaging modality of choice for stable AAD (**Figs. 5A** to **C**). CT scan can locate dissection flap and helpful in operative planning for ascending aortic dissection. CTA requires contrast bolus which is inappropriate for renal insufficiency patient. Also, hemodynamically unstable patient cannot leave the ED for CT angiography for AAD
- *Magnetic resonance imaging (MRI)*: MRI provide much more detail evaluation of location and extension of dissection with lack of radiation but less often used due to variable availability and many patients with AAD are not stable enough for MRI

Medical Management

- *Pain management*: Opioid analgesics can be used in titratable dose to relieve pain and decreasing the sympathetic tone, also augmenting the rate control and vasodilatation.
- *Beta-blockers*: Lowers blood pressure and heart both so beta-blockers are used as first-line therapy in aortic dissection.
  - Esmolol—first agent of choice in beta-blockers class, short-acting agent starting with 500 μg/kg bolus followed by infusion at 50–200 μg/kg/min titrated to its effect, rebolus also can be given.
  - *Labetalol*: Labetalol is alternative choice if esmolol is not available bolus 20 mg every 5–10 minutes up to 80–300 mg total dose infusion rate 1–2 mg/min.
- *Calcium channel blockers (CCBs)*: CCBs such as verapamil or diltiazem are not routinely used for AAD. This class of drug alternative to β-blockers if patient has contraindications.



FIGS. 3A AND B: (A) Widening of mediastinum on chest X-ray; (B) Medially displaced aortic calcification on chest X-ray.



FIGS. 4A AND B: (A) Transesophageal echocardiography (TEE) image showing presence of an intimal flap in the ascending aorta. (B) TEE image showing circumferential intimal flap in ascending aorta on.

FIGS. 5A TO C: (A) Aortic root dilatation; (B) CT angiographic image showing dissection flap in the arch of aorta; (C) CT angiogram in aortic dissection. ***(For color version, see plate 9)***

- *Nitroprusside*: Nitroprusside reduces preload and also afterload, once the heart rate is controlled and additional blood pressure control is required, nitroprusside vasodilator can be added. Nitroprusside should be added after β-blocker because independently, it causes reflex tachycardia (increases the aortic stress and worsening dissection).

Surgical Management

Surgical intervention is gold standard for type A dissection involving the ascending aorta. The main aim of the surgery is to prevent aortic rupture, cardiac tamponade, and relief from aortic regurgitation. Surgical procedure also improves the blood flow in the branches affected by the false lumen**.** Surgery is reserved in type B dissection for the patient who is having ongoing pain, refractory hypertension, major arterial occlusion, and leaking or rupture. Surgical management reduces the in-hospital mortality to 27% in comparison to 56% in medically treated type A dissection so patient should be transferred to tertiary care center if cardiac surgery is not available in particular center and aggressive medical management to continue.

Newer Interventions

Endovascular stenting is the newer intervention and alternative to surgery for patient with type B dissection with evidence of limb or visceral ischemia. Aortic fenestration is also used as alternative to endovascular stenting to restore the perfusion in patient with end organ damage. Aortic fenestration is a procedure where communication is created between false and true lumen of the aorta and this communication helps in flowing the blood toward the arteries which are originating from false lumen.

Pitfalls in Aortic Dissection Management

Acute chest pain is very common in ED. Aortic dissection as a cause of chest pain is infrequent as comparison to other causes such as acute coronary syndrome pulmonary embolism, pneumothorax, and esophageal rupture. This is usually noticed that emergency physician has less awareness about aortic dissection incidence risk factors and AAD evaluation. Even most of the institute have care pathways specific to more common chest pain presentation such as acute coronary syndrome and pulmonary embolism but not for the most dangerous and devastating AAD. Emergency physician is much more trained to give loading dose of antiplatelet and anticoagulant to acute onset chest pain suspecting acute coronary syndrome. Consider AAD evaluation in acute chest pain patient if risk factors, clinical features are as described earlier in this chapter or lack of response to chest pain management before jumping to potentially irreversible fibrinolytic therapy.

ACUTE AORTIC DISSECTION IN PREGNANCY

Several hemodynamic and physiologic changes occur in pregnant women. Hemodynamic changes in intravascular volume, compensatory cardiac output demand, and intimal wall connective tissue changes work as stressors. Pregnant women are at risk of expansion of aortic dissection and rupture in third trimester. Specialized vascular surgeon obstetric team is required for maintaining fetal viability. Emergency caesarean section delivery can also be performed with strict monitoring of maternal and fetal hemodynamic.

SUMMARY

Assessment of acute undifferentiated chest pain and diagnosis of AAD in the ED are one of the challenging things for emergency physician. AAD not always present with typical clinical feature. There are numerous and misleading clinical features related to cardiovascular, abdominal, neurologic, and other system. Emergency physician should have knowledge about typical and atypical presentation, able to carry out thorough physical examination, and routine/advanced imaging techniques, if high index of suspicion for AAD. Once AAD is diagnosed, pain, heart rate, and blood pressure control are priority followed by definitive surgical consultation can be taken. Consider AAD in given situation to avoid adverse outcome for patient and medicolegal liability for emergency physician.

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CHAPTER

Antithrombotic Therapy

Santosh Pandey

INTRODUCTION

Under normal circumstances, a delicate balance between coagulation and fibrinolysis prevents both thrombosis and hemorrhage. Alteration in balance in favor of coagulation results in thrombosis. Antithrombotic therapy is used to treat arterial and venous thromboembolic conditions. They also help to prevent occlusive vascular events in patients who are at risk of thrombosis. Antithrombotic drugs used to treat thrombosis are classified by their mechanism of action (**Fig. 1**). Antithrombotic drugs are used to treat acute coronary syndrome, acute venous thromboembolism, and arterial thrombosis, summarized in **Box 1** and also used to treat various stage of ischemic stroke (**Box 2**). This chapter reviews the agent commonly used for controlling fluidity, including:

- Coumarin anticoagulants that block multiple steps in coagulation cascade
- Direct oral anticoagulants, which inhibit factor Xa or thrombin
- Parenteral anticoagulants heparin and its derivative, which activate antithrombin, a natural inhibitor of coagulant proteases
- Fibrinolytic agents, which degrade fibrin
- Antiplatelets agents which attenuate platelet activation or aggregation
- Reversal agents for antithrombotic drugs

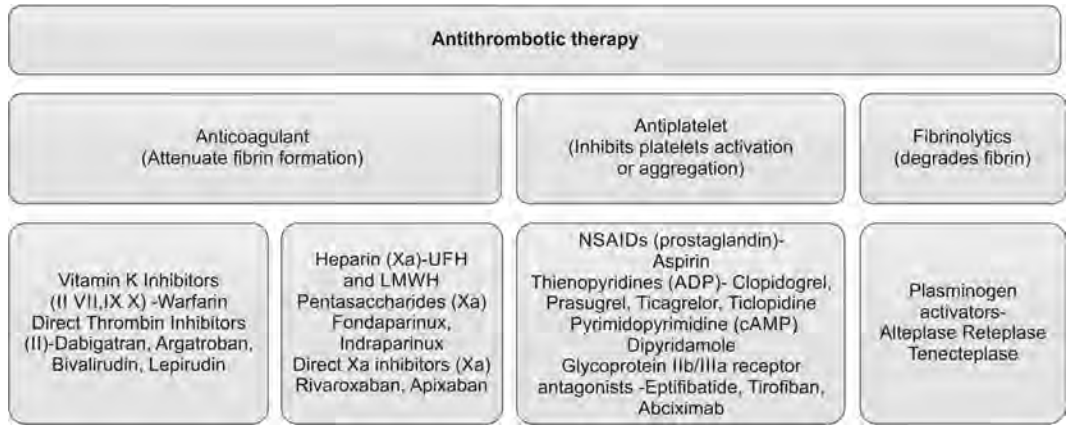
OVERVIEW OF HEMOSTASIS

The normal hemostatic system consists of a complex process that limits blood loss through the formation of a platelet (primary hemostatic) and the production of cross-linked fibrin (secondary hemostasis), which strengthens the platelet plug. These reactions are counter regulated by the fibrinolytic system (**Flowchart 1**).

ORAL ANTICOAGULANTS

Warfarin (Vitamin K Antagonists—VKAs)

A hydroxycoumarin derivative, which is commonly used as oral anticoagulant. Warfarin has both antithrombotic effect by inhibiting the synthesis of factors II, VII , IX, and X and a prothrombotic effect through inhibition of protein C and S production, but during maintenance therapy, the overwhelming effect is one of the anticoagulation. It is suggested to add



(ADP: adenosine diphosphate; NSAID: nonsteroidal anti-inflammatory drug; LMWH: low-molecular weight heparin; UFH: unfractionated heparin)

FIG. 1: Basic classification of antithrombotic agents.

BOX 1: Indications for antithrombotic therapy.

***Prophylaxis for deep vein thrombosis and pulmonary embolism*:**

- Unfractionated heparin 500-unit SC every 8–12 h:
  - Dalteparin 2,500–5,000 IU SC once a day
  - Enoxaparin 40 mg SC once daily in normal renal function 30 mg SC twice daily for trauma patient
  - Rivaroxaban 10 mg PO once daily
  - Apixaban 2.5 mg PO twice daily
  - Fondaparinux 2.5 mg SC once daily

***Treatment for deep vein thrombosis and pulmonary embolism*:**

- Unfractionated Heparin: 80 units/kg IV bolus followed by 18 units/kg/h, continuous infusion, with aPTT checked after 6 hours and infusion adjusted to maintain aPTT 1.5–2.5 times the standard
- *Enoxaparin*: 1 mg/kg SC every 12 h or 1.5 mg/kg daily
- *Dalteparin*: 200 units/kg SC once daily
- *Tinzaparin*: 175 mg/kg once daily
- *Fondaparinux*: <50 kg: 5 mg SC once daily 50–100 kg: 7.5 mg SC once daily >100 kg: 10 mg SC once daily
- *Warfarin*: 2–5 mg/day for 2–4 days , followed by 1–10 mg/day as indicated by INR
- *Dabigatran*: 150 mg PO twice daily (after 5–10 day of parenteral anticoagulation)
- *Apixaban*: 10 mg PO twice daily for 7 days, then 5 mg twice daily
- *Rivaroxaban*: 15 mg PO twice daily for 21 days, then 20 mg once daily
- Streptokinase 250,000 unit IV bolus followed by 100,000 unit/h continuous infusion for 1–3 days or alteplase 100 mg IV infused over 2 h or tenecteplase weight-tiered single IV bolus (<60 kg: 30 mg) (60–70 kg: 35 mg) (70–80 kg: 40 mg) (80–90 kg: 45 mg (>90 kg: 50 mg)

ST-Segment elevation myocardial infarction

Aspirin 150–300 mg PO once an day plus clopidogrel 300 mg PO loading dose and 600 mg if PCI is planned followed by 75 mg PO once daily

Or

Ticagrelor 180 mg PO loading dose followed by 90 mg PO twice daily

Or

Prasugrel 60 mg PO loading dose followed by 10 mg PO once day contraindicated in previous stroke patient and age >75 years

Unfractionated heparin 60 unit/kg (5,000-unit bolus followed by 12 unit/kg/h—max 1,000 unit) maintain aPTT 1.5–2.5 times of reference range

Or

Enoxaparin 30 mg IV bolus followed by 1 mg /kg SC every 12 h

Streptokinase 1.5 million units IV over 60 min

Or

Alteplase 15 mg IV bolus over 2 min, then 0.75 mg/kg IV OVER 30 min (max 50 mg), then 0.50 mg/kg IV over 60 min (max 35 mg)

Or

Reteplase 10 units IV bolus, then repeat 10 doses at 30 min

Or

Tenecteplase weight-tiered single IV bolus (<60 kg: 30 mg) (60–70 kg: 35 mg) (70–80 kg: 40 mg) (80–90 kg: 45 mg (>90 kg: 50 mg)

BOX 2: Antithrombotic therapy in stroke.

Acute ischemic stroke:

- Alteplase 0.9 mg/kg (max 90 mg) with 10% of the total dose given as an IV bolus over 1 min, then remainder as infusion over 60 min
- Tenecteplase 0.25 mg/kg IV bolus

Postischemic stroke:

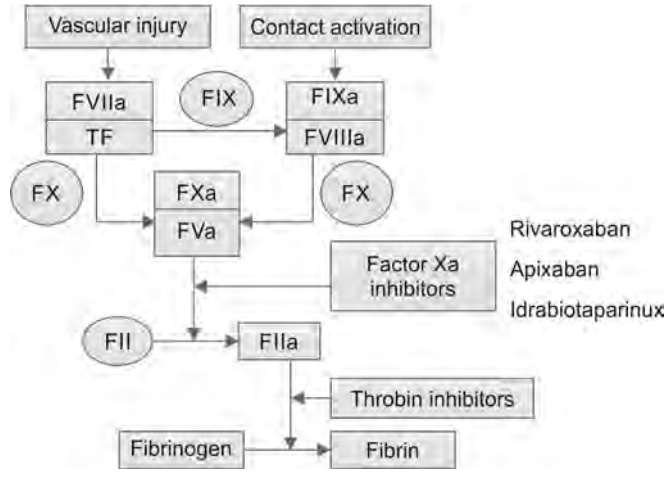
- Aspirin 75 mg PO once a day
- Clopidogrel 75 mg PO once a day (if patient allergic to aspirin)
- Dipyridamole 200 mg ER PO twice daily (usually combined with aspirin)

Transient ischemic stroke:

- Aspirin 75 mg PO once a day
- Clopidogrel 75 mg PO once a day (if patient allergic to aspirin)

Atrial fibrillation (stroke prevention):

- Warfarin dose adjusted to maintain INR 2.0–3.0
- Dabigatran: 150 mg PO twice daily
- Apixaban: 5 mg PO twice daily
- Rivaroxaban: 20 mg PO twice daily with evening meal



FLOWCHART 1: Hemostasis mechanism.

parenteral anticoagulant during the first 3–5 days of warfarin treatment. Its dosing is guided by desired therapeutic range, if INR of 2–3 in most of cases. Drug interaction with warfarin is numerous and complex. Bleeding and skin necrosis are two major complication. The risk is clinically significant when the INR is >4.5–5. Major limitations of vitamin K antagonist lead to development of various new direct thrombin inhibitors (DTIs) (**Table 1**).

Novel Oral Anticoagulants/Direct Thrombin Inhibitors (Nonvitamin K Antagonist)

Direct thrombin inhibitors were developed to overcome the limitations of vitamin K antagonist. Used in high-risk patient including stroke and with atrial fibrillation. Currently, five direct acting oral anticoagulants are available. Mechanism of action of novel oral anticoagulant (NOAC) is shown in **Figure 2**.

- *Dabigatran*: Oral direct thrombin inhibitor, which is used to reduce the risk of stroke and systemic embolism with nonvalvular atrial fibrillation. It has more predictable pharmacology activity than warfarin and broad therapeutic window. It is safer than warfarin, with notable exception of higher risk of major GI bleeding. For practical purposes, a normal thrombin clotting time excludes a significant coagulopathy due to dabigatran.
- *Apixaban, rivaroxaban, betrixaban, and edoxaban*: These oral direct factor Xa inhibitors have predictable pharmacological properties that do not require routine laboratory monitoring. Currently, used for prevention of thromboembolism in patients undergoing hip or knee replacement surgery and reduction of systemic embolism in nonvalvular atrial fibrillation. Currently, available antifactor Xa activity assay can be used specifically for their activity.

TABLE 1: Limitation and consequences of vitamin K antagonists (warfarin).

Limitations	*Consequences*
Slow onset of action	Necessitates overlap with rapidly acting parenteral anticoagulants when treating patients with thrombosis
Genetic polymorphism affects metabolism	Variable dose requirements
Multiple food and drug interactions	Coagulation monitoring required
Narrow therapeutic window	Coagulation monitoring required

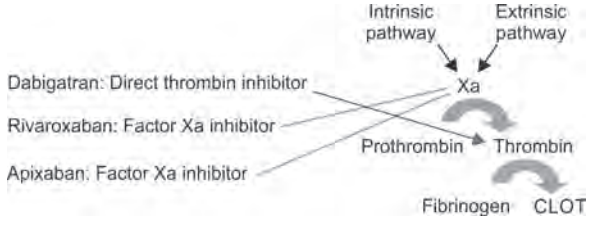


FIG. 2: Mechanism of action of novel oral anticoagulants (NOAC).

HEPARIN

Heparin derivatives have no intrinsic anticoagulant activity; rather these agents bind to antithrombin and accelerate the rate at which it inhibits various coagulation proteases. Antithrombin inhibits activated coagulation factors, particularly thrombin and factor Xa, by serving as "suicide substrate." Bleeding and HIT (heparin-induced thrombocytopenia) are major complication. Comparative features [unfractionated heparin and low-molecular weight heparins (UFH and LMWH)] are summarized in **Table 2**.

- *Unfractionated Heparin (UFH)*: It is a heterogeneous mixture of polysaccharides. It has unpredictable anticoagulant effects, which is generally monitored by aPTT.
- *Low-molecular weight heparins*: They are polysaccharide chains with commercial preparations (enoxaparin, dalteparin, and tinzaparin), LMWH possesses many clinical advantages compared to UFH.
- *Fondaparinux*: Synthetic pentasaccharide that binds to antithrombin and enhances its affinity for factor Xa, but not thrombin.

ANTIPLATELET AGENTS

Antiplatelet agents can be subclassified, on the basis of their site of action (**Flowchart 2**), into those that inhibit (1) adhesion, (2) activation, (3) aggregation, or (4) platelet-mediated links with inflammation. Of currently available agents, aspirin, clopidogrel, dipyridamole, and cilostazol inhibit platelet activation, whereas GPIIb/IIIa antagonist blocks platelet aggregation (**Table 3**). Bleeding secondary to antiplatelet therapy should be treated with supportive therapy, platelet transfusion, and possibly desmopressin.

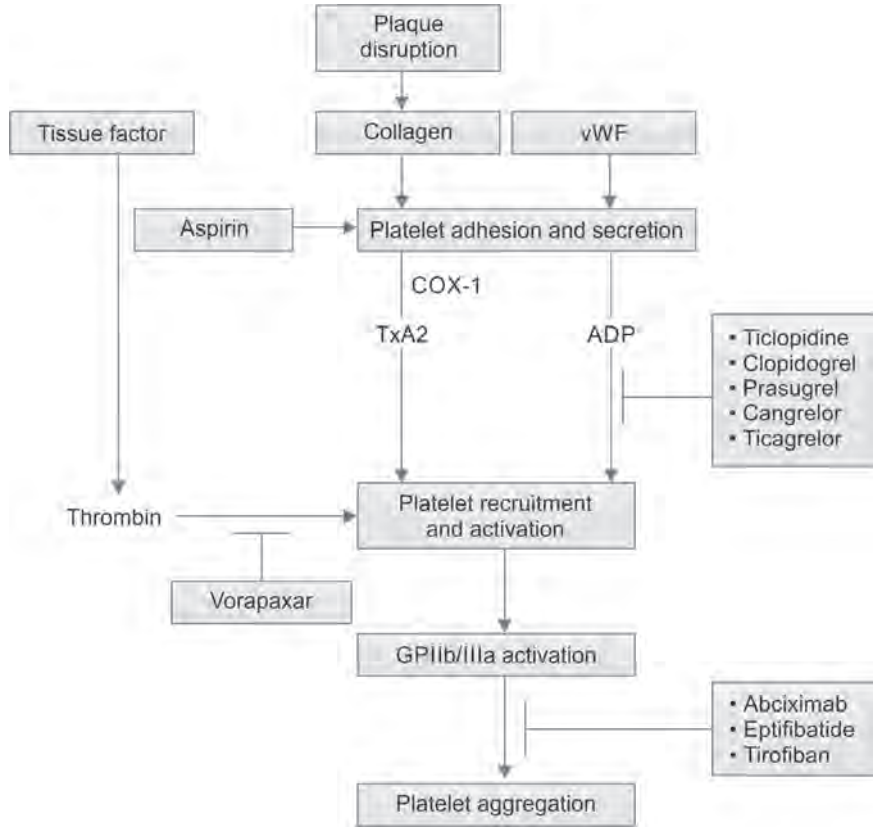
FIBRINOLYTIC DRUGS

Fibrinolytic drugs initiate the fibrinolytic pathway. Fibrinolytic agents stimulate conversion of plasminogen to plasmin. Approved fibrinolytic agents are included streptokinase, anistreplase, alteplase, reteplase, and tenecteplase.

- First generation—streptokinase and anistreplase
- Second generation—alteplase tissue plasminogen activator
- Third generation—reteplase and tenecteplase

TABLE 2: Comparison of features of subcutaneous heparin, LMWH, and fondaparinux.

Features	*Heparin*	*LMWH*	*Fondaparinux*
Sources	Biological	Biological	Biological
MMW (Da)	15,000	5,000	1,500
Target	Xa and IIa	Xa and IIa	Xa
Bioavailability (%)	30 (at low doses)	90	100
t1/2 (hour)	1–8	4	17
Renal excretion	No	Yes	Yes
Thrombocytopenia	<5%	<1%	<0.1%
Monitoring	More frequent	Unnecessary Antifactor Xa assay	Unnecessary Antifactor Xa assay
Antidote	Complete	Partial	None



FLOWCHART 2: Classification of antiplatelet drugs on the basis of sites of action.

TABLE 3: Antiplatelets agents.

Drugs	*Mechanism of action*	*Type of inhibition*	*Time to peak effect*	*Half life*	*Duration of effect*	*Typical dose*
Aspirin	Nonselective cyclooxygenase inhibitor	Irreversible	20–40 min	3–4 h	Up to 7 days	162–325 mg PO once per day
Clopidogrel	ADP receptor inhibitor	Irreversible	2–4 h	7–8 h	Up to 7 days	300 mg PO loading dose, then 75 mg PO per day
Prasugrel	ADP receptor inhibitor	Irreversible	1–2 h	7–8 h	5–7 days	60 mg PO loading dose, then 10 mg PO once a day
Ticagrelor	ADP receptor inhibitor	Reversible	2–3 h	7–9 h	3–5 days	180 mg PO loading dose 90 mg PO twice per day
Dipyridamole	Reduces platelet aggregation, vasodilator, weak phosphodiesterase	Reversible	N/A	Biphasic 40 min and 10 h	1–2 days	200 mg extended- release PO twice per day
Cilostazol	Phosphodiesterase inhibitor; reduces platelet aggregation, vasodilator	Reversible	N/A	11–13 h	3–4 h	100 mg PO twice per day
Abciximab	Glycoprotein IIb/IIIa antagonist	Non-competitive inhibition	–	10 min	24–48 h	0.25 mg/kg IV bolus, then 0.125 µg/kg/min infusion IV
Eptifibatide	Glycoprotein IIb/IIIa antagonist	Competitive inhibition	–	2.5 h	3–5 h	180 µg/kg IV bolus, then 2 µg/kg/min infusion IV
Tirofiban	Glycoprotein IIb/IIIa antagonist	Competitive inhibition	–	2 h	3–5 h	25 µg/kg /min IV for 30 min then 015 µg/kg/min infusion

TABLE 4: Contraindication to fibrinolytic therapy.	
Absolute	***Relative***
• Prior intracranial hemorrhage • Known structural cerebral vascular lesion • Known malignant intracranial neoplasm • Ischemic stroke within 3 months • Suspected aortic dissection • Active bleeding or bleeding diathesis (excluding menses) • Significant closed-head trauma or facial trauma within 3 months	• Uncontrolled hypertension (SBP > 180 mm Hg or DBP > 110 mm Hg) • Traumatic or prolonged CPR or major surgery within 3 weeks • Recent (within 2–4 weeks) internal bleeding • Noncompressible vascular punctures • For streptokinase, prior allergic reaction • Pregnancy • Active peptic ulcer • Current use of warfarin and INR >1.7

All fibrinolytic agents are associated with bleeding and which can be minor, major, or catastrophic in nature. Concomitant use of certain drugs can also enhance the risk of bleeding. Risk of bleeding can be reduced by applying the knowledge of contraindication of fibrinolytic therapy as summarized in **Table 4**.

ADVERSE EFFECTS

The major toxicity of all thrombolytic agents is hemorrhage. If heparin is used concurrently with tPA, serious hemorrhage will occur in 2–4% of patients. Intracranial hemorrhage is most serious problem. For this region, mechanical reperfusion is preferred in acute ST-segment elevation myocardial infarction (STEMI). In acute ischemic stroke also, current standard of care is mechanical thrombus extraction, with or without adjunctive tPA or tenecteplase. Anaphylaxis can occur at times with streptokinase and anistreplase. Fresh frozen plasma (FFP) and factor replacement with cryoprecipitate can be used in unstable patients. Antifibrinolytic agents (tranexamic acid or aminocaproic acid) with or without platelets can also be used.

SUMMARY

Thromboembolic disorders are a major cause of death and disability worldwide. Antithrombotic therapy is used to treat arterial and venous thromboembolic conditions and also to prevent occlusive vascular events in patients with increased risk of thrombosis. However, being emergency physicians, we need to know these agents can cause life-threatening complications. Consequently, there is an ongoing search for new antithrombotic drugs, particularly novel antiplatelet agents and anticoagulants. Therefore, a better understanding of the biochemical pathways involved in platelet activation and coagulation and of the links between these systems and the impact of thrombosis on inflammation is necessary. A larger number of new antithrombotic drugs are under development. With new targets and new drugs, antithrombotic therapy is evolving and our armamentarium of agents to combat thromboembolic disorders is rapidly expanding.

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CHAPTER

Antithrombotic Reversal Agents

Devendra Richhariya

INTRODUCTION

Antithrombotic therapy is indicated for the prophylaxis and treatment of thromboembolic disorders. Commonly used oral antithrombotic therapies (**Box 1**) are vitamin K antagonists, heparin, low-molecular-weight heparins (LMWHs), direct thrombin inhibitors (DTIs), and factor Xa inhibitors. Warfarin, novel oral anticoagulants, is commonly prescribes oral anticoagulants while heparin LMWH is important part of in hospital therapy. Antiplatelet agent is also important part of prescription for diseases such as coronary artery disease stroke. So the emergency physician must be able to manage the most common complication of antithrombotic/anticoagulant therapies—bleeding.

THE CLOTTING/COAGULATION CASCADE

Before learning about the reversal of anticoagulation, we need to understand the clotting cascade, a complex physiologic process used to maintain homeostasis between clot formation and degradation. In the setting of vascular endothelial injury, clot formation begins with primary hemostasis.

BOX 1: Common antithrombotic medications.

Anticoagulants:

- *Vitamin K antagonists (II, VII, IX, X)*: Warfarin
- *Heparins (Xa, others)*: UFH and LMWH
- *Pentasaccharides (Xa)*: Fondaparinux and idraparinux
- *Direct Xa inhibitors (Xa)*: Rivaroxaban and apixaban
- *Direct thrombin inhibitors (II)*: Dabigatran, argatroban, bivalirudin, and lepirudin

Antiplatelet agents:

- *NSAIDs (prostaglandin)*: Aspirin
- *Thienopyridines (ADP)*: Clopidogrel, prasugrel, ticagrelor, and ticlopidine
- *Pyridopyrimidine (cAMP)*: Dipyridamole
- *Glycoprotein IIb/IIIa receptor antagonists*: Eptifibatide, tirofiban, and abciximab

Fibrinolytics:

- *Plasminogen activators*: Alteplase, reteplase, and tenecteplase

Primary Hemostasis

It is binding of platelets with the damaged endothelium via an interaction between a glycoprotein (GP IIb-IIIa) and von Willebrand factor. With the process of platelet activation and degranulation, more and more platelets are recruited to the site of injury, thereby forming a platelet plug. The efficacy of the platelet plugs in achieving hemostasis is a function of platelet quantity and quality. These platelet qualities may depend on patient comorbidities (bleeding diathesis, advanced renal disease, etc.) and pharmaceutical therapy (e.g., nonsteroidal anti-inflammatory drugs or aspirin). After primary hemostasis (**Fig. 1**), secondary hemostasis (**Fig. 2**) begins with activation of the clotting/coagulation cascade (**Fig. 3**).

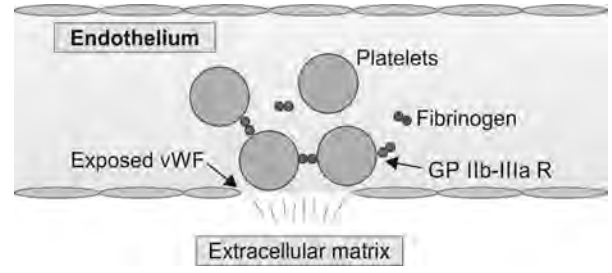

FIG. 1: *Primary hemostasis*. Platelets organize into a platelet plug at the site of endothelial injury by binding subendothelial von Willebrand factor (vWF) and circulating fibrinogen.

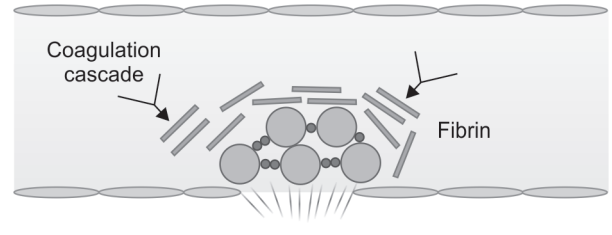

FIG. 2: *Secondary hemostasis*. Cross-linked fibrin cements and stabilizes the platelet plug formed at the site of endothelial injury.

Secondary Hemostasis

During secondary hemostasis, activated factor Xa catalyzes the conversion of prothrombin to thrombin (factor IIa). Thrombin, in turn, catalyzes the conversion of fibrinogen to fibrin. Ultimately, fibrin is responsible for cross-linking and strengthening the platelet plug. Secondary hemostasis process depends on the quantity of functional clotting factors, and their successful activation.

How to measure primary and secondary hemostasis?
Platelet function tests and platelet aggregation assays may be useful to assess primary hemostasis; however, many of these studies are time consuming and poorly standardized, limiting their clinical usefulness in the emergency setting. Bleeding time is no longer used clinically. The process of secondary hemostasis is measured using prothrombin time (PT), International Normalized Ratio (INR—extrinsic and common pathways; factors II, VII, and X), and activated partial thromboplastin time (aPTT—intrinsic and common pathways—all factors except factor VII).

REVERSAL OF WARFARIN

Warfarin is a vitamin K antagonist, inhibiting the hepatic enzyme vitamin K epoxide reductase, thereby limiting the synthesis of factors II, VII, IX, and X, and the anticoagulant proteins C and S. Warfarin is indicated for the prophylaxis and treatment of venous thromboembolism, pulmonary embolism (PE), thromboembolic complications associated with atrial fibrillation or cardiac valve replacement, and in myocardial infarctions (MIs) and cerebrovascular accidents for reduction of mortality risk secondary to emboli after.

Therapeutic doses of warfarin decrease the total amount of each active vitamin K–dependent clotting factor by approximately 30–50%. As mentioned before, anticoagulant effect of warfarin is measured by PT and INR (measures the extrinsic pathway of the coagulation cascade). The reversal of warfarin needs immediate and sustained therapy. Immediate reversal is achieved by the therapy of prothrombin complex concentrates (PCCs) and fresh frozen plasma (FFP), and sustained reversal is achieved through vitamin K administration (**Tables 1** and **2**).

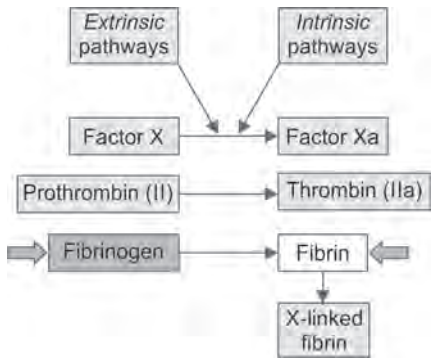

FIG. 3: *Coagulation cascades.* The plasma coagulation cascade funnels down to the conversion of soluble fibrinogen to insoluble fibrin.

Prothrombin Complex Concentrates

Prothrombin complex concentrates are available in three- and four-factor preparations. Three-factor concentrates contain factors II, IX, X, and minimal amounts of factor VII are approved by the US Food and Drug Administration (FDA) for the treatment of bleeding in hemophilia B (factor IX deficiency). In 2009, Holland and colleagues published data regarding three-factor PCC alone [25 international units per kilogram (IU/kg) and 50 IU/kg doses] satisfactorily decrease supratherapeutic INRs owing to the low factor VII content.

In 2013, the FDA approved a four-factor PCC, for the reversal of warfarin-related coagulopathy. Four-factor PCC contains factors II, VII, IX, and X, in addition to proteins C and S (heparin and antithrombin III are added to maintain factors in the inactivated form). Four-factor PCC is administered intravenously with recommended doses based on the patient's baseline INR (the initial dose is 25–50 IU/kg for significant bleeding).

Factor VIII inhibitor-bypassing activity (FEIBA) is activated PCC (aPCC), is useful for the treatment of bleeding episodes due to coagulation factors VIII or IX deficiencies. FEIBA contains primarily activated factor VII and smaller quantities of activated factors II, IX, and X. In 2009, Wójcik

TABLE 1: Management of vitamin K antagonists-induced high INRs and bleeding.

Condition	*Interventions*
Raised INR but <5; absent significant bleeding	Lower/omit dose, increase frequency of monitoring, resume therapy at a lower dose if INR more than minimally supratherapeutic
INR ≥ 5.0 but ≤ 10.0; absent significant bleeding	Omit 1–2 doses. Increase frequency of monitoring. Resume therapy when INR therapeutic Or Omit dose. Give 1.0–2.5 mg oral vitamin K. If the patient is at increased risk of bleeding, If requires more rapid reversal for a surgical procedure, give 2–4 mg oral vitamin K; the INR should decrease within 24 h If the INR remains elevated, additional vitamin K (1–2 mg orally) may be given
INR >10; absent significant bleeding	Hold warfarin therapy. Give 5–10 mg oral vitamin K; the INR should decrease within 24–48 h. Increase frequency of monitoring. Administer additional vitamin K if necessary. Resume therapy when INR within therapeutic range
Serious or life-threatening bleeding	Hold warfarin therapy. Give 10 mg vitamin K by slow IV infusion, in addition to four-factor PCC or FFP. Vitamin K may be given every 12 h

(FFP: fresh frozen plasma; INR: International Normalized Ratio; PCC: prothrombin complex concentrate)

TABLE 2: Reversal agents for warfarin.		
Vitamin K	1.25–10 mg orally or IV	Subcutaneous and intramuscular delivery not advised
PCC (Profilnine and Kcentra)	Strategy 1: INR and weight-based dosing • INR 2–4: 25 IU/kg IV push • INR 4–6: 35 IU/kg IV push • INR > 6: 50 IU/kg IV push Strategy 2: INR-based dosing • INR < 5: 500 IU • INR > 5 :1,000 IU Strategy 3: Fixed dose:1,500 IU	INR-based dosing is most effective with Profilnine (three-factor PCC). Fixed dosing should not be used with Profilnine. Any of the strategies may be used with Kcentra (four-factor PCC)
aPCC (FEIBA)	50–100 U/kg (U/kg)	Given the risk of thromboembolic events, use should be considered only when PCC is not available

(aPCC: activated prothrombin complex concentrate; INR: International Normalized Ratio; PCC: prothrombin complex concentrate; a: approved by the US Food and Drug Administration for warfarin-associated coagulopathy)

and colleagues 15 performed a retrospective chart review of patients who received FEIBA in the setting of life-threatening hemorrhage secondary to warfarin-induced coagulopathy. In this study, patients receiving FEIBA normalized the INR 12 times faster than those who received FFP. PCCs are contraindicated in persons with a history of anaphylaxis to PCCs or any of their components, or those with a history of disseminated intravascular coagulation, MI, and PE (increased risk of thrombosis). As far as thrombotic risk is concern, studies demonstrate that no statistically significant difference in the incidence of thromboembolic events in patients treated with three- and four-factor PCC versus FFP. FEIBA administration as associated with a thrombotic incidence of 8–9 per 100,000 infusions (the majority of data are from hemophiliacs). Sarode and colleagues have conducted the only clinical trial that directly compares four-factor PCC with FFP. There was no difference in the incidence of thrombotic events (8% PCC; 6% FFP). PCC should be considered superior to FFP. Each 500 IU (25 mL) vial of four-factor PCC is equivalent to 2 U (250 mL/U) of FFP. For treating the patient of with an INR of 10 kg and 80 kg weight (using reversal doses of 50 IU/kg of PCC and 15 mL/kg FFP) would require 8 vials (200 mL) of PCC or 16 U (4 L) of FFP.

Fresh Frozen Plasma

Fresh frozen plasma contains all of the coagulation factors. Although it is type specific, Rh compatibility is not required with individuals of the AB blood type being universal donors. Risks associated with transfusion of FFP include blood-borne infections and allergic reactions. The majority of resources advise the initial administration of 2 U of FFP for isolated intracranial bleeds and 4 U for extracranial bleeds (based on the generally accepted idea that one unit of FFP corrects clotting factors by 2–3% in a 70-kg individual); however, a volume of 10–15 mL/kg may be required to address life-threatening hemorrhage. The use of FFP in the reversal of anticoagulation for persons suffering from atrial fibrillation, cardiac valvular disease, and ventricular dysfunction, may be not ideal because significant increases in intravascular volume may result in decompensated heart failure or transfusion associated lung injury. Because the INR of FFP is 1.5, it is impossible to achieve an INR of <1.5 after FFP administration alone. The delivery of FFP is limited secondary to the product's frozen storage, requiring 15–20 minutes to thaw.

Vitamin K

Vitamin K is available in both oral and IV forms and an essential cofactor in the synthesis of factors II, VII, IX, and X, and proteins C and S. Vitamin K is not recommended by subcutaneous and intramuscular route due to unpredictable absorption and risk of hematomas formation. Time to onset of action of oral vitamin K starts in 6–10 hours, reaches to peak in 24–48 hours. Slow IV infusion (over 20 min) 5–10 mg of vitamin K should be given to actively bleeding patient. Intravenous route of vitamin K has rapid onset of action in 1– 2 hours, with peak effect in 12–24 hours. Parenteral vitamin K administration is associated with anaphylactic reactions. Of note, after vitamin K administration, therapeutic anticoagulation cannot be achieved for nearly 2 weeks. This consideration is important for providers to appreciate.

Recombinant Factor VIIa

Recombinant factor VII (rFVIIa; NoVo Seven) was developed for the treatment of bleeding episodes in individuals with factor VIII deficiency (hemophilia A), factor IX (hemophilia B), and congenital factor VII deficiency. The off-label use of rFVIIa in studies of nonhemophiliac trauma patients has demonstrated no benefit as compared with placebo. The administration of rFVIIa is not recommended as an adjunct for the reversal of warfarin due to increased risk of thromboembolic events.

REVERSAL OF DIRECT ORAL ANTICOAGULANTS

Direct Thrombin Inhibitors

Dabigatran etexilate mesylate (Pradaxa) is an oral DTI indicated for the reduction of stroke and systemic embolism in nonvalvular atrial fibrillation, for the treatment of DVT and PE, and for the prophylaxis of DVT and PE in patients who have undergone hip arthroplasty.

After hepatic metabolism, dabigatran binds the active site of free and clot-bound thrombin, inhibiting the conversion of fibrinogen to fibrin, and the feedback activation of factors VII, XI, and V. Laboratory monitoring of dabigatran's anticoagulant effect is rarely performed due to its reliable dose-proportional pharmacokinetics, INR response to DTIs is variable, and offers poor correlation to anticoagulation effect. Ecarin clotting time, diluted thrombin time, and aPTT are prolonged at the therapeutic levels of dabigatran prolong.

An elevated aPTT suggests at least therapeutic dabigatran effect, but a normal aPTT does not rule out dabigatran effect. A normal dilute thrombin time effectively excludes dabigatran effect. In 2015, the FDA approved idarucizumab (Praxbind), a humanized monoclonal antibody fragment, for the reversal of dabigatran in the setting of emergent/urgent surgical procedures, and life-threatening or uncontrolled bleeding. The recommended dose of idarucizumab is 5 g, provided as 2 separate vials containing 2.5 g/50 mL, administered no >15 minutes apart (data available for recommendation regarding repeat dosing is limited). Although a preexisting IV line may be used, per the manufacturer's guidelines, the line must be flushed with sterile sodium chloride before infusion, and no other infusion should be administered in parallel via the same.

In situations where idarucizumab is not available, hemodialysis should be performed because dabigatran predominately excreted through kidneys. The American Society of Hematology also recommends consideration of the administration of PCC or aPCC for life-threatening bleeds; however, this practice is supported by limited, poor-quality evidence, and is associated with thrombotic risk. **Table 3** contains a summary of reversal agents for DTIs.

Factor Xa Inhibitors

Factor Xa inhibitors include rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), and betrixaban (Bevyxxa). The factor Xa inhibitors are used to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In addition, rivaroxaban is indicated for DVT and PE prophylaxis in patients undergoing hip or knee arthroplasty, edoxaban is approved for the treatment of DVT/PE after initial parenteral therapy, and betrixaban is approved for venous thromboembolism prophylaxis in hospitalized patients.

Rivaroxaban, apixaban, edoxaban, and betrixaban act by selectively blocking the active site of factor Xa, when free or bound to the prothrombinase complex. By inhibiting factor Xa, these novel anticoagulants indirectly inhibit platelet aggregation-induced by thrombin. Within 2 hours of administration of rivaroxaban, apixaban, and edoxaban, and within 4 hours of betrixaban dosing peak plasma concentrations are achieved. After oral administration, in patients with normal renal function, elimination half-lives of the novel anticoagulants are >12 hours. At therapeutic doses, all factor Xa inhibitors prolong clotting time tests (PT, INR, and aPTT); however, responses are variable, and are not useful in monitoring anticoagulation effects.

Rivaroxaban and inhibition of factor Xa can be correlated very closely (a normal PT/INR or normal antifactor Xa suggests normal range of rivaroxaban levels). Standardized kits using rivaroxaban callipers and controls are preferred, but may not be widely available. Antifactor Xa activity, calibrated with apixaban controls, is recommended to assess the anticoagulation effect of apixaban, (normal antifactor Xa suggests normal range of apixaban levels). The recommended assay for an assessment of the extent of edoxaban anticoagulation is antifactor Xa activity, calibrated with heparin or edoxaban. Andexanet alfa (Annexa) was designed as a reversal agent for all factor Xa inhibitors. Further research and data are required before recommending the use of andexanet alfa. Reversal agents for factor Xa inhibitors are summarized in **Table 4**.

Antifibrinolytic Agents

Antifibrinolytic agents such as tranexamic acid and aminocaproic acid are relatively inexpensive and possess favorable safety profiles, experts recommend that they be considered in the setting of life-threatening bleeding, though their efficacy in direct oral anticoagulant-associated bleeding is unknown (**Table 5**).

TABLE 3: Reversal agents for direct thrombin inhibitors.

Reversal agents	*Doses*
Idarucizumab	• 5 g, provided by the manufacturer as 2 vials containing 2.5 g/50 mL • Data regarding repeat dosing lacking
PCC (Profilnine or Kcentra)	50 U/kg
FEIBA	50–100 U/kg
Cryoprecipitate	• 2 pools • Administer for patients with fibrinogen

(FEIBA: factor VIII inhibitor-bypassing activity; PCC: prothrombin complex concentrate)

TABLE 4: Reversal agents for factor Xa inhibitors.

Reversal agents	*Doses*
Four-factor PCC (Kcentra)	• 25–50 U/kg repeat doses beyond 50 U/kg not advised • Maximum dose to be administered: 5,000 U
Factor VIII inhibitor-bypassing activity (FEIBA)	50–100 U/kg repeat dosing may be considered after 6 h if significant bleeding persists

TABLE 5: Antifibrinolytic agents.

Reversal agents	*Doses*
Tranexamic acid	1 g IV (requires dosing adjustment for renal impairment)
Aminocaproic acid	4–5 g IV infusion during the first hour of treatment followed by 1 g/h for 8 h or until control of bleeding (rapid IV administration should be avoided: It may induce hypotension, bradycardia, or arrhythmia)

REVERSAL OF HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARINS

Heparin and the LMWHs (enoxaparin), dalteparin (Fragmin), and fondaparinux (Arixtra) are approved for the prophylaxis and treatment of DVT and PE. Another indication of enoxaparin is for the treatment of acute ST-segment elevation MI (STEMI), while enoxaparin and dalteparin may be used in non-STEMI (NSTEMI). Heparin and the LMWHs bind to antithrombin III, activating the antithrombin III complex, which inhibits factor Xa, and exhibits a variable inhibitory effect on factor IIa (thrombin). The aPTT is used to measure the anticoagulation effects of heparin, with a range of 1.5–2.5 times the control considered therapeutic. LMWH therapy is best monitored by the chromogenic antifactor Xa assay (gold standard). Discontinuation of heparin and protamine sulfate initiation is needed in case where urgent or emergent heparin reversal is required.

Protamine sulfate is a positively charged polypeptide, capable of reversing antithrombin III inhibition. Protamine dosing should be calculated based on time elapsed since heparin administration, and the dose of heparin delivered. If immediately after heparin administration, 1.0–1.5 mg of protamine sulfate should be given for every 100 U of heparin delivered. If 30–60 minutes have elapsed since the most recent dose of heparin, 0.50–0.75 mg/100 U of heparin are advised, and if >2 hours since the previous dose of heparin, 0.250–0.375 mg/100 U of heparin should be given.

Protamine sulfate may be used to reverse the anticoagulation effects of the LMWHs, enoxaparin, and dalteparin. It is important to note, however, that protamine is only 60% effective in reversing these anticoagulants owing to its limited ability to address factor Xa inhibition. Fondaparinux is not neutralized by protamine sulfate. If using protamine to reverse enoxaparin or dalteparin, it is recommended that 1 mg of protamine be administered for every milligram of these LMWHs previously administered (1:1 ratio). If bleeding continues, an additional 0.5 mg per 1 mg of enoxaparin or dalteparin is advised. Total protamine dosing should not exceed 50 mg because, at this concentration, paradoxical anticoagulation may occur secondary to factor V inhibition. Protamine is associated with the risk of anaphylaxis, hypotension, and bradycardia, so infusions should not exceed 20 mg/min. Andexanet alfa (Annexa) was designed in 2008 as a reversal agent for all factor Xa inhibitors. Additional data are required before making recommendations regarding the use of andexanet alfa in the reversal of heparin and LMWHs. Further studies are currently underway, **Table 6** contains a summary of the reversal agents for heparin and the LMWHs.

REVERSAL OF ANTIPLATELET THERAPY

Antiplatelet agents include aspirin, an irreversible inhibitor of cyclooxygenase-1, and cyclooxygenase-2; the thienopyridines, clopidogrel (Plavix), prasugrel (Effient), and ticlopidine, which irreversibly inhibit the P2Y12 receptor for adenosine diphosphate on platelets; ticagrelor (Brilinta) and cangrelor (Kengreal), adenosine diphosphate receptor inhibitors; and dipyridamole, a reversible inhibitor of adenosine diphosphate uptake by platelets.

Antiplatelet therapy is used in acute MI, NSTEMI, and unstable angina to prevent platelet aggregation and thrombosis. Antiplatelet agents are also indicated for the prevention of ischemic cerebrovascular accidents, MIs, and death in patients who have experienced acute coronary syndrome, and for the prevention of stent thrombosis after percutaneous coronary intervention. Currently, there are no clinical practice guidelines that direct the treatment of life-threatening bleeding in the setting of antiplatelet therapy (discontinuation of all antiplatelets and anticoagulants agents). Although in the PATCH trial platelet transfusion for spontaneous intracranial hemorrhage is ineffective in the reduction of bleeding.

At this point in time, further research is required before making recommendations regarding platelet transfusion for the reversal of antiplatelet therapy. Desmopressin (Stimate), or DDAVP, is a synthetic analog of antidiuretic hormone,

TABLE 6: Reversal agents for heparin and low-molecular-weight heparins.

Reversal agents	*Dose*	*Comments*
Protamine for heparin	Time elapsed since heparin dose: • *Immediate*: Administer 1–1.5 mg/100 U heparin • *30–60 min*: Administer 0.5–0.75 mg/100 U heparin • *>2 h*: 0.25–0.375 mg/100 U heparin	Doses should not exceed 50 mg at one time given the inhibition of factor V and potential for further anticoagulation
Protamine for low-molecular weight heparins	Dalteparin: • 1 mg of protamine neutralizes 100 U of dalteparin • If bleeding persists or aPTT remains prolonged 2–4 h after protamine: Consider administration of an additional protamine dose: 0.5 mg/100 U dalteparin Enoxaparin: • If <8 h since previous dose give 1 mg protamine per 1 mg of enoxaparin • If 8–12 h after the previous dose of enoxaparin, 0.5 mg protamine per 1 mg enoxaparin • If 12 h after previous dose of enoxaparin, protamine not required • If bleeding persists or aPTT remains prolonged, consider administration of a second dose of protamine: 0.5 mg per 1 mg enoxaparin	Protamine is only partially effective for the reversal of low-molecular-weight heparins. Fondaparinux is not neutralized by protamine sulfate

indicated for the treatment of bleeding episodes in persons with type I von Willebrand disease, or hemophilia. Current guidelines from the Neurocritical Care Society and Society of Critical Care Medicine support the use of a one-time 0.3 mg/kg intravenous dose of desmopressin in patients receiving antiplatelet therapy who experience intracranial hemorrhage (**Table 7**).

TABLE 7: Reversal agents for platelet inhibitors.

Reversal agents	*Dose*
Platelets	2–3 apheresis units or 2–3 units of pooled platelets (human studies have failed to demonstrate morbidity and mortality reduction following administration)
Desmopressin (DDAVP)	0.4 mg/kg IV (consider in addition to platelet transfusion)

SUMMARY

Rapid evaluation and treatment are required in actively bleeding anticoagulated patient presenting to emergency department. Evaluation and managing such patient are complicated by the ever-evolving antithrombotic treatment options used in medicine and the timeliness with which reversal decisions need to be made. Thus, emergency physician should be aware of the properties and general characteristics of a variety of antithrombotic agents. The available antithrombotic reversal agents include vitamin K, FFP, PCC, rFVIIa, platelets, and desmopressin. The novel anticoagulant medications, such as dabigatran and rivaroxaban, present particular challenges because there are no uniformly effective reversal options. Furthermore, the ability to measure anticoagulant effect of these medications is limited in the emergency setting. The approach to reversal is often guided by institutional protocol, with close attention to potential benefits of reversal carefully balanced against potential harm.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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Peripheral Arteriovascular Disease

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CHAPTER

Prasad Rajhans, Ujwal Prakash Dhundi

INTRODUCTION

Acute limb ischemia is the major complication of peripheral vascular disease with the potential of loss of limb or life. Emergency physician should be able to diagnose and manage the acute limb ischemia promptly as this is the one of the common presentation to emergency room.

ETIOLOGY/CAUSES

- Atherosclerosis
- Embolism—atrial fibrillation, valvular vegetation, aneurysm, atheroemboli, etc.
- In situ thrombosis
- Inflammation—drugs, radiation, mechanical trauma, and bacterial invasion
- Trauma—vascular surgeries
- Vasospasm—Raynaud's disease, Raynaud's phenomenon, livedo reticularis, acrocyanosis erythromelalgia, etc.

PATHOPHYSIOLOGY

Lack of blood supply to meet the tissue oxygenation and nutrient leads to acute limb ischemia. As time progresses, lack of nutrient and oxygen leads to cell death and irreversible tissue damage. Peripheral nerves and skeletal muscles are more sensitive to ischemia and irreversible changes occur in these tissues with 6 hours of anoxia. After the restoration of perfusion in complete or partial occlusion, reperfusion injury can occur due to the formation of oxygen free radicals. Reperfusion injury is characterized by the presence of myoglobinuria, renal failure, and peripheral muscle infarction. Laboratory features of reperfusion injury include hyperkalemia, myoglobinuria, metabolic acidosis, and an elevation in creatinine kinase level. The severity of the injury depends on the extent, location, and duration of blockage, collateral flow, and previous health of the limb involved. One-third of the deaths due to occlusive arterial disease occur due to metabolic complication on revascularization. *Atherosclerosis is the major cause of nonembolic limb ischemia in the vast majority of the patients.* Formation of atheromatous plaque within the artery intima results from lipid accumulation, the proliferation of smooth muscle cells, and fibrogenesis with the ultimate narrowing of the vessel lumen. Plaque rupture or endothelial erosion followed by thrombus formation can lead to complete or high-grade obstruction. Ischemic injury can then propagate through several *mechanisms*: (1) extension of the clot to occlude collateral vessels, (2) compartment syndrome due to ischemia-related distal edema, (3) fragmentation of clot into the microcirculation, and (4) edema of the microvasculature cells. Seldom, arterial thrombosis can occur in apparently normal vessels without atherosclerotic plaque, this should prompt evaluation for hypercoagulability.

CLINICAL PRESENTATION

Patient with peripheral arterial disease presents with change in appearance such as discoloration, swelling, or temperature change, or change in sensation. *Risk factors* such as cardiac disease, myocardial infarction, stroke, arrhythmias, transient ischemic attacks, renal disease, prior injuries, surgeries, history of pulmonary embolism, phlebitis, coagulation abnormality, or autoimmune diseases may be present at the presentation. Embolic or thrombotic peripheral arteriovascular disese can be differentiated by their distinct clinical feature as given in **Table 1**.

Acute Arterial Occlusion

It manifests as sudden limb-threatening ischemia. A typical patient description is of sudden struck to the leg by severe shocking pain. The patient often has to sit or fall to the floor during such sudden episodes. The patient often has some of the components of famous *five 'P's, i.e., (1) pain, (2) pallor, (3) pulselessness, (4) paresthesia, and (5) paralysis*. Paralysis and paresthesia warn about limb-threatening ischemia that will need surgical intervention regardless of the cause. In the patient with nonlimb-threatening ischemia, the pathophysiological distinction between the causes of ischemia whether embolic or in situ thrombosis in the vessel determines the line of management. Nonlimb threatening ischemia from arterial embolism can be managed by Fogarty catheter embolectomy. In situ thrombosis is managed nonoperatively as surgical interventions tend to aggravate the thrombosis. Patients with in situ thrombosis usually have long-standing peripheral arterial atherosclerosis with well-developed collateral circulation. History of claudication can be obtained from these patients while it is not available with the patient with acute embolism.

TABLE 1: Difference between arterial embolism versus thrombosis.

Clinical findings	*Embolus*	*Thrombosis*
Identifiable source of embolus	Usual, particularly atrial fibrillation	Less common
History of claudication	Rare	Common
Physical findings of occlusive disease	Few, proximal and contralateral limb pulses normal	Often present, proximal or contralateral limb pulses diminished or absent
Demarcation of ischemia	Sharp	Diffuse
Arteriography	Minimal atherosclerosis, sharp cutoff, few collateral	Diffuse atherosclerosis, tapered, irregular cutoff, well-developed collateral

Source: Brewster DC, Chin AK, Fogarty TJ. Vascular Surgery. Philadelphia: WB Saunders;1990.

Chronic Arterial Insufficiency

Chronic arterial insufficiency usually presents with two types of pain:

1. Intermittent claudication
2. Ischemic rest pain

Location of pain in claudication depends upon the location of arterial occlusion. In femoropopliteal disease, claudication present as cramping calf pain and complete relief with rest. In aortoiliac occlusive disease, claudication occurs in buttocks, hips, and calves. Calf pain in aortoiliac disease is more severe than that of hips and buttocks and is described as aching, weakness, or discomfort. Aortocclusive disease resulting in bilateral claudication usually presents with impotence in men. Progression of chronic arterial insufficiency leads to ischemic pain at rest. Rest pain usually occurs in feet distal to metatarsals and often awakens the patient from sleep. This type of pain is severe and nonresolving with limb elevation or analgesic but has a prompt relief by the activity involving standing position. Patients are often observed to sleep with feet dangling over the side of the bed or sleep in a chair to increase perfusion pressure to distal tissues. In the case of suspected arterial insufficiency, palpation of all peripheral pulses should be documented on a scale of 0 to +4. It is important to note that dorsalis pedis artery pulsations are absent in a 10% population.

Chronic and advanced ischemia is suggested by signs such as muscular atrophy, loss of hairs, delayed growth of fingernails, and their thickening. With advanced ischemia, skin becomes shiny and skeletonized from the atrophy of skin subcutaneous tissue and muscle. Delayed return of normal color as compared to the contralateral side on blanching of skin suggests reduced perfusion. Another clinical bedside test is Buerger's sign to detect severe advanced ischemia. In absent or questionable pulses, Doppler ultrasonography and measurement of ankle-brachial reflexes serve the purpose. Similarly, Allen's test will be helpful to assess the patency of radial and ulnar arteries in the upper limb.

DIAGNOSTIC STRATEGIES

Ankle Brachial Index (ABI)

Systolic blood pressure is measured by Doppler ultrasound in each arm, in dorsalis pedis and in posterior tibial arteries in each ankle. The higher or 2 arm pressure is selected. ABI of both limbs are estimated by formula given below:

$$\text{Right ABI} = \frac{\text{Increase right ankle pressure}}{\text{Increase right arm pressure}}$$

$$\text{Left ABI} = \frac{\text{Increase left ankle pressure}}{\text{Increase left arm pressure}}$$

Interpretation of Ankle Brachial Index (ABI) (**Flowchart 1**):

- *ABI*: >1.3 noncompressible
- *ABI*: 0.91–1.3 normal
- *ABI*: 0.41–0.90 mild-to-moderate peripheral arteriovascular disease
- *ABI*: 0.00–0.40 severe peripheral arteriovascular disease (critical leg ischemia).

Doppler Ultrasonography

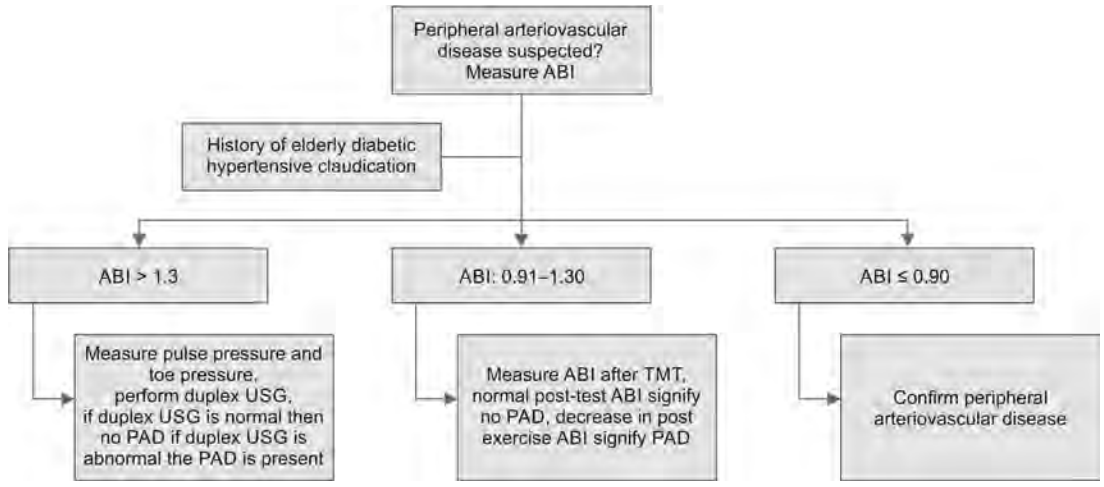
It measures the blood flow velocity using the frequency shift of sound reflected from RBCs as they move toward or away from the ultrasound probe.

A normal signal creates a triphasic velocity waveform. The arterial narrowing causes to change the waveform to biphasic or monophasic depending on severity. This examination detects significant arterial occlusive disease but can not identify the exact location of the occlusion. B-mode duplex ultrasonography is cheap, bedside noninvasive accurate diagnostic test for peripheral vascular disease. Colored imaging of blood flow with duplex scanning is also available and provides accurate detection of atherosclerotic plaque and stenosis and their effect on intraluminal blood flow. It is a procedure of choice for most conditions.

Contrast Arteriography

It is the definitive diagnostic test of abnormal arterial anatomy. It is more invasive and is associated with catheter and contrast-related complications. The indications of emergency angiography are:

- Acute arterial embolism or thrombosis where clinical diagnosis is uncertain.
- Conditions where emergency vascular bypass grafting is being considered.
- Characterization of vascular abnormality before emergency surgery.


Peripheral arteriovascular disease suspected? Measure ABI
History of elderly diabetic hypertensive claudication
ABI > 1.3
ABI: 0.91–1.30
ABI ≤ 0.90
Measure pulse pressure and toe pressure, perform duplex USG, if duplex USG is normal then no PAD if duplex USG is abnormal the PAD is present
Measure ABI after TMT, normal post-test ABI signify no PAD, decrease in post exercise ABI signify PAD
Confirm peripheral arteriovascular disease

FLOWCHART 1: Evaluation of patient in whom peripheral arteriovascular disease suspected.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) angiography is useful for the evaluation of abdominal aorta. In the peripheral arterial-vascular system, CT angiography is useful for atherosclerotic infected and false aneurysm and cerebral circulation. MR angiography can make an axial coronal sagittal section to provide accurate visualization of the anatomy. MRI also can differentiate between blood, thrombus, fat, and fibrosis.

MANAGEMENT

The objective of the treatment of acute arterial obstruction is to restore the blood flow, preservation of limb and life, prevention of thrombosis, and embolism. The definitive treatment of an obstructing clot should be done in conjunction with a vascular surgeon. Major treatment options available are catheter-directed thrombolysis and percutaneous mechanical thrombectomy revascularization procedures such as percutaneous transluminal angioplasty or direct surgical revascularization. Aspirin should be administered to all the patients if not contraindicated. Administration of aspirin reduced vascular mortality by 25%. Management of acute arterial occlusion is based on degree and cause of ischemia.

- *Patients with limb-threatening acute ischemia* from embolism should undergo emergency Fogarty catheter-directed embolectomy. While those with due to thrombosis should undergo direct or catheter-directed thrombectomy with vascular bypass grafting as thrombectomy alone often fails due to recurrence of thrombosis. Primary amputation is required in patients in whom the lesions cannot be bypassed, who have evidence of irreversible ischemia or who are too ill to tolerated revascularization.
- *Patients with nonlimb-threatening limb ischemia* due to embolism are treated with embolectomy while those with thrombosis are managed medically with immediate systemic heparinization with APTT monitoring and with intra-arterial fibrinolytic therapy. The intent of early heparinization is to prevent clot propagation, embolization, venous thrombosis, and occlusion after perfusion.
- *Systemic heparinization* is relatively contraindicated in patient with recent neurosurgery within 2 weeks, major surgery within 48 hours, labor within 24 hours, bleeding diathesis thrombocytopenia, and potentially hemorrhagic lesion and active bleeding
- *Fibrinolytic therapy* is reserved for the patient with nonlimb-threatening ischemia as clot take 6–72 hours to lyse and patient with limb-threatening ischemia cannot tolerate this period without limb loss or tissue loss. Intra-arterial fibrinolysis may uncover critical stenosis which may lead to another even of thrombosis. Hence, patient with successful fibrinolysis needs secondary bypass grafting or percutaneous angioplasty. Agents used for fibrinolysis are streptokinase urokinase and tissue plasminogen activator. Intravenous fibrinolysis is less effective than direct administration into the clot. Clots older than 30 days are less likely to achieve lysis.
- *Fogarty catheter thrombectomy*: It is more frequently used for iliac femoral and popliteal vessels and performed under local anesthesia. Newer thrombi are more likely to be removed than older one as older one are more firmly adhered to the vessel wall and will need direct surgical thrombectomy.
- *Supportive therapy*: Supportive therapy includes the administration of an analgesic, dependent positioning of the affected limb fluid administration and management of associated cardiac failure or arrhythmias, if present to improve the perfusion pressure to the affected limb.
- *Nonsurgical management of chronic obstructive arterial disease*: Nonsurgical management should focus on the combination of smoking cessation exercise and pharmacotherapy. Medical treatment of hypercholesteremia high blood pressure and good glycemic control and drugs to help in the cession of smoking help to modify risk factors associated with the progression of the disease. Cilostazol and pentoxifylline are also considered therapies for the treatment of claudication, however, pentoxifylline is no more recommended.

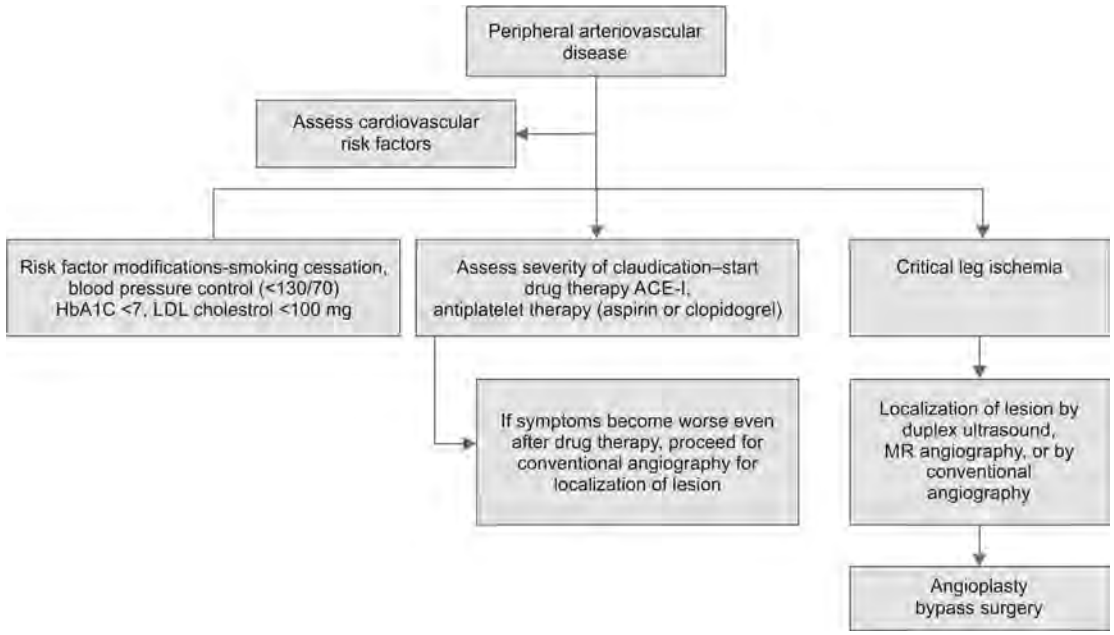
DISPOSITION

All patients requiring surgical intervention should be admitted to the hospital. Patients with the chronic peripheral arterial disease without an immediate threat to limb and lacking comorbidities needing immediate attention can be discharged and asked to follow-up with a primary care physician or a vascular surgeon. The patient should be informed to return to

the hospital in case of a worsening of symptoms. Aspirin 75–100 mg daily can be prescribed if there are no contraindications.

SUMMARY

Peripheral arteriovascular disease is a serious medical problem and an indicator of systemic atherosclerosis. Atherosclerosis is principally a systemic disease not limited to an isolated vessel segment and manifest as atherothrombosis in other vessel areas. In patients with primary diagnosis of the peripheral arteriovascular disease atherosclerotic manifestations in other vessel areas is higher than in coronary or cerebrovascular vessels. The diagnosis of peripheral arteriovascular disease is, therefore, a marker for more generalized and severe atherosclerosis. Patients with intermittent claudication have a relatively good prognosis, while otherwise the prognosis concerning overall survival is poor, with coronary artery disease being by far the most common cause of death. Patients with chronic critical limb ischemia have an even worse prognosis with a 20% mortality in the first year after presentation. A careful history taking and clinical examination remain the gold standard in diagnosis of peripheral arteriovascular disease. Calculation of the ankle–brachial index is established worldwide as the initial screening test. Duplex sonography as the primary diagnostic step for evaluation of morphology and for planning the kind of revascularization—endovascular or surgical technique—enables visualization and quantification of severity of lesions. This can be done by duplex ultrasound, computed tomographic angiography or magnetic resonance angiography (**Flowchart 2**). Technology and techniques of endovascular revascularization as a minimally invasive therapy for treatment of patients with peripheral arteriovascular disease have evolved rapidly during the last decade in the treatment of even complex cases.


Peripheral arteriovascular disease
Assess cardiovascular risk factors
Risk factor modifications-smoking cessation, blood pressure control (<130/70) HbA1C <7, LDL cholestrol <100 mg
Assess severity of claudication–start drug therapy ACE-I, antiplatelet therapy (aspirin or clopidogrel)
Critical leg ischemia
If symptoms become worse even after drug therapy, proceed for conventional angiography for localization of lesion
Localization of lesion by duplex ultrasound, MR angiography, or by conventional angiography
Angioplasty bypass surgery

FLOWCHART 2: Summary of evaluation and management of peripheral arteriovascular disease.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Cough

Bhawana Sharma

INTRODUCTION

Cough is the most common symptom observed in pulmonary disease patients and most frequent cause of visit to clinics. The patient's anxiety associated with the serious underlying cause is significant. Troublesome-associated symptoms such as chest pain from intercostal muscle strain or even a fractured rib and cough-induced urinary or fecal incontinence may lead to fear of social isolation, besides considering cough as communicable disease symptom by peer group. *What is cough*—a forceful expiration expels mucus and foreign material from the airways protecting lung against aspiration. Effectiveness of cough, i.e., ability to take deep breath and exhale forcefully—it depends on ability of an individual to take a deep breath, lung elastic recoil, expiratory muscle strength, and level of airway resistance.

- *Cough is usually ineffective in patients with*:
  - Cardiopulmonary diseases
  - Neurologic diseases, especially involving respiratory muscles and gag reflex
  - Systemic neuromuscular diseases
  - Early postoperative period due to painful respiratory movements, especially after pulmonary or upper abdominal surgeries and trauma
- *Often expiratory flow is limited by factors such as*:
  - Bronchospasm (e.g., asthma)
  - Reduced lung elastic recoil (as in emphysema)
  - Muscle weakness
- *Consequences of ineffective cough*:
  - Atelectasis
  - Retained secretions
  - More prone to develop pneumonia and/or hypoxemia

ACUTE, SUBACUTE, AND CHRONIC COUGH

Broadly acute cough is defined as which last for a maximum of 3 weeks, upper respiratory tract infections (URTIs), acute bronchitis, or tracheobronchitis due to bacterial or more frequently viral infections are the common causes. Acute cough of viral etiology are self-limiting and subsides within 1–2 weeks along with the clearing of the infection and very few need medical attention. But there is no parameters to predict which cough will persist into the subacute (pneumonia) or chronic cough (tuberculosis). Further situation may be complicated by the ineffective therapy which leads to persistent cough and later progress to subacute (3–8-week duration) or chronic cough (>8 weeks duration). Emergency physician should be aware that recurrent acute episodes of cough can be a manifestation of an undiagnosed chronic disease (e.g., asthma). Nevertheless, keeping these pitfalls in mind, a relatively "standard" diagnostic and therapeutic approach based on the duration of the cough should be used.

MECHANISM OF COUGH

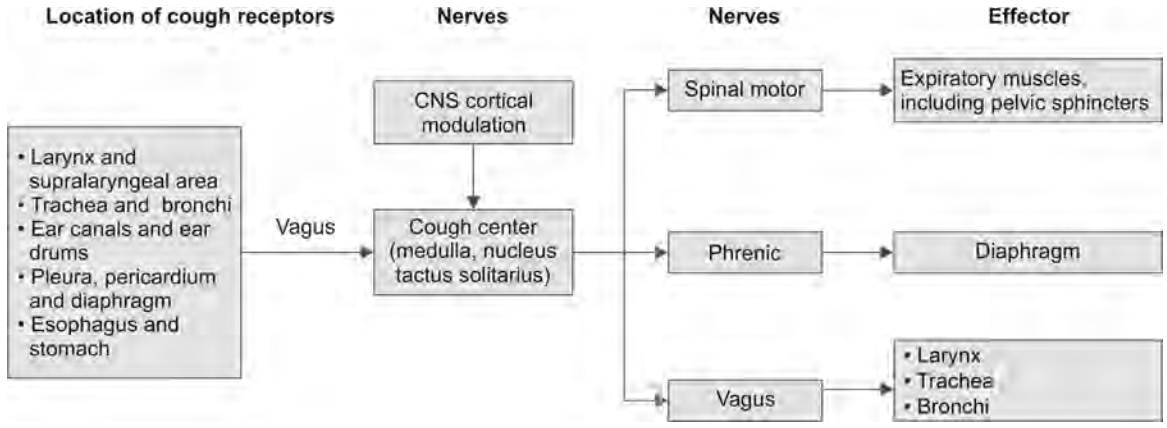
When cough receptors are stimulated by inflammation, mucus, foreign materials, or noxious gases. Receptors are located primarily in larynx, trachea, and large bronchi. Mechanism of cough explained in the **Flowchart 1**.

ETIOLOGY OF COUGH

Most common cause of acute and self-limiting cough is a viral infection of upper airway. Chronic cough is one lasting 8 weeks or longer. Chronic cough carries with it considerable frustration and anxiety for patients with decreased quality of life and depression. When a detail history and thorough examination fail to find evidence of disease [e.g., cancer and human immunodeficiency virus (HIV) disease] and the chest radiograph is normal, >90% of chronic cough cases are accounted for by upper airway cough syndrome (formerly called postnasal drip), asthma, and gastrointestinal reflux. Chronic cough has numerous common and uncommon causes that sometimes may have multiple sources (**Box 1**).

CHARACTERISTICS OF COUGH

Characteristics of cough are described (**Table 1**) in terms of productive or nonproductive cough, acute or chronic cough, nocturnal or day time cough. Dry or nonproductive cough



(CNS: central nervous system)

FLOWCHART 1: Mechanism of cough signaling pathway in development of cough.

BOX 1: Etiology of chronic cough in adults (>8 weeks duration).

Common causes:
- Upper airway cough syndrome (formerly known as "postnasal drip")
- Pulmonary tuberculosis
- Asthma
- Gastroesophageal reflux
- Chronic bronchitis associated with cigarette smoking
- Environmental exposure
- Angiotensin-converting enzyme-1 (ACE-1) cough (caused by antihypertensive drug ACE inhibitors)
- Nonasthmatic eosinophilic bronchitis

Less common causes:
- Postinfection (e.g., pertussis and mycoplasma)
- Interstitial lung disease
- Bronchiectasis
- Obstructive sleep apnea
- Primary lung cancer
- Heart failure

Uncommon causes:
- Sarcoidosis
- Recurrent aspiration
- Chronic tonsillar enlargement
- Chronic auditory canal irritation
- Foreign body aspiration
- Endemic fungi
- Peritoneal dialysis
- Cystic fibrosis
- Tracheomalacia
- Habit or "tic cough"

typical of restrictive lung disease. *Loose or productive cough*—more often associated with inflammatory obstructive disease such as bronchitis or asthma.

ASSOCIATED FEATURES OF CONCERN (RED FLAGS)

- Fever
- Rashes
- Chest pain
- Palpitations
- Hemoptysis
- Breathlessness
- Dizziness or vomiting with cough
- Loss of consciousness while coughing
- Hypotension

COMPLICATIONS OF COUGH

- *Circulatory*: Decrease in cardiac output due to raised intrathoracic pressure, especially in patients with cor pulmonale or right heart failure
- *Syncope*: Post-tussive—nearly always occur in man
- *Raised intra-abdominal pressure*: Hernia, collapse of rectum, or vagina
- Intraocular hemorrhage

INVESTIGATIONS

Depending on history, clinical examination investigation may be decided as:
- Throat swab for Gram stain and culture
- Ear, nose, and throat (ENT) evaluation
- Sputum examination—Gram stain, culture for bacterial, fungal or protozoal causes
- Complete blood count (CBC), erythrocyte sedimentation rate (ESR), serologic markers for various bacterial, fungal, protozoal, or viral infections
- Chest X-ray
- High-resolution computed tomography (HRCT) or contrast-enhanced computed tomography (CECT) chest
- Blood culture
- Bronchoscopy
- Mediastinoscopy
- Video-assisted thoracoscopic surgery (VATS)
- Open lung biopsy

TABLE 1: Characteristics of cough in specific etiologies.	
Causes	***Characteristics of cough***
Sinusitis or nasopharyngitis	Cough following an upper respiratory syndrome or sinus symptoms; sensation of a need to clear the throat; postnasal drip
Acute infections of lung	
Tracheobronchitis	Cough associated with sore throat, running nose and eyes
Lobar pneumonia	Cough often preceded by symptoms of upper respiratory infection; dry cough—initially painful later become productive
Bronchopneumonia	Cough dry/productive, usually begins as acute bronchitis
Mycoplasma and viral pneumonia	Paroxysmal cough, productive—mucoid/blood-stained sputum associated with flu-like syndrome
Exacerbation of chronic bronchitis	Productive cough—mucoid then purulent
Chronic infections of lung	
Bronchitis	• Productive cough on most days for > 3 consecutive months and for > 2 years • Mucoid sputum until acute exacerbation, when it becomes mucopurulent
Bronchiectasis	Copious, foul smelling, purulent sputum often since childhood; forms layers on standing
Tuberculosis or fungal infection	Persistent cough for weeks to months, often with blood-tinged sputum
Parenchymal inflammatory disease	
Interstitial fibrosis and infiltrations	Persistent, nonproductive cough—depends on origin
Smoking and inhalation of irritants	Persistent slightly productive cough, mostly in mornings, usually associated with infected pharynx, if succeeded by chronic bronchitis copious purulent sputum may be present
Tumors	
Bronchogenic carcinoma	Nonproductive cough→productive in weeks to months, may be associated with recurrent mild hemoptysis
Adenocarcinoma in situ or minimally invasive adenocarcinoma	Same as above, some cases may present with copious, watery to mucoid sputum
Benign tumors in airways	Nonproductive cough, occasional hemoptysis
Mediastinal tumors	Cough with dyspnea—caused by compression of trachea and bronchi
Aortic aneurysm	Brassy cough
Gastrointestinal	
Gastroesophageal reflux disease (GERD)	Nonproductive cough—often followed by meals or with recumbency, may or may not be associated with other symptoms of GERD (e.g., heart burn, bitter oral taste, and belching)
Foreign body	
Immediate while still in upper airway	Cough associated with progressive evidence of asphyxiation
Later, when lodged in lower airway	Persistent, nonproductive cough associated with localized wheeze
Cardiovascular	
Left ventricular failure	Cough and dyspnea worsens when supine
Pulmonary infarction	Cough with hemoptysis, usually with pleural effusion
Drug induced	
Angiotensin-converting enzyme (ACE) inhibitors	More common in females, dry cough, may occur at any time (soon after starting drug or many years later)

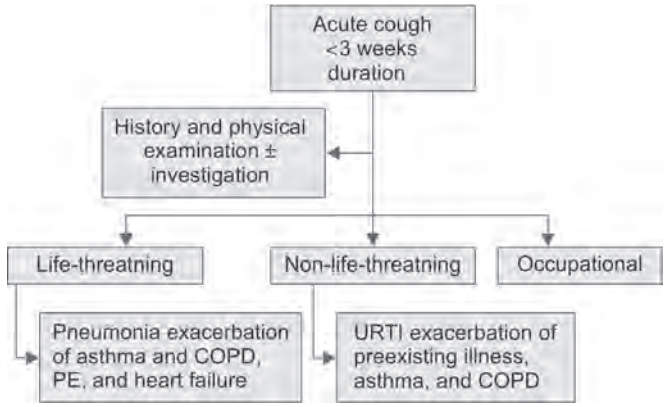
TREATMENT

Acute and subacute cough is need to be treated effectively as soon as possible to maintain adequate quality of life and productivity of the patient. Many patients resulting in substantial morbidity, if cough is not controlled adequately. First symptom-related approaches are adopted in the treatment of the cough. Then various interventions are required (history, physical examination, and investigations) to identify the causes of cough and aim at removing the underlying cause of cough (**Table 2**). Ideally, treatment of the underlying cause(s) of cough with specific treatments of underlying cause is the only strategy which eliminate cough. Sometime no cause could be found to establish the diagnosis and treatment of underlying cause could not be initiated, so in view of deterioration in the quality of life of the patient empiric treatment with antitussive agents is often needed. Another concept of treating the cough earlier is to prevent it becoming

TABLE 2: Specific treatment approaches to cough.

Etiology of cough	*Treatment approach*
Upper/lower respiratory infection	Appropriate antibiotics
Smoking/chronic bronchitis	Cessation of smoking/avoidance of pollutants
Pulmonary tuberculosis	Antitubercular drugs
Asthmatic cough	Inhaled beta-2 agonists/ipratropium/corticosteroids
Postnasal drip due to allergic/perennial rhinitis	Avoidance of precipitating factors, corticosteroid nasal spray, and H1 antihistaminic
Gastroesophageal reflux disease	Bed head elevation, light dinner, diet modification, H2 blocker, proton pump inhibitors, and cisapride
ACE inhibitor-associated cough	Substitute ACE inhibitor by losartan, calcium channel blocker, and NSAIDs

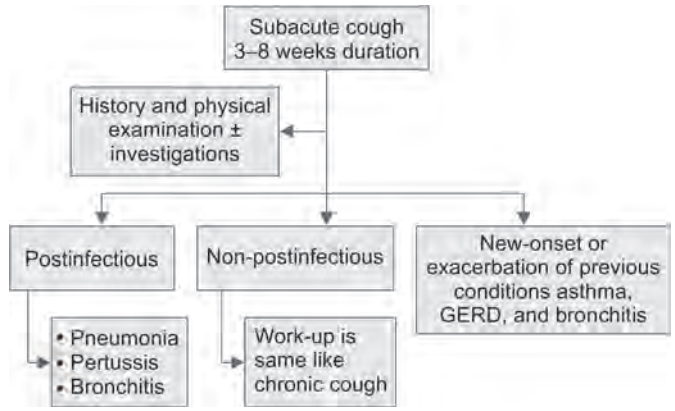
(ACE: angiotensin-converting enzyme; NSAIDs: nonsteroidal anti-inflammatory drugs)



(COPD: chronic obstructive pulmonary disease; PE: pulmonary embolism; URTI: upper respiratory tract infection)

FLOWCHART 2: Evaluation of management of acute onset cough <3-week duration.

the persistent cough and decreasing the spread of infectious virus and bacteria. Cough-related complications are also can be prevented, such as fatigue, sleep deprivation, hoarseness, musculoskeletal pain, sweating, and urinary incontinence. Two mechanisms can be involved for the development of acute phase of the cough; a respiratory virus or by gastroesophageal reflux disease (GERD) through direct stimulation of cough receptors. Sometime this could be a possibility that a cough that does not respond to specific therapies "idiopathic"



(GERD: gastroesophageal reflux disease)

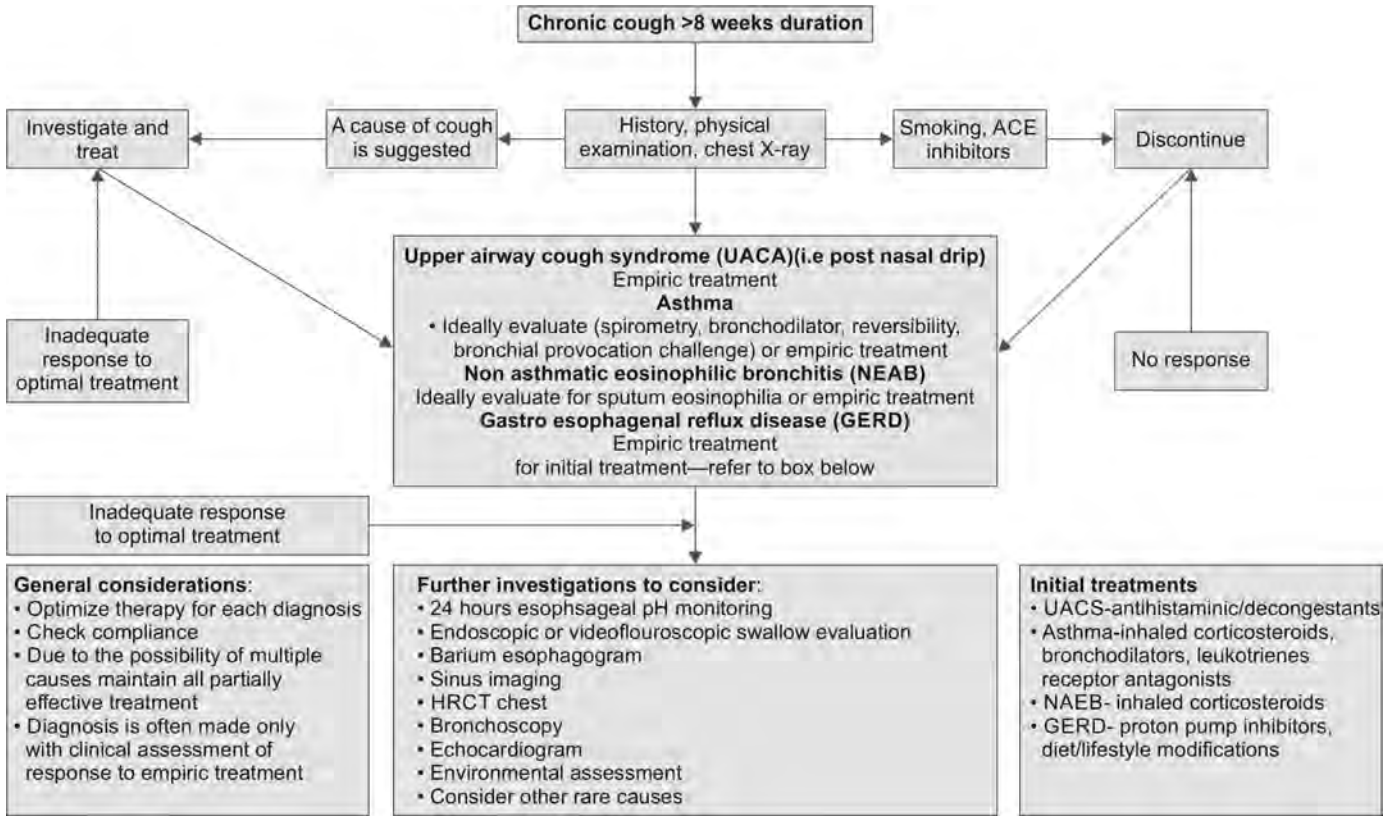
FLOWCHART 3: Evaluation and management of subacute onset cough 3–8 weeks duration.

cough which need a nonspecific approach to evaluation of cough. Evaluation and management of acute, subacute, and chronic onset of cough are summarized in **Flowcharts 2** to **4**.

SUMMARY

Cough is one of the most common symptoms that results in medical consultations and is the most frequent complaint of patients seeking advice from practicing pulmonary physicians, accounting for up to 40% of the practice outpatient care activity. Coughing is considered as defensive reflex that helpful in clearance of secretions and particulate matter from the airways and protects from aspiration of foreign materials occurring as a consequence of aspiration or inhalation of particulate matter, pathogens, accumulated secretions, postnasal drip, inflammation, and associated inflammatory mediators. Under normal conditions, cough plays an important protective role in the airways and lung parenchyma, but in some conditions, coughing may become excessive and nonproductive, and is troublesome and potentially harmful to the airway mucosa. Treating of cough should be started early, helps in preventing the vicious cycle of cough perpetuating cough. Symptom-related approaches are beneficial in treatment of cough. Antitussive agents are usually helpful as empiric treatment particularly needed when associated with deterioration in the quality of life. Drugs available for symptomatic treatment of cough include both peripheral and central products. Recommendation is against the use of over the counter products for coughs and colds, including central antitussives, in infants, and young children. Various academies and society have advised not to use dextromethorphan as well as codeine for treating any type of cough in the pediatric as well as adult population. Treatment of cause should be the priorities.

"Do not suppress the cough—Treat the Cause"!


Chronic cough >8 weeks duration
Investigate and treat
A cause of cough is suggested
History, physical examination, chest X-ray
Smoking, ACE inhibitors
Discontinue
Upper airway cough syndrome (UACA)(i.e post nasal drip)
Empiric treatment
Asthma
• Ideally evaluate (spirometry, bronchodilator, reversibility, bronchial provocation challenge) or empiric treatment
Non asthmatic eosinophilic bronchitis (NEAB)
Ideally evaluate for sputum eosinophilia or empiric treatment
Gastro esophagenal reflux disease (GERD)
Empiric treatment
for initial treatment—refer to box below
Inadequate response to optimal treatment
No response
Inadequate response to optimal treatment
General considerations:
• Optimize therapy for each diagnosis
• Check compliance
• Due to the possibility of multiple causes maintain all partially effective treatment
• Diagnosis is often made only with clinical assessment of response to empiric treatment
Further investigations to consider:
• 24 hours esophsageal pH monitoring
• Endoscopic or videoflouroscopic swallow evaluation
• Barium esophagogram
• Sinus imaging
• HRCT chest
• Bronchoscopy
• Echocardiogram
• Environmental assessment
• Consider other rare causes
Initial treatments
• UACS-antihistaminic/decongestants
• Asthma-inhaled corticosteroids, bronchodilators, leukotrienes receptor antagonists
• NAEB- inhaled corticosteroids
• GERD- proton pump inhibitors, diet/lifestyle modifications

(ACE: angiotensin-converting enzyme; HRCT: high-resolution computed tomography)

FLOWCHART 4: Evaluation and management of chronic cough 3–8-week duration.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Hemoptysis

Veerottam Tomer

INTRODUCTION

Hemoptysis is the expectoration of blood from the airways; it can originate from the alveoli to glottis. Hemoptysis is derived from Latin "hemo-" "of blood" + Greek *ptusis* "spitting". It can range from blood-tinged to severe life-threatening. For most patients, any degree of hemoptysis can be frightening and needs earliest medical evaluation. The location may be upper respiratory tract, vocal cords, tracheobronchial tree, or lung parenchyma. Identification of location is important for proper management of the symptom. It is very scary to see patients dying from asphyxiation even in spite of intubation. It is the most challenging emergency faced by emergency physician and intensivist because course of bleeding is unpredictable and varies from trivial to large amount.

Hemoptysis is a manifestation of underlying disease process. Till now there is no consensus regarding the optimal management of these patients. A quick history, examination, investigations, and timely intervention play a very crucial role in the management of hemoptysis. At the same time, it is very important to differentiate hemoptysis from pseudohemoptysis, hematemesis, and epistaxis (**Table 1**).

The most common causes of mild hemoptysis are bronchitis, bronchiectasis, bronchogenic carcinoma, and tuberculosis. 20–40% of cases of minor hemoptysis are due to bronchitis and bronchiectasis; while bronchogenic and metastatic carcinomas account for 20% of the cases. However, in India, tuberculosis is the most common cause of mild-to-massive hemoptysis, where it can be seen in active disease or as its sequelae. In Western part of the world, malignancies are the main cause of massive hemoptysis.

It is important to keep in mind that the cause of death in hemoptysis is asphyxiation and not blood loss. It is also dependent on rate of blood loss and underlying lung condition. There is no clear definition for the degree of hemoptysis, however according to the general consensus we can grade hemoptysis into the following grades. *Minor hemoptysis* usually is <15–20 mL/day and is commonly seen to resolve spontaneously. *Massive hemoptysis* ranges from ≥100 mL in 24 hours to >1 L in 24 hours. It can also be judged by its clinical consequences such as requiring hospitalization, the risk of airway occlusion, laboratory evidence of blood loss, or even risk of death. *Bad prognostic factors* if bleeding rate: ~1,000 mL/24 h, aspiration into contralateral lung, massive bleeding requiring single lung ventilation, and bronchogenic carcinoma as an underlying etiology.

PULMONARY CIRCULATION

Lungs have dual blood supply:

- *Pulmonary artery*: Primarily involved in gas exchange process, arises from right ventricle. It is a low resistance system and a high-volume system. It accounts for >99% of blood supply and <10% of causes of hemoptysis. Beyond terminal bronchioles it anastomoses with bronchial circulation for gas exchange.
- *Bronchial artery*: Serves as a nutritional source of circulation. It arises from the systemic vascular bed. There are one or two arteries per lung commonly arising from aorta and at times from intercostal arteries. It is a high pressure (systemic pressure) system. In diseased lungs it often

TABLE 1: Differentiating points: Hemoptysis, hematemesis epistaxis.

Symptoms	*Hemoptysis*	*Hematemesis*	*Epistaxis*
Cough	Common	Uncommon	Uncommon
Dyspnea	Common	Uncommon	Uncommon
Abdominal symptoms	Uncommon	Common	Absent
Frothy secretions	May be present	Absent	Absent
Mixed with food	Absent	May be present	Absent
Mixed with sputum	Common	Uncommon	Uncommon
Color	Bright red	Coffee	Bright red
pH	Alkaline	Acidic	Alkaline
Chest symptoms	May be present	Absent	Absent
Nasal bleed	Absent	Absent	Present

becomes tortuous and anastomosis with the pulmonary veins also get exaggerated (e.g., Rasmussen's aneurysm). Thus bleeding from bronchial artery rupture is more profuse than pulmonary artery rupture.

ETIOLOGY OF HEMOPTYSIS

When considering the etiology of hemoptysis, it is important to be familiar with the pulmonary circulation. Lung has dual blood supply from pulmonary and bronchial circulations. Pulmonary circulation is mainly for gas exchange and accounts for 99% of total blood supply to the lungs. It is a low-pressure (25 mm Hg systolic, 8 mm Hg diastolic, and 15 mm Hg mean) high-flow system that receives the entire cardiac output and causes bleeding in <10% of cases. The bronchial circulation is high-pressure (systemic), low-flow system, which tends to be the major source of hemoptysis because it is more likely to be the source of the collaterals and neovascularization that characteristically occurs in the setting of chronic infection or malignancy. It supplies bronchial mucosa by formation of anastomosis in the peribronchial space and gives rise to small penetrating arteries in mucosa. It causes bleeding in 90% cases. Nonbronchial circulation can also contribute to hemoptysis, especially in lung parenchymal diseases where pleural involvement is present. The neovascularization arises from internal mammary, thyrocervical, coronary, and carotid arteries. Etiology of hemoptysis is summarized in **Table 2**.

EVALUATION OF PATIENT WITH HEMOPTYSIS

History and physical examination are useful in localization of lesion in around 50% of cases (**Table 3**).

As the patient presents to the emergency, one should try to answer the following questions:

1. Rate of bleed and amount of bleeding
2. Underlying pulmonary reserve
3. Etiologic diagnosis
4. Site of bleed

The following questions can be asked regarding present episode:

1. Amount of blood coughed out
2. Nature of expectoration—purulent or mucoid
3. Is the episode recurrent?
4. Any other site of bleed—nose, rectum, and gums
5. Is it associated with breathlessness, rash or loss of weight, and fever?

Determine any risk factors:

1. Is the patient smoker? If yes then pack years, whether current or past
2. Is there a known bleeding disorder?
3. Is the patient taking any medication—antiplatelet, anticoagulant, and aspirin?
4. History of tuberculosis or exposure to the same?
5. Was there history of thoracic stenting, recent hospitalization, deep vein thrombosis or any other suspected pulmonary, and renal or cardiac disease?

TABLE 2: Etiology of hemoptysis.

Airway disease	*Infection*	*Pulmonary vascular disease*	*Others*
• Airway trauma • Bronchitis • Bronchiectasis • Bullous emphysema • Bronchovascular fistula • Bronchial adenoma • Bronchogenic carcinoma • Metastatic cancer (bronchus, trachea) • Foreign body in airway	• Tuberculosis (active or cavitary) • Invasive mycetoma • Bronchiectasis • Cystic fibrosis • Pneumonia (*Staphylococcus*, *Klebsiella*, and *Legionella*) • Lung abscess • Hydatid cyst	• Congenital heart defects • Congestive heart failure • Mitral stenosis • Tricuspid endocarditis • Pulmonary arteriovenous malformation • Pulmonary artery *pseudoaneurysm* • Pulmonary embolism • Pulmonary veno-occlusive disease • Pulmonary hypertension	• *Drugs and toxins* (*Argemone* alkaloid and cocaine use) • *Pulmonary renal syndrome* (Wegener's granulomatosis and Goodpasture syndrome) • Immunologic lung disease and SLE • *Genetic defects of collagens* (Ehlers–Danlos syndrome) • Bone marrow transplantation • *Disorders of coagulation:* ○ Anticoagulant and antiplatelet medications ○ DIC ○ Thrombocytopenia ○ Liver disease ○ Von Willebrand disease • *Iatrogenic*: ○ Bronchoscopy with endobronchial biopsy or TBLB or TBNA ○ Transthoracic needle aspiration ○ Pulmonary artery catheterization ○ Airway stent ○ *Idiopathic*: Idiopathic pulmonary hemosiderosis • *Trauma*: ○ Blunt trauma chest ○ Penetrating lung injury • *Catamenial hemoptysis*

(DIC: disseminated intravascular coagulation; SLE: systemic lupus erythematosus; TBLB: transbronchial lung biopsy; TBNA: transbronchial needle aspiration)

TABLE 3: Evaluation (history and physical examination) of patient with hemoptysis.	
History	
Smoking and asbestos exposure	Bronchogenic carcinoma
Risk factors for aspiration (alcohol, swallowing disorder, altered sensorium, or diminished conscious)	Lung abscess, pneumonia, and FB aspiration
Recent chest trauma or procedure	Traumatic or iatrogenic lung injury
Previously diagnosed pulmonary cardiac or systemic disease	Important clue
Symptoms	
Hoarseness of voice	Bronchogenic carcinoma
Purulent sputum	Pneumonia, lung abscess, bronchiectasis, and bronchitis
PND/orthopnea	MS/LVF
Dyspnea and pleuritic chest pain	• Pneumonia • Pulmonary embolism
Weight loss, night sweats, cough, and fever	• Tuberculosis • Bronchogenic carcinoma
Signs	
• Localized decreased breath sounds • Localized wheeze • Stridor	• Bronchogenic carcinoma • FB aspiration • Tracheal tumor
Bronchial breath sounds	Pneumonia
Pleural rub	Pneumonia and pulmonary embolism
Diastolic murmur	Mitral stenosis
Clubbing	Suppurative lung disease, bronchiectasis, and bronchogenic carcinoma
S3 gallop	LVF
• Oral aphthous ulcers, genital ulcers, and uveitis • Saddle nose, rhinitis, and septal perforation	• Behçet's disease in which AVMs are present • Wegener's granulomatosis

(AVM: arteriovenous malformations; FB: foreign body; LVF: left ventricular failure; MS: mitral stenosis; PND: paroxysmal nocturnal dyspnea)

Ask few questions related to family history:

1. Similar episode in family—in addition history of gastrointestinal bleed and epistaxis
2. History of pulmonary embolism in family

Note down finding on physical examination:

1. Is the patient dyspneic (using accessory muscles of respiration, tachypneic, or cyanotic)?
2. Is the patient clubbed (suggestive of bronchiectasis and lung cancer)?
3. Is there blood in the nose?
4. Are there telangiectasias in the lips, tongue, or oral cavity?
5. Are there skin rashes suggestive of vasculitis, systemic lupus erythematosus (SLE), infective endocarditis, or fat embolism?
6. Are there any adventitious sounds on auscultation (crepitations and bronchial breath sounds)?
7. Is there a P2 component or murmur of tricuspid component (TR) suggestive of pulmonary hypertension?
8. Is there a bruit suggestive of pulmonary arteriovenous malformation (AVM)?
9. Is there a heart murmur suggestive of mitral stenosis, mitral regurgitation, or septic emboli?
10. Is there calf muscle tenderness suggestive of deep vein thrombosis?
11. Saddle nose deformity with septal perforation and rhinitis suggestive of Wegener's granulomatosis.

MANAGEMENT OF PATIENT WITH HEMOPTYSIS

Initial Immediate Management

The initial approach to managing life-threatening hemoptysis involves resuscitation and protection of airway [airway, breathing, and circulation (ABC) approach]. The second step is directed at localizing the site and cause of bleeding and final step is the application of definitive and specific treatments to prevent recurrent bleeding. Hemoptysis can be mild or severe requiring intensive care unit (ICU) admission, so thorough history and complete physical examination to confirm that the patient truly has hemoptysis and not hematemesis or epistaxis. Massive hemoptysis remains a challenge for critical care expert. After a quick physical examination of the patient, resuscitation should be started without delay followed by laboratory investigations chest radiograph.

Airway Protection

Patency of the airway should be the first priority to prevent exsanguination. To achieve immediate control of the airway, patient should be intubated with large single-lumen endotracheal tube (ETT) for proper suctioning; it will also help in initial diagnostic and therapeutic bronchoscopy. Double-lumen ETT can be placed to isolate and ventilate the lung if bleeding from one side. If the bleeding can be localized from one side then with the help of bronchoscope, ETT can be placed in normal lung side to protect it from aspiration. Double-lumen ETT should be placed by experienced person with the help of pediatric bronchoscope to confirm the tube position (**Fig. 1**).

Breathing

The patient must lie in lateral decubitus position towards the bleeding side to prevent the normal lung from exsanguination, and supplement the oxygen to maintain oxygen saturation (SpO_2) > 95%.

Circulation

A large bore intravenous (IV) cannula or central venous line should be inserted and IV fluid started. Intra-arterial catheter is necessary for more accurate monitoring of blood pressure. If the general condition of the patient is rapidly deteriorating

FIG. 1: Double-lumen endobronchial tube—blue colored part is the bronchial tube and transparent one is the tracheal tube. ***(For color version, see plate 10)***

FIG. 2: Chest X-ray posteroanterior (PA) view suggestive of bilateral lower and middle zones, cystic shadows suggestive of bronchiectasis.

O-positive (in childbearing women O-negative) should be transfused while waiting for blood grouping—crossmatching. Arterial blood gas (ABG) should be sent immediately.

Specific Medical Therapy

On the basis of history and physical and laboratory examination, specific therapy should be started to correct the cause because invasive therapeutic interventions do not help to control bleeding secondary to coagulopathies, immunologically-mediated disorder like Goodpasture syndrome. Specific therapies such as antibiotics, correction of coagulopathies with platelet, fresh frozen plasma (FFP), cryoprecipitates, blood transfusion, steroids, immunosuppressive therapies, or plasmapheresis are mandatory to control the precipitating factor. Vitamin K supplements and tranexamic acid are also used to control bleeding. IV vasopressin has also been used but caution is advised in patients with coexistent coronary artery disease or hypertension. Vasoconstriction of the bronchial artery may also hamper effective bronchial artery embolization (BAE) by obscuring the site of bleeding, leading to difficulties in cannulation of the artery. Recombinant activate factor VIIa (rFVIIa) has been used in hemoptysis with community-acquired pneumonia. Danazol or gonadotropin-releasing hormone (GRH) has been used in catamenial hemoptysis. Systemic antifungal agents have been tried in the management of hemoptysis related to mycetoma, but results are not satisfactory. However, percutaneous or bronchoscopic direct instillation of these drugs in cavity is having promising results. This technique is useful in cases bleeding after failed BAE and in those who are not fit for surgery. Radiation therapy has been used in vascular tumor or mycetoma-related massive hemoptysis by necrosis of feeding vessel and vascular thrombosis due to perivascular edema.

Laboratory Investigations

The following investigations are essential in all patients: Complete hemogram, coagulation profile, renal function test, liver function test, ABG, D-dimer, urine analysis, and any other specialized tests needed according to the suspected underlying disease. Sputum and bronchoalveolar lavage should be sent for examination of Gram stain, aerobic culture, acid-fast bacilli (AFB), fungus culture, and cytological.

Chest X-ray

It helps in localizing the bleeding in 33–82% of cases and underlying cause in 35% like tuberculosis or tumors; however, found inconclusive in about 20–60% cases but rarely normal in massive hemoptysis. Chest X-ray is useful in identifying lung mass, cavitary lesion, or vasculitis lesion (**Fig. 2**).

Multidetector Computed Tomography

Multidetector computed tomography (MDCT) angiography is more useful in localizing the site, source of bleeding, and underlying lung pathology. With the help of MDCT, mapping of thoracic vasculature can be done and a detailed study of bronchial and nonbronchial circulation can be seen. Contrast computed tomography (CT) was found accurate in 84% of patients to find feeding vessels in massive hemoptysis. However, it is not wise to shift an unstable patient from ICU to CT unit, unless some therapeutic intervention is planned. In such patients, bed side bronchoscopy should be performed initially. Computed tomography is useful in determination of site of bleed and parenchymal lesions such as pulmonary tuberculosis, bronchogenic carcinoma, aspergilloma, and airway lesions like bronchiectasis (**Figs. 3** and **4**). Contrast-enhanced films are preferred as these would show structures such as AVMs and aneurysms.

Bronchoscopy

Localization of Site

Bronchoscopy is the first investigation of choice. Bronchoscopy done early during massive hemoptysis increases the likelihood of localization. However, during bouts of massive hemoptysis, fiberoptic bronchoscope usage becomes difficult given its narrow working channel.

FIG. 3: Bilateral upper lobar cavities with aspergilloma with bronchiectasis changes.

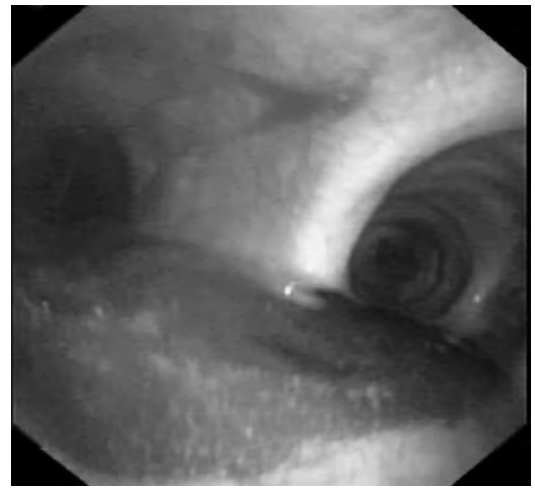


FIG. 5: Bronchoscopy showing bleeding from left main bronchus and spilling into right main bronchus. ***(For color version, see plate 10)***

FIG. 4: Bilateral consolidation—patient presented with moderate hemoptysis.

Spiral contrast-enhanced computed tomography (CECT) chest can be ordered before bronchoscopy. It gives clue for type and site of lesion and can also detect bronchial and nonbronchial arterial vascular lesions like AVMs. The ideal time for bronchoscopy is controversial, however general consensus is to perform it early in rapidly deteriorating patients, delayed bronchoscopy, that is within 24–48 hours of admission can be done in stable patients. Rigid bronchoscopy is ideally recommended in massive hemoptysis for better suctioning and maintenance of airway. Flexible fiberoptic bronchoscopy (FOB) is a very friendly tool for pulmonologist that can be done bedside without the use of general anesthesia. Overall accuracy in localizing the site of bleeding is 10–50%. FOB can reach up to the upper lobe and lesions located distal up to the sixth bronchial generation. The disadvantage of FOB is nonvisualization and clogging of channel by blood clots. Due to limitations with both flexible and rigid bronchoscopy, they can be combined to achieve maximum bleeding control and evaluation (**Fig. 5**). In case of blood clot seen in a segment, it is advisable not to remove it as it may restart massive hemoptysis.

Topical bronchoscopic therapy: Various therapeutic measures can be done with FOB to control bleeding—lavage with 4°C cold saline in the involved lung. Lavage with cold saline up to 1,000 mL in 50 mL aliquots at the bleeding site. Administration of topical hemostatic agents like diluted epinephrine (1:20,000) or thrombin fibrinogen. *Topical epinephrine* should be used with caution as it can precipitate tachyarrhythmias and accelerate hypertension. Newer agents like alcohol dehydrogenase (ADH) derivatives like ornipressin have been successfully used.

Bronchoscopy-guided Topical Hemostatic Tamponade

Oxidized regenerated cellulose (ORC) mesh, a sterile kitted fabric is use. It saturates in contact with blood and swells up to form a brownish gelatinous mass clot and can immediately stop bleeding with success rate of up to 98%. In life-threatening hemoptysis, endobronchial tamponade using balloon catheter (**Fig. 6**) (4 Fr 100 cm Fogarty balloon catheter) has a good success rate to prevent aspiration to the contralateral normal lung and preserve gas exchange; they can be inserted through working channel of FOB. A double-lumen balloon catheter with detachable valve at proximal end can be passed through working channel of bronchoscope and can leave the catheter in bronchus by removing detachable valve. They can be used as bridge therapy before embolization and surgery. Disadvantages are that they can cause ischemic mucosal injury and postobstructive pneumonia.

Endobronchial airway blockade (silicone spigot) can be placed with the help of flexible bronchoscope to control bleeding and stabilize the patient before embolization or surgery. Endobronchial biocompatible glue n-butyl cyanoacrylate which has prothrombin activity is commonly used in mild hemoptysis. It is injected into the bleeding airway through a catheter via flexible bronchoscope. It solidifies on contact with humidity.

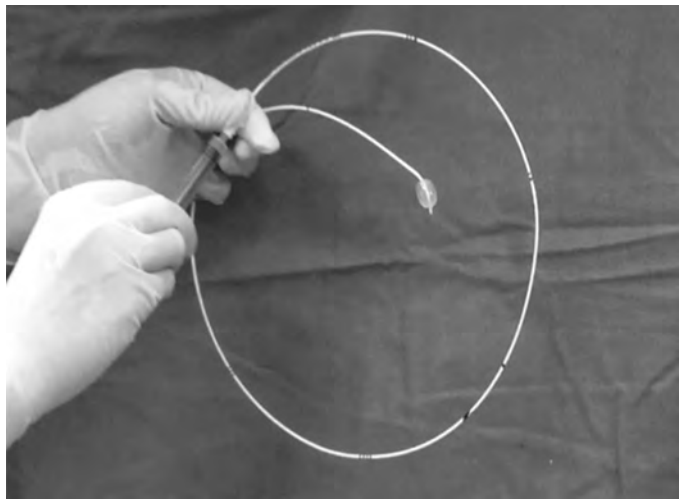


FIG. 6: Fogarty catheter with inflated balloon before insertion.

Bronchial Artery Embolization

This procedure was first reported by Remy and colleagues in 1973 and has been found very useful in massive hemoptysis. Once the bleeding bronchial artery is identified and cannulated, particles of polyvinyl alcohol foam, isobutyl-2-cyanoacrylate, Gianturco steel coils, or absorbable gelatin pledgets are infused into the artery. The immediate success rate is 64–100%, although the recurrent nonmassive bleeding has been reported in 16–46% of patients. 13% technical failure are reported and caused by nonbronchial artery collaterals from systemic arteries such as internal mammary, subclavian, intercostal, and phrenic arteries. Complications of BAE include vessel perforation, intimal tears, chest pain, pyrexia, hemoptysis, systemic embolization, and neurological complication. When anterior spinal artery is identified as originating from bronchial artery, embolization should be avoided to prevent infarction and paraparesis. With newer coaxial microcatheter, selective catheterization and embolization of bronchial artery can be achieved and occlusion of anterior spinal artery can be avoided. BAE is time-buying procedure so definitive diagnosis and definitive treatment should be given. In AVM, BAE is the definitive treatment. In case of normal bronchial artery angiography, pulmonary angiogram should be obtained to investigate pulmonary circulation.

Surgical Management

With the development of different endobronchial tamponade and BAE techniques and higher success rates, practice of thoracic surgery has decreased. Recently, however, surgical resection is indicated when BAE is unavailable or the bleeding is unlikely to be controlled by embolization. It remains the treatment of choice for the management of life-threatening hemoptysis due to a leaking aortic aneurysm, hydatid cyst, iatrogenic pulmonary rupture, chest injuries, bronchial adenoma, selected case of AVMs, or hemoptysis related to mycetoma resistant to other treatments. Surgery is considered the treatment of choice for the localized lesions. Surgical mortality ranges from 1 to 50% in different series depending upon surgical criteria. Surgery is contraindicated in patients with inadequate respiratory reserve or those with inoperable lung cancer due to direct thoracic spread, inability to lateralize the bleeding site, diffuse disease like vasculitis, multiple AVMs, and cystic fibrosis. In patients with poor respiratory reserve or extensive pleural adhesions, physiological lung exclusion strategy has been used. Here the bronchus and pulmonary artery to the involved lobe or segment are surgically ligated and the pulmonary veins left intact and without lung resection.

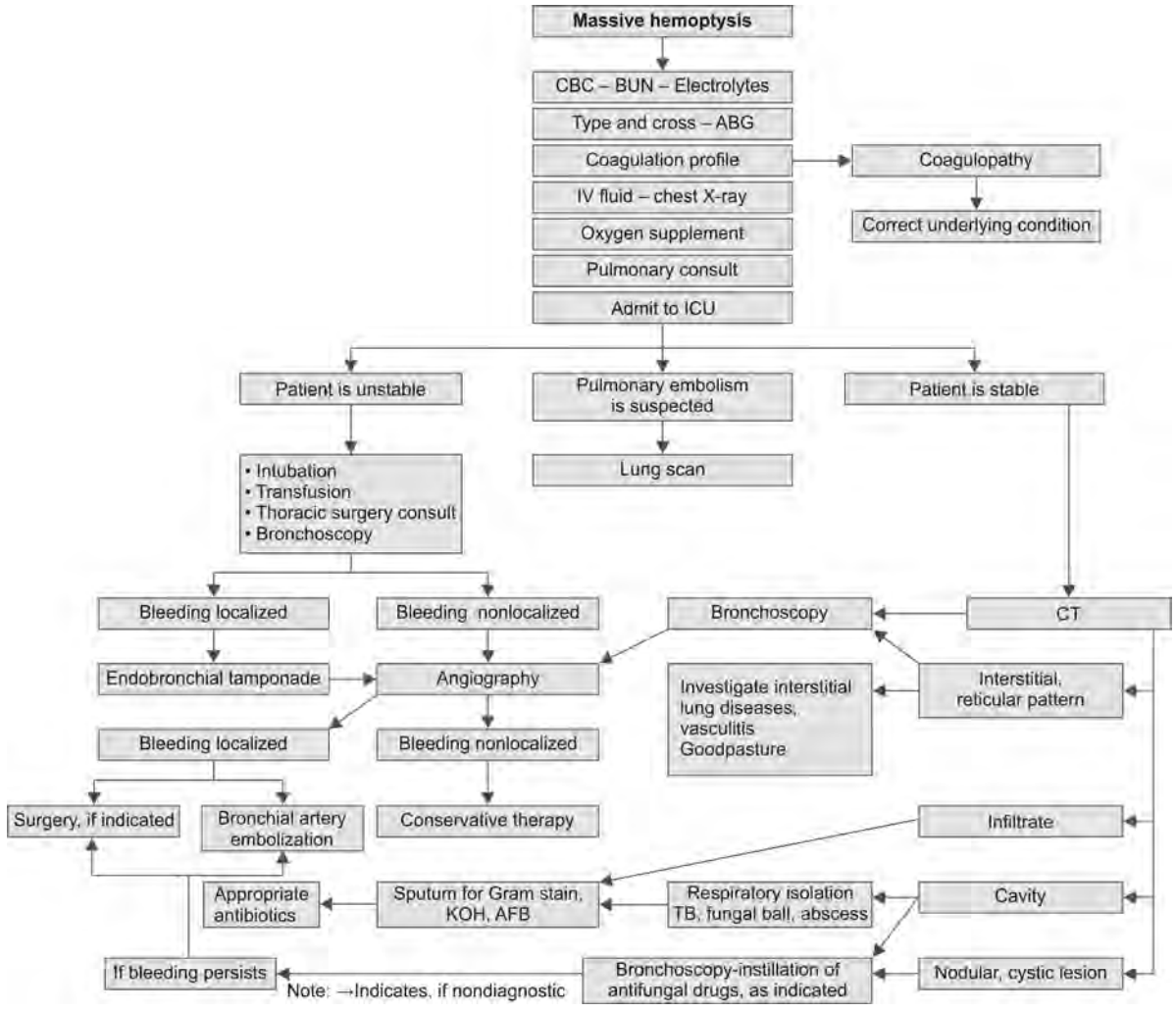
Radiation Therapy

It has been used in hemoptysis due to vascular tumor or mycetoma. It acts by inducing vascular necrosis of feeding vessel or vascular thrombosis due to perivascular edema.

Neodymium-doped yttrium aluminum garnet (Nd:YAG) or argon plasma coagulation (APC) are also used in tumors in which chemotherapy and radiotherapy have been exhausted with success rate up to 60%. APC is a noncontact electrocoagulation tool.

SUMMARY

Hemoptysis is a condition that warrants evaluation. Due to unpredictable course of massive hemoptysis, quick resuscitation, airway protection, and correction of coagulopathy is required. Massive hemoptysis is potentially life-threatening condition and patients should be admitted in ICU. History and clinical evaluation is helpful in assessing site of bleed. Laboratory investigations such as coagulation profile and hemoglobin should be sent on an urgent basis. Radiological investigations such as chest X-ray and MDCT thorax are indicated. Bronchoscopy, especially flexible one is the first-line investigation, tamponade measures may be unsuccessful in massive cases; however, it is useful in localizing site. BAE is successful in stopping bleeding in about 74–90% of cases. Surgery is the definitive management in some cases. Massive hemoptysis has a worser outcome when underlying lung is diseased, rate of bleed is high, and bleeding volume is massive. However, timely interventions, especially choosing proper candidates for interventions have significantly improved outcomes. An algorithm approach to hemoptysis is shown in **Flowchart 1**.



(ABG: arterial blood gas; AFB: acid-fast bacilli; BUN: blood urea nitrogen; CBC: complete blood count; ICU: intensive care unit; IV: intravenous; KOH: potassium hydroxide; TB: tuberculosis)

FLOWCHART 1: Algorithm approach to patient with massive hemoptysis.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Clubbing and Cyanosis

Vivek Chauhan, Suman Thakur

CLUBBING

Examination of nails is an integral part of physical examination. While examining nails we specifically look for presence or absence of clubbing. Diagnosis is easy when the grade of clubbing is high, but clinical value lies in picking up earlier grades of clubbing. The diagnosis of digital clubbing should always be taken seriously and needs further workup. The diseases of lung, heart, gastrointestinal, and hepatobiliary system predominate the causes of clubbing. Rare presentations of clubbing include congenital clubbing and unilateral clubbing. In this chapter we will know more about the pathophysiology and approach towards a case of clubbing.

Causes

Causes of clubbing have been classified into various systems such as cardiac, pulmonary, gastrointestinal, and endocrinal. We have classified them into common and uncommon causes for the ease of understanding (**Table 1**).With a careful history taking, examination, and focused investigation most of the common causes can be ruled out.

TABLE 1: Common and uncommon causes of clubbing.

Clubbing	*Etiology*
Common causes	• Lung cancer • Cyanotic congenital heart diseases • Infective endocarditis • Pulmonary tuberculosis • Interstitial lung diseases • Lung abscess, empyema, and bronchiectasis • Metastatic cancers and lymphomas • Inflammatory bowel disease • Biliary cirrhosis
Uncommon causes	• Uncommon malignancies and metastatic cancers • Asbestosis • Pulmonary AV malformations • Celiac disease • Chronic active hepatitis • Thyroid acropachy • Cystic fibrosis • Atrial myxoma

(AV: arteriovenous)

Pathophysiology of Clubbing

- Historic attempts were directed at the growth hormone as the cause of clubbing, but it was not found elevated in patients of lung cancer having clubbing.
- In 1987, megakaryocytes and platelet clumps were reported to be associated with clubbing. In normal patients, megakaryocytes from bone marrow get trapped in the pulmonary capillaries and are later fragmented into platelets to be released into the circulation. However, in those patients with a right-to-left blood shunt or platelet excess such as cyanotic congenital heart diseases, lung cancers, subacute bacterial endocarditis, and inflammatory bowel disease, the megakaryocytes and platelet clumps get impacted in the nail capillaries.
- *Platelet-derived growth factor (PDGF)* released by the impacted platelets and megakaryocytes is shown to be responsible for the excessive growth of the tissue in the nail bed resulting in clubbing.
- *Vascular endothelial growth factor (VEGF)* is another factor released by the clumped platelets which along with the PDGF was found to be significantly elevated in the patients with clubbing.
- *Additional factors* that were studied but not found elevated in clubbing include basic fibroblast growth factor, transforming growth factor-beta 1 and carbonic anhydrase IX.
- *Hypoxia* is an important inducer of VEGF and PDGF from platelets and therefore many conditions that cause clubbing are also having hypoxemia. Octreotide is a powerful inhibitor of VEGF and hypertrophic osteoarthropathy (HOA), a form of clubbing, was shown to be responsive to treatment with octreotide. This provided strong indirect evidence of pathogenic role of VEGF in clubbing.
- *Prostaglandin E2 (PGE2)* was demonstrated to be elevated in lung cancer patients with debilitating symptoms of HOA

that reduced on taking cyclooxygenase-2 (COX-2) inhibitors and recurred on stopping them. PGE2 can upregulate VEGF messenger ribonucleic acid (mRNA) expression that is inhibited by dexamethasone. In addition, PGE2 stimulates osteoblasts and osteoclasts and is, therefore, capable of inducing periostosis and acro-osteolysis, in addition to local vasodilatation, all features of HOA.

- *PDGF, VEGF, and PGE2* are the three factors currently most strongly associated with the development of clubbing and are helped by the conditions favoring malignancy, hypoxia, or right-to-left shunting of blood.

Clinical Presentation

- Patients are mostly asymptomatic for clubbing unless it is associated with a syndrome (HOA) that involves periostosis of long bones and occasionally painful joint enlargement. Most cases of HOA are associated with lung malignancies which gave it the name of hypertrophic pulmonary osteoarthropathy (HPOA), but later it was found to be associated with nonpulmonary causes and the word "pulmonary" was thus dropped. Nonpulmonary HOA is also called pachydermoperiostosis.
- Thus, patients with clubbing can present with asymptomatic enlargement of nail folds or can be associated with painful debilitating periostosis of long bones and joints (HOA).

Various Signs in Clubbing

- *Schamroth's sign*: This sign is present in normal persons without clubbing. When the dorsal surfaces of terminal phalanges of corresponding right and left fingers are placed together, a diamond-shaped window is formed between the two fingers. This window gets obliterated in clubbing.
- *Fluctuation test*: Increased fluctuation and softening of the nail bed is the earliest sign of clubbing that can be elicited.
- *Profile sign or Lovibond's angle*: In normal people, the angle made by nail as it exists from the proximal nail fold is usually <180° and is called profile sign or Lovibond's angle.
- *Phalangeal depth ratio*: It is the ratio of digit's depth measured at the junction between skin and nail and at the distal interphalangeal joint. Normally, the depth at distal interphalangeal joint is more than the depth at nail bed. In clubbing fingers, connective tissue deposition expands the pulp in the terminal phalanx and the ratio becomes reversed. This ratio is also independent of age, sex, and ethnicity of population. A phalangeal depth ratio of over 1 measured by calipers or a photograph is indicative of clubbing.
- *Digital index*: It is the sum of phalangeal depth ratio of all 10 fingers. Digital index is more specific for clubbing and an index of 10.2 or higher is suggestive of clubbing.

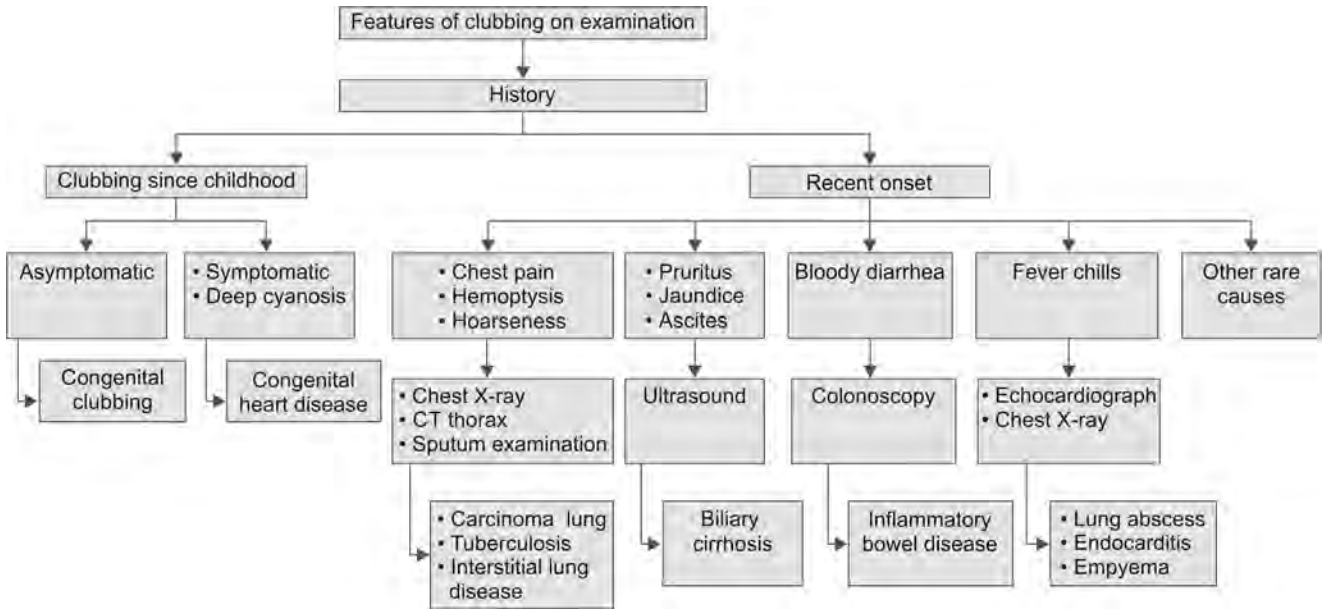
Features of Concern (Red Flags)

- *HOA* is a red flag sign in a patient with clubbing as it is more often than not associated with an underlying serious disorder like malignancy. So in patients with clubbing, we must always palpate the wrists and ends of long bones for tenderness arising from periostosis.
- Presence of hoarseness, hemoptysis, engorged neck veins, generalized lymphadenopathy, and pleural effusion are also red flag signs pointing towards possibility of an advanced malignancy in a patient of clubbing.
- Similarly, presence of diffuse cyanosis in a previously acyanotic congenital heart disease patient points towards Eisenmenger's syndrome that has poor prognosis for the patient.

Evaluation (History and Physical Examination)

Evaluation (**Flowchart 1**) starts with careful history taking can lead us to the etiology for clubbing.

- *Congenital clubbing*: Long-standing history since childhood points towards this etiology. Patients are



FLOWCHART 1: Approach towards a patient of clubbing.

mostly asymptomatic and this condition may be familial and present in other members of the family too. Further investigation may not be needed for congenital clubbing.

- *Congenital cyanotic heart diseases*: History of cyanotic spells, differential cyanosis, repeated childhood pneumonias, palpitations, and dyspnea points toward a possibility of congenital heart diseases with right-to-left shunts. These patients will need cardiology consultation for definitive diagnosis.
- *Lung carcinoma*: Chest pain, sputum production, hemoptysis, dyspnea, hoarseness, dysphagia, swollen, and engorged neck and chest veins in a chronic smoker point towards a lung carcinoma. These patients will need a pulmonary workup to rule out lung carcinoma.
- *Biliary cirrhosis*: Prolonged icterus, pruritus, and abdominal distention in a middle-aged female with clubbing points towards biliary cirrhosis.
- *Inflammatory bowel disease*: Chronic diarrhea with clubbing and blood in stools points towards inflammatory bowel disease.
- *Tuberculosis*: History of past or recent tuberculosis may be present in many patients with cough, dyspnea, and clubbing.
- *Pulmonary infections*: Production of excess sputum and localized chest pain point towards bronchiectasis or lung abscess and empyema, respectively.

Physical examination and signs pointing towards various etiologies of clubbing:

- Engorged neck and chest veins are seen in lung cancer with mediastinal syndrome due to secondaries in lymph nodes or local spread.
- Jaundice, itch marks, and ascites are seen in biliary cirrhosis.
- In a dyspneic patient, bilateral end inspiratory fine crepts, more so in the basal regions, are found in interstitial fibrosis of lungs.
- Unilateral loss of lung volume with crowding of ribs in previously treated tuberculosis is suggestive of post-tubercular lung fibrosis.
- Differential cyanosis, diffuse cyanosis, heart murmurs, parasternal heave, and precordial thrill are found in various congenital heart diseases.
- Fever with chills and rigors, heart murmurs, splenomegaly, Roth spots, Janeway lesions, etc., lead towards infective endocarditis.
- Unilateral absence of breath sounds and local tenderness over the region, mostly in the basal portion of the lungs points towards empyema.
- Various authors and books have divided clubbing into grades. The earliest is increased fluctuation *(Grade 1)* followed by increase in the Lovibond's angle > 180° *(Grade 2)* and later increased phalangeal depth ratio *(Grade 3)*. Finally, the clubbing becomes obvious due to its clubbed appearance *(Grade 4)* (**Fig. 1**).
- The clinical importance of various grades of clubbing in clinical setting is uncertain. Clubbing should be picked up early when the associated diseases are still treatable. To be confident of early clubbing, fluctuation sign should be practiced in all patients routinely.
- Imaging of individual fingers from a side angle using digital cameras is helpful in measurement of phalangeal depth ratio, digital index, and Lovibond's angle.

FIG. 1: Grade 4 clubbing of all nails of the hands. ***(For color version, see plate 10)***

- Painful HOA must be looked for in all patients of clubbing. Its presence requires further investigation to rule out lung cancers and other malignancies.

Investigation

- Investigations should be directed towards the probable etiology of the clubbing based upon history and physical examination. A chest X-ray must be done in all patients of clubbing to rule out pulmonary etiologies. Specific tests are directed towards specific etiologies, e.g., CT chest is done for diagnosing lung cancer, idiopathic pulmonary fibrosis, lung abscess, empyema, post-tubercular fibrosis, bronchiectasis, lymphoma, etc.
- Colonoscopy gives diagnosis of inflammatory bowel disease.
- Ultrasound, ascitic fluid examination, and serology are needed to diagnose biliary cirrhosis.
- Electrocardiography, echocardiography, and cardiac catheterization studies for congenital heart disease, pulmonary arteriovenous (AV) malformations, and atrial myxoma.
- Echocardiography and paired blood cultures are done for subacute infective endocarditis.
- Thyroid functions must be done to rule out thyroid acropachy. It may also be associated with thyroid dermopathy and ophthalmopathy.
- Bone scan may be needed to confirm the presence and extent of HOA.

Treatment

- In cases of clubbing, the treatment is directed towards specific etiologies. Cancers may be treatable or untreatable depending upon their stage and grade. Clubbing regresses with treatment over months.
- Many conditions associated with clubbing are treatable, e.g., lung abscess, empyema, deep abscesses, some congenital heart diseases, inflammatory bowel diseases, infective endocarditis, and atrial myxoma.
- The painful debilitating HOA responds to COX-2 inhibitors and corticosteroids.
- Congenital clubbing does not require any treatment and is mostly asymptomatic.

CYANOSIS

Cyanosis word has been derived from *cyan,* a blue green color. Cyanosis of the skin or mucus membranes is an important finding on examination needing careful workup to find its genesis in each patient. The etiology behind cyanosis may be anything from innocuous (polycythemia of high altitude) to grave (severe interstitial lung disease). Physicians have started relying more on pulse oximeter values and oxygen saturation (SpO_2), forgetting that there are many cases where oximeters are unreliable, e.g., methemoglobinemia, sulfhemoglobinemia, and carboxyhemoglobin. Knowledge of cyanosis, its origin, testing, and clinical implications are thus essential for better patient care.

Causes

Skin and mucosae become cyanotic when concentration of any the following pigments is increased in the blood. Various causes of cyanosis in different type of pigments are given in **Table 2**.

- Deoxyhemoglobin
- Methemoglobin (MetHb)
- Sulfhemoglobin (SulfHb)
- Methemalbumin
- Metals (silver, gold, and hemosiderin)
- Miscellaneous causes (chlorpromazine and amiodarone)

TABLE 2: Various causes of cyanosis in different types of pigments.

Type of pigment	*Causes*
Deoxyhemoglobinemia	
Decreased arterial oxygenation	Cardiopulmonary diseases, high altitude, hypoventilation syndromes, neuromuscular and skeletal defects, vascular shunts, etc.
Increased tissue extraction	Sluggish blood flow, heart failure, local ischemia, exercise, shock, atherosclerosis, deep venous thrombosis, Raynaud's phenomenon, hypothermia, etc.
Abnormal hemoglobin	Hemoglobin M (HbM)
Methemoglobinemia	
Genetic	Autosomal recessive
Dietary	Fava beans, nitrate-containing foods, and *Ginkgo biloba*
Toxic/drug induced	Dapsone, benzocaine, nitroglycerine, nitroprusside, and mothballs
Idiopathic	
Sulfhemoglobinemia	
Drugs	Sulfonamides, sulfasalazine, sumatriptan overdose, and metoclopramide
Industrial exposures	Hydrogen sulfide (H_2S) gas, phenazopyridine, and volatile sulfur-containing compounds
Methemoglobin	Massive hemolysis
Metals	Silver, gold, and hemosiderin
Miscellaneous causes	Chlorpromazine and amiodarone

Pathophysiology of Cyanosis

The normal skin color results from a combination of oxyhemoglobin, deoxyhemoglobin, melanin, carotene, and from the optical effect of scattering (Tyndall effect that gives blue color to the sky). White light that falls upon our skin has a spectrum ranging from blue at one end and red at the other. Blue skin coloration would result if the quantity of blue wavelengths reflected is disproportionately increased or if the quantity of red wavelengths reflected is disproportionately decreased. The same venous blood that gives blue color to our skin does not appear blue when taken out in a test tube. Deoxyhemoglobin is less red than oxyhemoglobin and absorbs more red spectrum therefore appearing bluish. By subtraction of red wavelengths, the blue spectrum is allowed to predominate in the reflected light (i.e., something that is less red is more blue).

Deoxygenated hemoglobin (Hb) is apparent as cyanosis on clinical examination of skin and mucosa when its amount is >4–6 g/dL in the capillaries. In presence of a normal cardiac output, Hb, and tissue extraction of oxygen, an arterial SpO_2 of <80% would be required to cause cyanosis. Cyanosis cannot be produced in severe anemia if Hb concentration is below the threshold of cyanosis, i.e., 4–6 g/dL. Also anemic individuals need more profound oxygen desaturation to produce cyanosis.

Methemoglobin is normally formed in body around 3% per day when ferrous form of iron is converted to ferric form in the Hb. MetHb is not capable of binding to oxygen and thus leads to hypoxia when in excess. Cytochrome b5 reductase reduces MetHb to Hb using nicotinamide adenine dinucleotide as a cofactor and keeps its levels below 1%.

Sulfhemoglobin excess is relatively rare in the blood and the pigment is a greenish derivative of Hb, with an absorption peak at 620 nm, but cannot be converted back to normal, functional Hb unlike deoxyhemoglobin and MetHb. In vitro, SulfHb forms when hydrogen sulfide (H_2S) is added to Hb, hence the name; in vivo, naturally occurring SulfHb is postulated to be derived from H_2S produced by intestinal bacteria, but the mode of formation has not yet clear. Cyanosis is reported to be detectable at SulfHb levels as low as 0.5 g/dL.

Gold- or *silver*-containing substances when ingested can produce bluish skin coloration. It is most prominent in sun-exposed portions of the body. The bluish skin color associated with *hemosiderin* deposition is more apparent in parts of the body with less melanotic pigment and a more bronze color is seen in the presence of melanin.

The oxidation products of *chlorpromazine*, when deposited in the skin and other organs, can result in a blue to purple color. A new antiarrhythmic agent, *amiodarone*, can cause lipofuscin deposition in the skin. In sun-exposed areas, a blue skin color is seen in a small percentage of patients on long-term therapy.

Clinical Presentation

Many authors divide cyanosis into central and peripheral cyanosis.

Central cyanosis: It is mostly seen with systemic disorders. Some common diseases presenting with central cyanosis include chronic obstructive lung disease, pneumonia, interstitial lung disease, embolism and ventilation perfusion mismatch, acute respiratory distress syndromes, high altitude, congestive heart failure, anatomic shunts, right-to-left shunt in congenital heart disease, AV malformation, and intrapulmonary shunts.

Peripheral cyanosis: All causes of central cyanosis have peripheral cyanosis too. Isolated peripheral cyanosis however, is seen in conditions with sluggish blood flow with increased oxygen extraction, e.g., Raynaud's phenomenon, congestive heart failure, hypovolemic shock, and hypothermia.

Clinical signs of deoxygenation vary depending upon the etiology. A resident of high altitude can have deep cyanosis, polycythemia, and still be asymptomatic. A patient of anemia on the other hand may be markedly desaturated with only mild or no cyanosis. Thus, knowledge of Hb levels of the patient helps us understand the correlation with the severity of cyanosis and oxygen desaturation.

Cyanotic individuals are expected to have SpO_2 levels of <80% and thus have worse outcomes if associated with some underlying pathological condition. Prolonged desaturation can lead to hypoxic encephalopathy, which may become irreversible.

Cyanosis occurs at MetHb levels of level of 1.5 g/dL, 15% of total Hb. Anxiety, headache, and dizziness can occur at MetHb levels >20%. Levels between 30% and 50% can produce fatigue, confusion, and tachypnea. At levels >50%, arrhythmias, acidosis, seizures, and coma can occur.

Sulfhemoglobin produces cyanosis at 0.5 g/dL levels, but the patient may have normal SpO_2 and be asymptomatic.

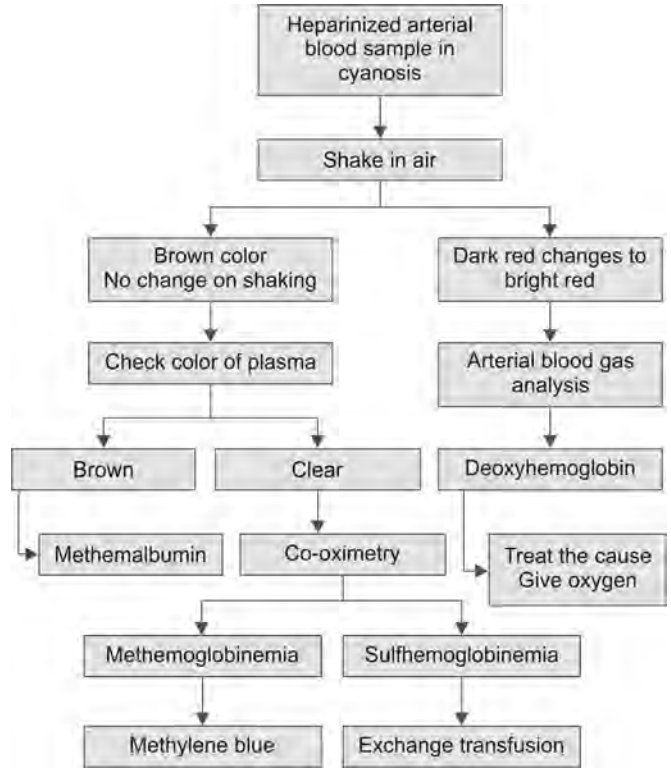
Features of Concern (Red Flags)

In the presence of cyanosis, the following additional findings may be the red flags:

- Low blood pressure
- Altered sensorium
- Tachypnea and dyspnea

Evaluation (History and Physical Examination)

- Approach to patient with cyanosis starts with history and physical examination (**Flowchart 2**).
- History should be focused towards the presenting complaint and contributing past history of illness.
- A high proportion of cases with cyanosis have a long-standing cardiopulmonary illness. The acute events such as viral or bacterial infection, arrhythmia, pneumothorax, pleural effusion, myocardial infarction, pulmonary embolism, congestive heart failure, and myocarditis can worsen a stable long-standing cardiopulmonary illness and produce cyanosis.
- In absence of a long-standing illness and obvious cardiopulmonary involvement, we must take history of recent drug intake or toxin exposure (both intentional and accidental) and rule out cyanosis due to rare pigments such as MetHb, SulfHb, and nonheme pigments.
- Since the sensitivity to detect cyanosis at the threshold levels of deoxyhemoglobin is not very high, it becomes important to know the technique and practice it routinely. Lighting is important as cyanosis is best appreciated when lighting matches the spectral composition of that of the sunlight. So, the artificial sources of light should be similar to sunlight. Tungsten filament bulbs and certain fluorescent bulbs are satisfactory for detecting cyanosis. Too intense light is also inappropriate to detect cyanosis. Some people recommend <20 footcandles of illumination for this purpose.
- *Sites to look for cyanosis:* Parts of skin and mucosa that lack melanin pigment are appropriate to look for cyanosis. Lips, tongue, hands, and ears are the most commonly observed sites (**Fig. 2**). Trunk, nail bed, conjunctiva, and circumoral areas also have been described to look for cyanosis. The tongue is the most sensitive, but lips are more specific sites for cyanosis.



FLOWCHART 2: Approach towards a patient of cyanosis.

FIG. 2: Peripheral cyanosis in one of the hands. ***(For color version, see plate 10)***

- Many cases of cyanosis also have associated clubbing. These conditions mostly have some form of right-to-left shunt either within the heart, lungs, or in the periphery.

Cyanosis as a tool for detecting arterial hypoxemia is neither sensitive nor specific. Definite cyanosis was not apparent to 25% of observers even at arterial SpO_2 of 71–75% [partial pressure of oxygen (PaO_2) 35–40 mm Hg]. In contrast, 6% and 17% of the observers believed definite cyanosis to be present when arterial SpO_2 were 96–100% and 91–95%, respectively. The sensitivity of this sign is decreased when examining deeply pigmented individuals. In blacks, 3–6% more arterial oxygen desaturation may be required for detection of cyanosis. Still, early detection of cyanosis may point toward an underlying serious disorders such as congenital heart disease like tetralogy of Fallot in children, methemoglobinemia, and sulfhemoglobinemia in absence of profound symptoms of any disease.

Investigations

Whenever we detect cyanosis, we must confirm the arterial saturation by pulse oximetry followed by arterial blood gas (ABG) analysis. Nail polish can decrease the oximetry values by 6% therefore the pulse oximeter should be applied sideways to the fingers.

In cases where there is a mismatch between the oximetry values and ABG, we go for co-oximetry. Pulse oximeter measures light at two wavelengths, oxyhemoglobin and deoxyhemoglobin. Co-oximetry measures the absorption of light at four different wavelengths corresponding to oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and MetHb.

Once the diagnosis of the type of cyanotic agent is clear, we then focus our attention towards the etiological agent or disease. For deoxyhemoglobin based upon our probable diagnosis, we get further investigations done that may include chest X-ray, electrocardiogram, echocardiogram, computed tomography of chest, pulmonary and coronary angiogram, ventilation perfusion scan, sleep studies, etc. Diagnosis of the disease responsible for oxygen desaturation is often easily obtained with the above investigations. For rarer forms of heme and nonheme pigments responsible for cyanosis, we focus our attention towards the drug, toxin, or accidental exposures. Deficiency of nicotinamide adenine dinucleotide hydride (NADH) MetHb reductase system is inherited in autosomal recessive pattern.

Abnormal Hb like HbM that has decreased affinity for oxygen can be diagnosed with the help of electrophoresis.

A practical approach to the etiology of cyanosis has been described by snider et al.

- Obtain a heparinized arterial blood specimen.
- If the sample is dark red and becomes bright red on shaking in air, one should perform blood gas analysis on another specimen to confirm arterial hypoxemia.
- If the specimen obtained is brown and does not change color on shaking in air, the plasma should be allowed to separate.
    - If the plasma is brown, methemalbumin is likely to be present.
    - If the plasma is clear, one should suspect the presence of MetHb or SulfHb.
- A bright red arterial specimen obtained in a patient with generalized blue skin color should lead one to suspect deposition of nonheme pigment in the skin.

Treatment

Deoxyhemoglobin

Treat the underlying cause and give supplemental oxygen to improve the Hb oxygenation.

Methemoglobin

First step in treatment of MetHb is to remove the culprit medication. This often is sufficient in mild cases. Methylene blue is the treatment of choice in severe cases of methemoglobinemia. It accelerates the reduction of MetHb via the nicotinamide adenine dinucleotide phosphate (NADPH) MetHb reductase pathway and it should be given intravenous (IV) at a dose of 1–2 mg/kg for 5 minutes. The maximum effect of methylene blue occurs quickly, at 30 minutes. Additional doses of methylene blue may be given after 1 hour if response is inadequate. Co-oximetry is not helpful in monitoring these patients because it does not have the ability to distinguish between MetHb and methylene blue. High doses (7 mg/kg) can lead to hemolysis and a paradoxical rise in MetHb levels of up to 10%. Less responsive forms of include aniline and dapsone induced MetHb. MetHb can cause hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency too.

Sulfhemoglobin

These patients can show cyanosis at 0.5 g/dL levels of SulfHb. Cyanosis is not responsive to oxygen administration. Patients may be asymptomatic at much higher levels of SulfHb and PaO_2 is usually normal. SulfHb is irreversible and stays till the life span of affected red blood cells, i.e., 120 days. Oxygen should be given to all patients and exchange transfusion has been suggested and tried as a treatment modality in cases that are symptomatic.

SUMMARY

To summarize, testing for presence of clubbing is an integral part of routine examination of all patients. To pick up subtle clubbing early in the disease process may be of huge clinical value as it may lead to curative treatment of cancers. Patients are usually unaware of the presence of changes in their nails and the clinical utility of various grades of clubbing beyond presence or absence of clubbing is uncertain. However, association of clubbing with HOA portends ominous value to clubbing diagnosis as it is mostly associated with malignancies. VEGF, PDGF, and PGE2 in the setting of hypoxemia and malignancies are responsible for most proliferative changes in the clubbed nails. Careful history taking, directed physical examination, and focused investigations often lead the clinicians to the etiological diagnosis of clubbing. Changes of clubbing reverse upon successful treatment of the underlying etiology, but in case of malignancies and progressive disorders, it persists. Knowledge of various tests to pick up early clubbing is important for every clinician and use of digital photographs of fingers is a handy tool to diagnose and measure clubbing in fingers.

Cyanosis is visible on specific body parts when various types of heme and nonheme pigments accumulate in our body beyond normal limits. Some of these pigments such as deoxyhemoglobin and MetHb are normally produced in our body, but they are regularly replaced by oxygenated Hb. Many physiological and pathological states are associated with cyanosis. The clinical examination is now aided by oximetry, ABG analysis, and co-oximetry in finding the cause of cyanosis. Careful history and focused examination gives us the diagnosis in most cases. Treatment of cyanosis revolves around the inciting agent or disease. Oxygen administration helps in most cases, but IV methylene blue injection in MetHb and exchange transfusion in SulfHb may be needed to remove the abnormal pigments.

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CHAPTER

Acute Respiratory Failure

Chitra Mehta

INTRODUCTION

Acute respiratory failure (ARF) is a commonly encountered condition in intensive care unit (ICU) and emergency department (ED). It may be the primary disease, or may be a complication of other conditions like cardiac failure or acute renal insufficiency.

DEFINITION

Acute respiratory failure occurs when the respiratory system fails to meet the oxidative, ventilatory and metabolic demands of the body. There is a failure of gas exchange mechanisms in maintaining adequate oxygen delivery to the tissues, and/or adequate removal of carbon dioxide (CO_2) from the body. Acure respiratory failure is one of the common presentation in emergency department and major cause of morbidity and mortality in ICU setting, its incidence increases with the presence of comorbidities and in the geriatric age group. Hospital mortality has been found to be 30–40% in patients requiring ventilatory support. Mortality also varies according to the etiology. For acute respiratory distress syndrome (ARDS) it is about 40–45%, and for acute exacerbation of chronic obstructive pulmonary disease (COPD) it is around 30%.

CLASSIFICATION

Acute respiratory failure has been divided into four types primarily:

1. *Type I (hypoxemic) respiratory failure*: It is characterized by the arterial oxygen tension [partial pressure of oxygen (PaO_2)] below 60 mm Hg (8.00 kPa) with normal or low arterial CO_2 tension [partial pressure of carbon dioxide ($PaCO_2$)]. This is the most common form of respiratory failure.
2. *Type II (hypercapnic) respiratory failure*: It is characterized by $PaCO_2$ of >45 mm Hg, often accompanied by hypoxemia that gets easily corrected with supplemental oxygen.
3. *Type III (perioperative) respiratory failure*: It specifically occurs in postoperative patients, most commonly secondary to atelectasis, related to low functional residual capacity in the setting of altered chest wall and/or abdominal wall compliance. Both type I and II respiratory failures can occur during this period.
4. *Type IV (shock related) respiratory failure*: This refers to hypoperfusion-induced respiratory failure. It commonly occurs in a hemodynamically unstable patient during the process of resuscitation.

Acute versus Chronic Respiratory Failure

It is also important to differentiate between acute, chronic, and acute on chronic respiratory failures. This is particularly important in type II respiratory failure. Acute hypercapnic respiratory failure develops rapidly over minutes to days with inadequate compensation. This results in pH less than 7.3. On the other hand, chronic hypercapnic respiratory failure develops gradually over days to months, allowing adequate time for renal compensation to take place. So there is a near-normal pH with raised serum bicarbonate levels. Elevated $PaCO_2$ with partial compensation, resulting in pH less than 7.35, characterizes acute-on-chronic ventilatory failure. Other signs such as polycythemia and cor pulmonale may also help in identifying them. Acute and chronic differentiation may be relevant to type I respiratory failure as well. This is important in patients with interstitial lung diseases, and in patients residing at high altitude areas.

Some people consider definition of hypoxemic respiratory failure too simplistic, as it gives no idea about the tissue oxygenation, and overlooks the major determinants of oxygen delivery—cardiac output and hemoglobin level.

PATHOPHYSIOLOGY

Efficacy of the lung is evaluated by its oxygenation and ventilation capacity. PaO_2 reflects oxygenation and $PaCO_2$ reflects ventilation. Alveolar-arterial oxygen gradient ($AaDO_2$)

aids in evaluating oxygenation. It also helps in understanding the pathophysiological mechanisms. $AaDO_2$ can be determined with the help of alveolar gas equation:

$$PaO_2 = FiO_2 \times (P_{atm} - pH_2O) - PaCO_2/R$$

Where, PaO_2 = Alveolar PO_2
FiO_2 = Fraction of inspired oxygen
P_{atm} = Barometric pressure, 760 mm Hg at sea level
pH_2O = Pressure of water vapor at standard temperature, normally 23 mm Hg
$PaCO_2$ = Arterial PCO_2
R = Respiratory quotient (R = 0.8)

The normal value of $AaDO_2$ increases with age and FiO_2. $PaCO_2$ is a function of CO_2 production and alveolar ventilation, as can be seen in following relationship:

$$PaCO_2 = VCO_2 \times k/V_A$$

Where, $PaCO_2$ = partial pressure of CO_2 in arterial blood
VCO_2 = CO_2 production
V_A = Alveolar ventilation
K = constant (0.863)

And

$$V_A = V_T - V_D$$

Where, V_T = Tidal volume and V_D = Dead space volume

So $PaCO_2$ will rise if there is an increased CO_2 production, fall in tidal volume, or an increase in dead space volume.

Respiratory failure may occur as a result of malfunction of any of respiratory components such as airways, parenchyma, chest wall, respiratory muscles (intercostal + diaphragm), and central and peripheral nervous systems.

Hypoxemic Respiratory Failure Type 1

Pathophysiological mechanisms responsible for type I failure are:

- Low FiO_2
- Ventilation/perfusion mismatch (V/Q)
- Shunt
- Diffusion abnormalities
- Hypoventilation
- Venous admixture (low mixed venous oxygen)

Low FiO_2 as a cause of hypoxemia is of importance at high altitude where barometric pressure is low. In clinical practice, one can suspect this, if there is sudden desaturation of a patient receiving supplemental oxygen. Interruption or disconnection of oxygen supply should be ruled out in this condition. Diffusion abnormalities become clinically relevant only if there is a significant decrease in blood transit time in the pulmonary capillary bed, and if there is coexistent V/Q abnormalities.

For all practical purposes, V/Q mismatch and shunt mechanisms are the dominant causes of hypoxemia. Both result in an elevated $AaDO_2$.

Ventilation/Perfusion Mismatch

It is the most common mechanism resulting in hypoxemia. Ideal gas exchange can only exist if V/Q ratio is 1. Normal V/Q ratio is 0.8. A relative decrease in ventilation reduces the ratio, which impairs oxygenation and ventilation. If this ratio becomes near zero, it represents a shunt mechanism. A relative decrease in perfusion results in ratio more than 1, representing increased dead space. Clinically, this becomes important only if the abnormality is quite severe. Response to supplemental oxygen can help in differentiating between V/Q mismatch and shunt.

Shunt

It is the right-to-left shunting of deoxygenated blood, which is responsible for causing hypoxemia. The deoxygenated blood bypasses the gas exchange area and mixes with the oxygenated blood coming from other ventilated alveoli resulting in fall in oxygen content. This may occur in presence of anatomical right-to-left shunts (like atrial septal defect) or may occur in presence of physiological shunting when the V/Q ratio approaches (like collapse, and ARDS). Under normal circumstances also the anatomical shunts are present. This is secondary to admixture of blood from pulmonary circulation with bronchial circulation. It amounts to about 2–3% of shunt. Both anatomical and physiological shunts show poor response to supplemental oxygen.

In addition to above mechanisms, it has been observed that tissue hypoperfusion exacerbates the degree of hypoxia caused by other diseases. This is due to excess oxygen extraction at tissue level, resulting in low mixed venous oxygen saturation. Hypoxia can also occur if there is an increase in abnormal hemoglobin like carboxyhemoglobin or methemoglobin. In this situation, PaO_2 may remain normal but oxygen saturation falls resulting in low arterial oxygen content. Various causes of type I respiratory failure are elicited in **Box 1**.

Hypercapnic Respiratory Failure Type II

This type results when there is an imbalance between ventilatory demand and ventilatory capacity. Excessive increase in load or a drastic fall in capacity may precipitate it. It may also occur when there is coexistent increased load and reduced capacity, though each may be of moderate severity. Pure hypoventilation as a sole cause can be identified by presence of normal $AaDO_2$. Hypercapnia can also occur as a part of hypoxic failure if the gas exchange derangements are quite severe. Causes of hypercapnic respiratory failure are shown in **Box 2**.

BOX 1: Causes of type I respiratory failure.

- *Low FiO_2*: High altitude
- *Airways*: COPD, asthma, postintubation laryngeal edema, mucus plug, bronchiectasis, and vocal cord paralysis
- *Lung parenchyma*: Pulmonary edema, ARDS, pulmonary hemorrhage, lung contusion, pneumonia, alveolar proteinosis, hypersensitivity pneumonitis, transfusion-related lung injury, lung resection, aspiration, and radiation injury
- *Interstitial*: Pulmonary fibrosis and viral or atypical pneumonia
- *Pulmonary vasculature*: Pulmonary veno-occlusive disease, pulmonary embolism, and intracardiac or intrapulmonary shunt
- *Pleural*: Pneumothorax and pleural effusion
- *Chest wall*: Kyphoscoliosis, thoracoplasty, massive obesity, chest wall trauma—flail chest, burns

(ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; FiO_2: fraction of inspired oxygen)

BOX 2: Causes of type II respiratory failure.

- *Respiratory drive* (reduced): Ondine's curse, drug overdose, obesity hypoventilation syndrome, traumatic brain injuries, carotid body resection, and metabolic alkalosis
- *Neural transmission* (reduced)
- *Spinal cord*: Cervical spine injury and tumor
- *Anterior horn cells*: Poliomyelitis and amyotrophic lateral sclerosis
- *Peripheral nerves*: Phrenic nerve injury, Guillain–Barré syndrome, critical illness polyneuropathy, Lyme disease, beriberi, and diphtheria
- *Neuromuscular junction*: Neuromuscular blocking agents, tick paralysis, organophosphorus poisoning, botulism, tetanus, myasthenia gravis, and Lambert–Eaton syndrome
- *Respiratory muscles*: Muscular dystrophy, polymyositis, malnutrition, dyselectrolytemia, and hypothyroidism
- *Chest wall*: Kyphoscoliosis, thoracoplasty, fibrothorax, flail chest, ankylosing spondylitis, and asphyxiating thoracic dystrophy

TABLE 1: Clinical manifestations.

Hypoxic respiratory failure	*Hypercapnic respiratory failure*
Central or peripheral cyanosis	Coma
Tachycardia or bradycardia	Asterixis
Hypertension or hypotension	Headache
Tachypnea accessory muscle use	Somnolence
Diaphoresis	Abdominal paradox (diaphragmatic fatigue)
Altered mentation	Warm extremities with bounding pulses
Anxiety	Myoclonic jerks
Confusion	Papilledema
Lactic acidosis	Slurred speech
Seizures	Signs of airway obstruction

TABLE 2: Berlin definition 2012 of acute respiratory distress syndrome (ARDS).

Timing	Within 1 week of known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities on chest radiograph or chest computed tomographic scan
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload
Oxygenation	
Mild	PaO_2/FiO_2 ratio 200–300 mm Hg with PEEP or CPAP ≥ 5 cmH_2O
Moderate	PaO_2/FiO_2 ratio 101–200 mm Hg with PEEP ≥ 5 cmH_2O
Severe	PaO_2/FiO_2 ratio ≤ 100 mm Hg with PEEP ≥ 5 cmH_2O

(CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen; PEEP: positive end-expiratory pressure)

CLINICAL PRESENTATION

Patients with respiratory failure have a varying clinical presentations. Dyspnea is the hallmark of respiratory failure. Neurological symptoms may also be present. Various clinical presentations are shown in **Table 1**.

DIAGNOSTIC APPROACH

Given the vast differential diagnosis of ARF, it is imperative to obtain an extensive history from the patient. History of fever with chills indicates underlying infection. Sudden onset shortness of breath or chest pain may point toward pulmonary embolism, pneumothorax, or myocardial infarction (if left-sided chest pain). Increased cough and sputum in a smoker suggests acute exacerbation of COPD. Cardiogenic pulmonary edema is associated with chest pain, paroxysmal nocturnal dyspnea, or orthopnea. Presence of sensorimotor abnormalities may suggest neuromuscular respiratory failure. Additional exposure history may help in diagnosing inhalational injury, aspiration, transfusion-related lung injury, hypersensitivity pneumonitis, pneumoconiosis, etc. A focused physical examination of cardiopulmonary system is also necessary.

All patients must have basic investigations including arterial blood gas analysis, chest radiography, electrocardiogram, and routine blood chemistry. A normal $AaDO_2$ gradient indicates hypoventilation as the only cause for respiratory failure. Abnormal hemoglobins can also be picked up in arterial blood gas analyzer with co-oximetry facility. Oxygen requirement gives an idea about the severity of the disease. A chest X-ray may help in making the correct diagnosis. A clear chest X-ray in presence of hypoxia and hypo- or normocapnia points towards pulmonary embolism, shock, or anatomical shunts. A clear chest X-ray in presence of hypercapnia would indicate COPD, asthma, drug overdose, or neuromuscular pathology. Localized shadow may indicate pneumonia or an infarct. Diffuse infiltrates suggest pulmonary edema, atypical pneumonia, pulmonary hemorrhage, or pulmonary fibrosis. ARDS, which is a common cause of type I respiratory failure, has been redefined (**Table 2**).

Some special investigations may be required to substantiate the diagnosis such as computed tomography of chest, echocardiography, serum chemistry such as thyroid profile, calcium, magnesium, phosphorus levels, sputum, and blood cultures, urinalysis, and cardiac biomarkers like troponins. Diagnostic pleural tap should be done if pleural effusion is present. In presence of severe hypoxemia, therapeutic decisions may have to be taken even if the data is incomplete. Decisions can later be revised when additional information is available. In recent times, bedside cardiothoracic ultrasound has been found to be a useful complementary diagnostic tool.

MANAGEMENT

The management of respiratory failure is directed towards its cause, its clinical impact, and patient's underlying status. *Primary aims of treatment are: (1) to ensure adequate oxygenation, (2) to improve respiratory acidosis, (3) to improve*

cardiac output if reduced, (4) to treat the primary condition, and (5) to avoid predictable complications. It is essential to do the airway-breathing-circulation assessment right at the time of presentation.

When encountered in the ED, timely decision for hospitalization should be taken. Clinical features indicating the need for ICU admission are as follows:

- Severe breathlessness
- Poor/deteriorating general condition
- Altered mentation
- Significant comorbidities
- Cyanosis
- Acute onset
- Not able to speak full sentences
- Severe acidosis
- High oxygen requirement
- Hypotension

Supplemental Oxygen

A reasonable goal is to achieve PaO_2 of 65–70 mm Hg with oxygen saturation of >90%. Various devices are used to deliver oxygen. They are divided into low- or high-flow systems, or open or closed systems. This depends upon their capacity to deliver oxygen at sufficient flow rates so as to meet the patient's flow demands. In a low-flow system, lower the oxygen flow, and higher the patients flow requirements, higher the probability of entraining room air leading to lower FiO_2. Examples of low-flow systems are nasal cannula or face mask. Examples of high-flow devices are Venturi masks, face masks with reservoir bag, and resuscitation bag-valve-mask unit. Venturi mask is a fixed performance device ensuring delivery of precise oxygen concentrations from 24% to 60%. These are extremely useful in COPD patients where oxygen saturation has to be carefully titrated so as not to blunt the hypoxic drive of the patients.

Initial choice of the device is dependent on the severity of hypoxemia. A higher FiO_2 of 0.5–1.0 can be achieved with a non-rebreathing face mask with reservoir bag. For FiO_2 requirement of more than 0.7, early institution of mechanical ventilation (MV) should be considered, especially in the presence of hemodynamic instability.

The level of acidosis, which needs to be treated, remains debatable. Recently it has been advocated that pH of more than 7.15 does not require bicarbonate therapy. However, in presence of coexistent cardiac arrhythmias, shock or decreased level of consciousness, secondary to no other obvious cause, pH may need to be increased to around.

In addition to above, optimization of cardiac output and adequate hemoglobin concentration are essential in managing compromised oxygenation state. Intravenous fluids should be infused in a targeted and controlled manner. This is to prevent positive fluid balance, which is a predictor of poor outcome in ICU.

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) therapy maintains a continuous positive airway pressure throughout the respiratory cycle, and is similar to positive end-expiratory pressure (PEEP) of MV. It has been found useful in alleviating hypoxemia by recruiting collapsed alveoli. It has been found beneficial in acute cardiogenic pulmonary edema, postsurgical respiratory failure, and in chest trauma patients. It can be provided either by a face mask or nasal mask or helmet as an interface.

Noninvasive Ventilation

It is defined as a process of delivering positive-pressure ventilation through a noninvasive interface (nasal mask and face mask). It can be delivered through either the modern ventilators or portable noninvasive ventilation (NIV) devices. It has been found to be useful in acute exacerbation of COPD, immunocompromised patient with respiratory failure, acute cardiogenic pulmonary edema, postextubation support, and postoperative respiratory failure. Both NIV and CPAP have proven clinical benefit in above situations. They, however, have been found to have no impact on outcome in patients with ARDS or pneumonia. In fact, therapeutic trial with either of them in these two conditions may actually cause unnecessary delay in intubation. NIV has been found to obviate the need for intubation in >50% of properly selected patients. *Contraindications to NIV* use are:

- Inability to protect airway or clear secretions
- Cardiac or respiratory arrest
- Facial surgery or trauma
- Recent upper airway or esophageal surgery
- High risk of aspiration
- Anticipation of prolonged ventilatory support
- Obtundation except hypercapnic encephalopathy
- Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score > 34
- Initial pH < 7.1
- Excessive secretions
- Upper airway obstruction
- Nonrespiratory organ failure—upper gastrointestinal bleeding and hemodynamic instability
- Facial burns
- Nonacceptance of NIV
- Excessive air leak around the interface

Mechanical Ventilation

Initiation of MV is a clinically based bedside decision. Broad indications for mechanical ventilation are:

- Inadequate oxygenation by noninvasive means
- Increased $PaCO_2$ resulting in obtundation and respiratory muscle fatigue
- Increased work of breathing
- Inability to clear secretions
- High risk of aspiration
- Decreased level of consciousness [Glasgow Coma Scale (GCS) < 8]
- Bulbar dysfunction
- Severe respiratory acidosis

Current initial recommendations for ventilator strategies are:

- FiO_2 = 1.0
- Tidal volume = 8–10 mL/kg
- PEEP = 5
- Mode = volume control

This can be later be modified to following settings:

- Low tidal volume strategy (<6 mL/kg)
- Peak airway pressure < 35 cmH_2O
- Permissive hypercapnia
- Higher levels of PEEP (5–15 cmH_2O)
- Early use of ventilator modes allowing spontaneous respiratory efforts

Additional approaches for improving pulmonary gas exchange are recruitment maneuvers, prone positioning, high frequency ventilation, inverse ratio ventilation, inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO), or extracorporeal CO_2 removal ($ECCO_2R$). None of the above approaches except prone positioning and extracorporeal gas exchange therapy have been found to have unequivocal benefit.

High-flow Oxygen Therapy

It is a technique where heated and humidified oxygen is delivered at high-flow rates (up to 50 L/m) through an especially designed nasal cannula. It can provide FiO_2 of 30–100%. This modality has been found to be associated with an enhanced patient comfort and decreased work of breathing. It acts primarily by generating a low level of PEEP and by reducing the physiological dead space. Its use is now being advocated prior to use of NIV in patients with ARF. It can also be safely used if NIV is contraindicated. All the above-mentioned therapies provide only temporary benefit if the underlying disease is not treated simultaneously.

Definitive Therapy

Appropriate empirical antimicrobial agents should be initiated at first suspicion of underlying pneumonia. Bronchodilators and steroids should be prescribed in presence of asthma or COPD. Adequate humidification and mucolytics should be used for avoiding secretions from becoming tenacious. Diuretics should be started when pulmonary edema or fluid overload are suspected. Intercostal drains should be inserted for pneumothoraces or pleural effusions. Chest physiotherapy should be started timely and early mobilization of the patients should be done.

Type III or postoperative respiratory failure presents usually to the ICU. It has to be managed on similar lines. Various strategies have been suggested to prevent its development such as preoperative optimization of chronic lung diseases, early initiation of lung expansion maneuvers (incentive spirometry and deep breathing exercises), adequate analgesia, and use of CPAP where appropriate.

SUMMARY

Acute respiratory failure is one of the most common conditions encountered in general emergency practice. Timely decision of admission to ICU is a prerequisite to successful treatment. ARF can have wide clinical manifestations ranging from sympathetic overactivity to encephalopathy with somnolence. All patients must have arterial blood gas analysis and chest radiography at the earliest. Supplemental oxygen and assisted ventilation should be initiated while waiting for the ICU shift.

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CHAPTER

Acute Severe Asthma

Bhawana Sharma, Devendra Richhariya

INTRODUCTION

Bronchial asthma (BA) is a chronic respiratory illness which is because of hyper-responsive airways and is mainly characterized by symptoms of wheezing, dyspnea, chest tightness cough, and by variable expiratory airflow limitation. The most important aspect of asthma is that it is very much reversible and variable. Though various phenotypes of asthma such as allergic, nonallergic, late onset, with fixed airflow, and obesity have been identified, but genetic influence and family history still remains very important. Asthma predominantly involves the larger airways. It affects 1–18% of populations in different countries. In India, the estimated prevalence of asthma is 2.05% among those aged >15 years, and a total burden of 18 million asthmatics. The global initiative for asthma has defined asthma as *"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath (SOB), chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation"*.

ACUTE ASTHMA

Exacerbations of asthma are episodes characterized by a progressive increase in symptoms of SOB, cough, wheezing or chest tightness, and progressive decrease in lung function, i.e., they represent a change from the patient's usual status that is sufficient to require a change in treatment.

PATHOPHYSIOLOGY

Pathophysiologic hallmarks of asthma are airways are abnormally filled with eosinophil, lymphocytes, mast cells macrophages, and myofibroblast. Further diameter of airways is reduced due to contraction of smooth muscles, vascular congestions, bronchial wall edema, and thick secretions. *Pathophysiologic changes lead to airflow obstruction and give rise to various clinical manifestations, i.e.,* increased work of breathing, increased airway pressure, decreased in expiratory flow rates, hemodynamic instability, ventilation perfusion mismatch, hypoxemia, hypercarbia, and ventilatory failure due to respiratory muscle fatigue. Continuous airway inflammation and prolonged bronchospasm leads to permanent airway remodeling, fibrosis hyperplasia, hypertrophy of smooth muscle cells, mucous gland hyperplasia and hypersecretion, and angiogenesis. All these changes leads to irreversible loss of lung functions. Stimulus or triggers for acute asthma are acute respiratory viral infections (most common 40–80%) pollution, indoor agents like dust, occupational exposures, vapors, gases, aspirin, β blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs). Cold air exposure, hormonal changes during menstruation, and pregnancy emotional stress also can give rise to acute asthma.

Though the clinical presentation of both the diseases asthma and chronic obstructive pulmonary disease (COPD) is very similar, both present as acute onset dyspnea but there is no histopathological correlation. They have got different involvement at cellular level as cited in the **Table 1**, which is very important for management point of view. Chronic asthma sometimes behaves like COPD and there is now a clinical entity called *asthma–COPD overlap syndrome (ACOS)*. The pathogenesis may be similar to some extent and the Dutch hypothesis though disproved.

TABLE 1: Histopathological changes in asthma and COPD.

Inflammation	*Asthma*	*COPD*
Cells	Mast cells, eosinophil, CD4+ T cells, and macrophages +	Neutrophils, CD8+, T cells, and macrophages+++
Mediators	LTD4, histamine, IL-4, IL-5, and ROS+	LTB4, IL-8, TNF-α, and ROS+++
Effects	All airways, little fibrosis, epithelial shedding	Peripheral airway, lung destruction, fibrosis, and squamous metaplasia
Response to steroids	+++	–

(COPD: chronic obstructive pulmonary disease; IL: interleukin; LTB4: leukotriene B4; LTD4: leukotriene D4; TNF-α: tumor necrosis factor-α)

CLINICAL EVALUATION

History Taking

Breathing difficulty (acute dyspnea) is the most common manifestation with which the patients come to emergency department (ED). It requires several steps for differentiation and the risk stratification of patients presenting with SOB (**Table 2**). There should be methodological approach by the doctors present in ED. A proper history as well as a quick determination of the best management is mandatory. History taking should include:

- Family history of asthma
- Cough—perennial or seasonal/wheezing/smoking history
- Any cardiac disease
- Fever/sputum/hemoptysis/chest pain
- Previous intubation and intensive care unit (ICU) admission
- Chronic use of oral corticosteroid and medication compliance
- Use of short-acting beta2-agonists (SABA), nocturnal awakening, and night symptoms

Clinical Examination

After taking brief history patient needs to be evaluated for severity of symptoms and clinical examination done. Typically, asthma present with dyspnea wheezing and cough. Physical examination includes vital signs (tachycardia and tachypnea) and chest findings (wheezing). Clinical finding must be correlated with possible associated clinical conations (**Table 3**). Clinical examination findings help us to identify the associated comorbid illness like pneumonia pneumothorax, upper airway obstruction due to foreign bodies generally mimic the acute severe asthma and fail to respond to therapy and revisit ED and labeled as "refractory asthma".

Severity of Asthma

The *assessment of severity can be done based on Global Initiative for Asthma (GINA) guidelines*. On physical examination, cyanosis, nasal flaring, use of accessory muscles of respiration leading to intercostal or supraclavicular indrawing, tachycardia, tachypnoea, hypotension, and altered level of consciousness are at higher risk of fatal asthma and need special attention. On auscultation bilateral ronchi can be present. Silent chest without wheezing indicated severe airflow obstruction. Symptoms and finding do not correlate well with severity of symptoms so forced expiratory volume in 1 second (FEV_1) and peak expiratory flow rate (PEFR) are important parameters in categorizing the severity of acute asthma. *The other parameters to classify severity of asthma are summarized in **Flowchart 1***.

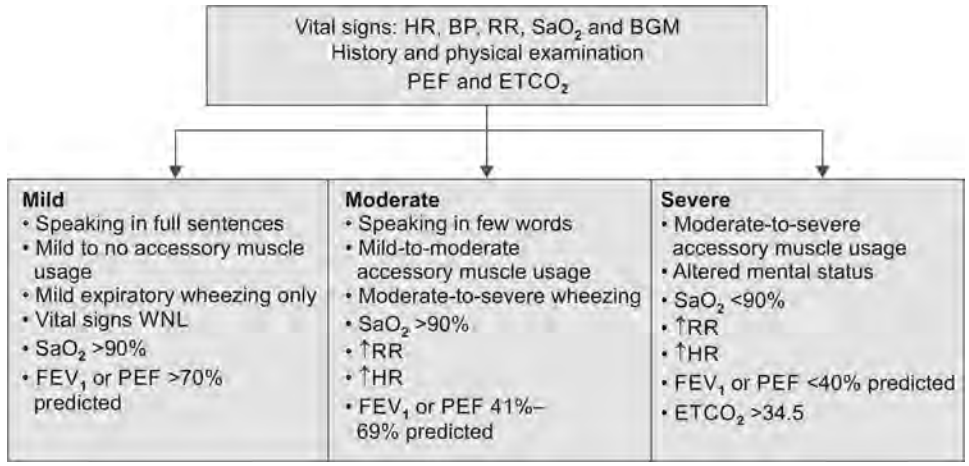
TABLE 2: The differential diagnosis for acute dyspnea.

Head and neck	***Cardiac***	***Miscellaneous***
Angioedema	ACS	Hyperventilation
Anaphylaxis	Decompensated heart failure	Anxiety
Pharyngeal infection	Pulmonary edema (flash)	Pneumomediastinum
Deep neck infection	High output failure	Lung tumor
Foreign body	Cardiomyopathy	Massive pleural effusion
Neck trauma	Arrhythmia	Intra-abdominal process
Pulmonary	Valvular dysfunction	Ascites
COPD exacerbation	Cardiac tamponade	Pregnancy
BA exacerbation	***Toxic/metabolic***	Massive obesity
Pulmonary embolism	Organophosphate	***Neurological***
Pneumothorax	Salicylate	Stroke
Pneumonia	CO poisoning	Neuromuscular disease
ARDS	Toxic ingestion	***Chest wall***
Lung contusion or injury	DKA	Rib fracture
Hemorrhage	Sepsis	Flail chest
	Anemia	

(ACS: acute coronary syndrome; ARDS: acute respiratory distress syndrome; CO: carbon monoxide; DKA: diabetic ketoacidosis)

TABLE 3: Correlating finding with associated condition in acute dyspnea patient.

Breath sound (BS)	***Quality***	***Associated conditions***
Wheeze or rhonchi	Whistling/sibilant and musical	Caused by narrowing of airways, such as in asthma, chronic obstructive pulmonary disease, and foreign body
Stridor	Whistling/sibilant and musical	Epiglottitis, foreign body, laryngeal edema, and croup
Crackles	Cracking/clicking/rattling	Pneumonia, pulmonary edema, interstitial lung disease, and heart failure
Hamman's sign (or mediastinal crunch)	Crunching and rasping	Pneumomediastinum and pneumopericardium
Silent chest	Decreased or no breath sound	Acute severe asthma, bilateral emphysema, or bullous lung
Unilateral decreased BS	Breath sound decreased or absent on one side	• Pleural effusion (dull percussion note) • Pneumothorax (hyper-resonant percussion note)



(BGM: blood glucose monitoring; BP: blood pressure; $ETCO_2$: end-tidal CO_2; FEV_1: forced expiratory volume in 1 second; HR: heart rate; PEF: peak expiratory flow; RR: respiratory rate; SaO_2: arterial oxygen saturation; WNL: within normal limits)

FLOWCHART 1: Categories of severity of asthma.

INVESTIGATIONS

The base line (routine) investigations which needs to be done urgently are vital signs—heart rate (HR), blood pressure (BP), arterial oxygen saturation (SaO_2) and consciousness level [Glasgow Coma Scale (GCS) scoring], chest X-ray, electrocardiogram (ECG), blood glucose monitoring (BGM) [arterial blood gas (ABG)], peak expiratory flow (PEF) and end-tidal CO_2 ($ETCO_2$), total leukocytes count with differential, renal function test (RFT), liver function (LFT), C-reactive protein (CRP), and procalcitonin.

Laboratory Investigations

There is no specific laboratory test to clearly identify the as the etiology of dyspnea. The tests which are done to identify causes like infective exacerbations. The total leukocyte counts with differential count may show high neutrophil counts in bacterial infective exacerbations). RFT and LFT also should be done. Increased CRP and procalcitonin (procalcitonin) can be suggestive of infective exacerbations. Though these may be not accurate in settings of viral and fungal infections or may be falsely high in case of renal failure patients. N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and cardiac enzymes [troponin I/T and creatine phosphokinase-myocardial band (CPK-MB)] may be raised indicating possible cardiac etiology. D-dimer although used for its negative predictive value, can be advised if pulmonary thromboembolism is suspected.

Microbiology

Sputum Gram stain and cultures are advice for all admitted patients. In emergency, first goal is to stabilize the patient then send samples. Sputum for acid-fast bacilli (AFB) should be obtained for nonresponders as per Revised National Tuberculosis Control Programme (RNTCP) guidelines. We can use sputum as well as other respiratory samples such as bronchial washings and endotracheal secretions for microbiological sampling.

Radiology

Chest X-ray is almost mandatory for patients with acute dyspnea. It is not very specific test but is very much sensitive in detecting lung/cardiac causes of dyspnea. Pneumothorax, pneumonia or patchy consolidation or interstitial pattern can be seen on chest X-ray. Signs of heart failure such as bat wing appearance, cardiomegaly, bilateral shadows, and Kerley B lines may be seen. If chest X-ray is not informative, then we may have to ask for chest CT or CT-pulmonary angiography. Two-dimensional (2D) echocardiography and venous Doppler are also advised based on chest X-ray findings. Ultrasound of chest is also useful for detection of pleural pathology.

Electrocardiogram

Electrocardiogram is an essential component in evaluating patients for acute dyspnea. Increased mortality has been linked to adverse cardiovascular events. ECG is very sensitive in detecting cardiac events such as acute coronary syndrome (ACS) and arrhythmias. We can also get ECG changes in pulmonary embolism (S1Q3T3). The ECG changes are COPD because of clockwise rotation of heart, right atrial and ventricular hypertrophy, and P-wave verticalization due to flattening of the diaphragm leading to downward displacement of heart. The ECG changes are:

- S waves in leads I, II, and III;
- R/S ratio less than 1 in leads V5 or V6; and
- The lead I sign—isoelectric P wave, QRS amplitude less than 1.5 mm, and T wave amplitude less than 0.5 mm in lead I.

Arterial Blood Gas Monitoring

Arterial blood gas is a routine practice in emergency for patients of asthma and COPD. Though oxygen saturation (SPO_2) is very sensitive and noninvasive, ABG is more accurate for hypercarbia and hypoxemia status. Sometimes the venous sample may also demonstrate about the CO_2 retention and can be used as surrogate to avoid the painful procedure of arterial puncture.

Ultrasonography

Ultrasonography (USG) is a very specific investigation and can be used if available in emergency to differentiate between cardiac or respiratory causes. It has been found to be very accurate in diagnosing COPD or asthma exacerbation. The protocols which have been used are *lung ultrasound in critically ill (LUCI), bedside lung sonography in emergency (BLUE), and fluid administration limited by sonography (FULL)*.

TREATMENT

Acute asthma is classified as mild, moderate, and severe and the management varies accordingly. Purpose of commonly used drugs such as oxygen therapy, β agonist, anticholinergics, inhaled/systemic intravenous (IV) corticosteroid is to reverse the airflow obstruction by repetitive and continuous administration (**Table 4**).

Oxygen Therapy

Severe repiratory distress, bronchospasm, and respiratory failure is more common with acute severe asthma. Hypoxia may be with hypercapnia (CO_2 narcosis) which is basically type 2 respiratory failure and is found commonly in advance stage COPD and is rare in acute asthma. In asthmatic attack, the patients are hyperventilating so hypocapnia or normocapnia are common. Oxygen therapy is recommended in both type 1 and 2 respiratory failure to relieve severe respiratory distress and prevent tissue hypoxia. Oxygen therapy in case of COPD should be judiciously used to prevent CO_2 retention and respiratory acidosis. SPO_2 to be maintained between 88 and 94%. Pulse oximetry must be used to continuously monitor SPO_2. Blood gas monitoring is very useful in guiding the oxygen therapy and gives information about CO_2 status. The various delivery devices for oxygen comprises of nasal cannula, venturi mask, non-rebreather mask, reservoir cannula, and transtracheal catheter.

TABLE 4: Drugs most commonly used for airway managements.

Beta2-agonists	
• *Short-acting beta2-agonists (SABA)*—salbutamol (albuterol), salmeterol, levosalbutamol, and terbutaline • *Long-acting beta2-agonists (LABA)*—formoterol, salmeterol, indacaterol, and arformoterol	• *Albuterol*—nebulizer 2.5–5 mg every 20 min total three doses then 2.5–10 mg every 1–4 hourly. MDI four to eight puffs every 20 min up to 4 h (90 µg/puffs) • *Injectable terbutaline*—2 *µg/kg over 5 min* then start infusion 5 µg/kg/h • *Epinephrine (α + β agonist)*—1:1,000 (1 mg/mL) 0.5 mg every 20 min by s/c or IM route
Anticholinergics	
• Short-acting anticholinergics (SAMA)—ipratropium and oxitropium • Long-acting anticholinergics (LAMA)—tiotropium, aclidinium, glycopyrronium, and umeclidinium	• *Ipratropium bromide*—nebulizer 0.5 mg every 20 min for three doses then as per requirement • *MDI*—eight puff every 20 min up to 3 h (18 *µg/puffs)*
Combinations (beta2-agonists + anticholinergics)	*Ipratropium + albuterol*
• Short-acting beta2-agonists + anticholinergic • Long-acting beta2-agonist + anticholinergic	• *Nebulizer* 3 mL every 20 min for three doses (nebulizer solution of 3 mL contains 0.5 mg of ipratropium and 2.5 mg of albuterol • *MDI*—eight puffs every 20 min (each puff contains 18 *µg/puffs ipratropium + 90 µg/puffs of albuterol)*
Inhaled corticosteroids (ICS)	
Beclomethasone, budesonide, fluticasone, and mometasone	
Systemic corticosteroids (IV)	
Hydrocortisone, methylprednisolone, and prednisolone	• *Prednisolone*—40–80 mg/day oral in two divided doses 5–10 doses till PEFR reaches 70% of predicted or 1–2 mg/kg/day IV for 5–10 days • *Methylprednisolone*—1 mg/kg IV every 4–6 h
Combination (beta2-agonists + corticosteroids)	
long-acting beta2-agonists + corticosteroids	
Others	
• Methylxanthines—aminophylline, theophylline • Phosphodiesterase-4 (PDE4) inhibitors—roflumilast • Leukotriene receptor antagonists—montelukast and zafirlukast	
• *Mild asthma*—short-acting bronchodilators (SABDs) • *Moderate asthma*—SABDs + oral corticosteroids ± antibiotics • *Severe asthma*—emergency visit and hospitalization, patients may be in respiratory failure	

Inhaled Bronchodilators

In emergency setup it is the most important aspect of therapy for acute bronchospasm. We have various modes of delivery for inhaled bronchodilators. Both nebulizers as well as handheld inhalers can be used in exacerbations. If patient is acidotic, nebulizers preferably should be given by compressed air rather than oxygen (to avoid CO_2 narcosis). In ED, nebulization with either single or dual bronchodilators like salbutamol with ipratropium bromide can be given. Nebulized salbutamol can be given back-to-back till resolution of bronchospasm.

Inhaled/Systemic Corticosteroids

Inhaled as well as systemic corticosteroids are regularly used for acute spasm. It is also considered first line in the emergency management of the acute asthma. *Inhaled corticosteroids like beclomethasone 50–400 μg; budesonide 100, 200, and 400 μg; fluticasone 50–500 μg through nebulization or handheld devices can be used.* Systemic corticosteroids are the main stay of therapy for acute severe spasm in asthma. Both the oral and the parenteral route have same bioavailability. If patient can take oral, parenteral treatment are reserved for patients who cannot take oral medication as there is no major difference between oral and IV with regards to relapse rate, treatment failure, or mortality. Patients during hospitalization can be given oral/IV steroids and once stable should be discharged on oral corticosteroids for 7–14 days. *The equivalent dose: ~20 mg hydrocortisone, ~5 mg prednisolone, ~4 mg methylprednisolone, and ~0.75 mg dexamethasone.* The mode of delivery is mostly in inhaled form, may be through metered dose inhalers, dry powder inhalers or nebulization which have their own pros and cons (**Table 5**).

Theophylline

If bronchospasm persists and the patient is still breathless in spite of adequate steroids and inhaled bronchodilators, we can add parenteral aminophylline after excluding cardiac cause. Because of its high toxicity and drug interaction (with commonly used drugs such as ciprofloxacin, clarithromycin, allopurinol, and phenytoin), it should be maintained within therapeutic range—10–20 μg/mL.

Other Drugs

Intravenous magnesium sulfate, though not supported by the Global Initiative for Obstructive Lung Disease (GOLD) or GINA guidelines, can be given as it has been found to reduce hospital admissions when other drugs had failed to reduce symptoms. It can be given slow IV over 20 minutes in normaly functioning kidneys. *Parenteral terbutaline and intramuscular epinephrine* can also be given in centers with experience of using the drugs. *Heliox (mixture of 80% helium and 20% oxygen)* can also be considered as an adjuvant in the management of severe asthma. For the penetration of drugs such as bronchodilator, anticholinergic, and anti-inflammatory agents, the lower density of helium serves as a better transport modality than room air or oxygen-driven nebulizers.

Antibiotics

Based on local bacterial resistance and stewardship guidelines, antibiotics can be started for patients with history of producing purulent sputum. Change in amount, color, and consistency of sputum leads towards infective exacerbations and antibiotics should be started. Initial empiric treatment should consist of an aminopenicillin, a macrolide, or a tetracycline. If *Pseudomonas* or Enterobacteriaceae is suspected, combination therapy with antipseudomonal antibiotics like piperacillin/tazobactam or imipenem or meropenem plus amikacin or levofloxacin can be given.

STATUS ASTHMATICUS

Status asthmaticus *or acute severe asthma (FEV_1 or PEFR <25% of predicted)* is clinically characterized by hypoxemia and tachypnea. Tachycardia accessory muscle use wheezing impending respiratory arrest and usual dose of bronchodilators and steroid does not improve the clinical conditions.

TABLE 5: Mode of delivery of corticosteroid.

	Advantages	***Disadvantages***
Pressurized metered-dose inhalers (pMDI)	• Compact and portable • Multidose • Quick treatment time • Drug in sealed canister • Inexpensive	• High oropharyngeal deposition • Difficulty in hand mouth coordination • Propellant may cause "cold Freon" effect and affect climate change
Dry powder inhaler (DPI)	• Compact and portable • Quick treatment time • Breath-actuated function removes need for coordination	• Need adequate inhalation flow to dispense • High oropharyngeal deposition • Humidity can cause drug degradation • Patients may be intolerant to additives, e.g., lactose
Nebulizers	• Large doses of drug can be given • Can be used with relaxed tidal breathing • Suitable for young, old, and acutely ill patients • Many drug solutions can be aerosolized	• Bulky cumbersome and expensive • Wasted drug in nebulizer reservoir • Variations in aerosol output performance between models • Time consuming • Need for power source • Regular cleaning and maintenance

Rapid and aggressive treatment is required to prevent the cardiopulmonary arrest. Adjuncts treatment is also required apart from the bronchodilators and early corticosteroid.

Magnesium

Up to 1–2 g IV over 30 minutes. Nebulized magnesium is also added along with aggressive bronchodilators and inhaled corticosteroid therapy and effective in improving the pulmonary functions. Doses for nebulization magnesium sulfate 95 mg in four divided doses, 20 minute apart. Monitor vitals and deep tendon reflexes while using magnesium in any form. Though hypotension and neuromuscular blockade are rare adverse effects.

Admission to Intensive Care Unit

If the patient's condition further deteriorates [persistent respiratory distress, inability to maintain oxygen level above 90%, persistent hypercapnia, abnormal ABG—partial pressure of oxygen (PaO_2) <60 mm Hg and/or partial pressure of carbon dioxide ($PaCO_2$) > 60 mm Hg, alteration of mental status, acute confusion, and drowsiness) even after above said measures then he can be shifted to ICU and noninvasive positive pressure [noninvasive ventilation (NIV)] should be tried.

Noninvasive Ventilation

For patients with respiratory failure, assisted mode of ventilation must be given first trial through noninvasive mode and if patients do not tolerate it or noncooperative then invasive mode of ventilation is applied after endotracheal intubation. NIV assists the patient in taking a breath and helps to maintain adequate oxygen. Noninvasive positive-pressure ventilation (NIPPV) is most popular mode of providing NIV, in combination with continuous positive airway pressure (CPAP) with pressure support ventilation (PSV). It is the treatment of choice for persistent hypercapnic ventilator failure. NIV has proven role in acute exacerbation of chronic obstructive pulmonary disease (AECOPD). However, use of NIV in acute severe asthma has no clear benefit for reduced intubation or mortality.

Mechanical Ventilation

Intubation can be considered in patients with the following:

- *NIV failure*: Worsening of ABG and/or pH in 1–2 hours; lack of improvement in ABG and/or pH after 4 hours
- *Severe acidosis* (pH <7.25) and hypercapnia ($PaCO_2$ > 60 mm Hg)
- *Tachypnea* >35 breaths/minute
- *Other complications*: Metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, and massive pleural effusion

PULMONARY FUNCTION TEST

Pulmonary function test (PFT) is helpful in quantifiable measurement of lung functions. PFT is useful in monitoring the course of the disease which affects either heart or the lung. PFT is also helpful in observing the environmental, occupation, and drug exposure on the lungs. PFT is also necessary as preoperative evaluation, preemployment, and insurance purposes.

SPIROMETRY

Spirometry is the most commonly used test to measure the volume and capacity of the lungs during various breathing manuvre. There are four lung volumes and four lung capacities are desribed. Lung volumes and lung capacities are mesured by spirogram (**Fig. 1**).

Lung Volumes

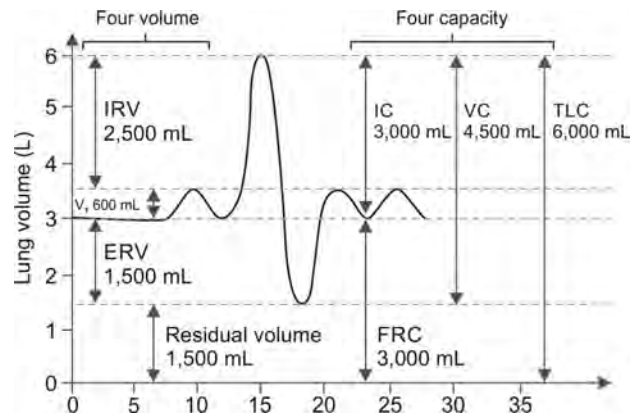
Lung volumes parameters are mesured directly by spirometer. There are four types of lung volumes, i.e., tidal volume (TV), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), and residual volume (RV). Values are small.

Lung Capacities

Values are calculated by combining two or three volumes. There are four types of lung capacities, i.e., vital capacity (VC), inspiratory capacity (IC), total lung capacity (TLC), and functional residual capacity (FRC). Values are large. Spirometry is indicated in diagnostic and monitoring purposes (**Table 6**).

Method

Test is done with the help of spirometer, full inhalation is done by the patient before the exhalation. There shoud be no hesitation, coughing, and glottic closure during exhalation. There should be no evidence of leak and obstruction of the mouth piece. Satisfactory duration of the test is minimun of 6 seconds and up to 15 seconds in patient with airflow obstruction. Good initial effert of exhalation is indicatd by sharp increase in volume from zero in the volume-time curve and well-defined peak in expiratory flow in volume-flow curve (**Figs. 2A** and **B**).

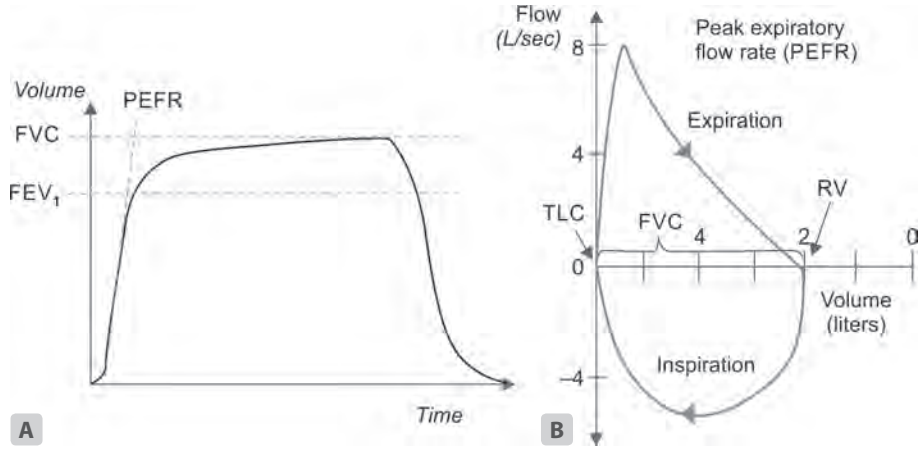


(ERV: expiratory reserve volume; FRC: functional residual capacity; IC: inspiratory capacity; IRV: inspiratory reserve volume; TLC: total lung capacity; VC: vital capacity)

FIG. 1: Spirogram showing volume and capacity of the lungs.

TABLE 6: Indications of spirometry.		
Diagnostic	***Screening and monitoring***	***Others***
• Evaluation of clinical features and abnormal laboratory results • Assessment of effects of disease on the lungs • Spirometry is important in diagnosing and managing the asthma • Obstructive an restrictive pattern of the lung disease only be identified by the spirometry	• Spirometry is used to assess the efficacy of bronchodilators steroid treatment on asthma and heart failure patient • Assessment of course of disease (COPD, ILD, CHF, and neuromuscular disease) • Assessment of occupation exposure of asbestos, diisocyanates, and smoke	• Rehabilitation • Preemployment • As insurance evaluation • Preoperative evaluation

(CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; ILD: Interstitial lung disease)



(FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity)

FIGS. 2A AND B: Normal spirogram. (A) Volume-time curve sharp incraese in volume from zero; (B) Volume-flow curve well-defined peak in expiratory flow.

INTERPRETATION OF THE PULMONARY FUNCTION TEST

Interpretation of PFT is done by comparing the measured value with the reference values (**Table 7**) of the normal healthy and nonsmoker person. Quality of the test is depending on the quality of equipment, good test performance, appropriate reference values, good algorithm for interpretation, and absence of artefact. There are two basic type of lung dysfunction; restrictive and obstructive lung diseases (**Table 8**). *Restrictive pattern* means that lung volume is reduced (reduction in TLC—volume of air in the lung at the end of maximum inhalation) and *airflow obstruction means—reduced FEV_1/VC. Response to bronchodilator therapy—15% change in forced vital capacity (FVC) or FEV_1 after bronchodilator is considered as substantial response.* Abnormal spirogram with obstructive and restrictive pattern is shown in **Figure 3**.

TABLE 7: Normal (reference) values of pulmonary function test.	
Pulmonary function test	***Normal values (95% confidence interval)***
FEV_1	80–120%
FVC	80–120%
Absolute FEV_1/FVC ratio	Within 5% of the predicted ratio
TLC	80–120%
FRC	75–120%
RV	75–120%
DLCO	>60 to <120%

(DLCO: diffusing capacity of carbon monoxide; FEV_1: forced expiratory volume in 1 second; FRC: functional residual capacity; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity)

SUMMARY

Asthma is a common and potentially serious chronic inflammatory disorder of the airways, characterized by variable expiratory flow, airway wall thickening, respiratory symptoms, and exacerbations (flare-ups), which sometimes require hospitalization and may be fatal. Exposure to external agents, such as indoor and outdoor allergens, air pollutants, and respiratory tract infections are the most common causes of the exacerbations of asthma. Severe asthma exacerbations are a major cause of functional impairment and increased risk of

TABLE 8: Types of lung dysfunction.

Obstructive lung diseases	*Restrictive lung disease (parenchymal)*	*Restrictive (extraparenchymal)*
• Asthma • COPD • Bronchiectasis • Cystic fibrosis • Bronchiolitis	• Sarcoidosis • IPF • Pneumoconiosis • Drugs or radiation-induced lung disease	• Neuromuscular (diaphragmatic paralysis, myasthenia gravis, muscular dystrophies, and cervical spine injuries) • Chest wall related-kyphoscoliosis obesity, and ankylosing spondylitis)

(COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis)

morbidity and mortality. Despite optimal guideline-directed treatment and irrespective of underlying disease severity, asthma patients experience exacerbations. Risk for future severe exacerbations in any asthma patients can be estimated by frequent emergency department visits and frequent hospitalization in intensive care unit. It is important to note that prevention of exacerbations of asthma remains a major need in asthma management. Thus, it is important to identify high-risk patients who can progress to severe exacerbations. To prevent and/or decrease exacerbations patient education, written plans of management, control of triggering/risk factors and comorbid conditions, monitoring of asthma control and pulmonary function and optimal pharmacotherapy are important aspects. A better understanding of the pathogenesis of asthma exacerbations is helpful in development of better strategies and novel treatments in view of preventing and treating severe asthma exacerbations.

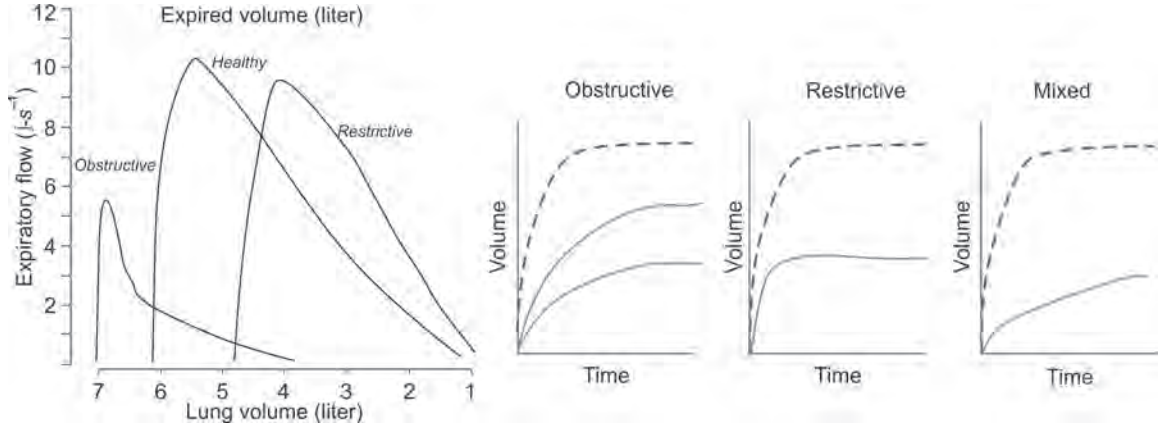


FIG. 3: Abnormal spirometry (abnormal restrictive and obstructive airflow pattern in volume-flow curve and volume-time curve).

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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Chronic Obstructive Pulmonary Disease

86 CHAPTER

Sudha Kansal

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world, but is projected to be the third leading cause of death by 2020. COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality.

RISK FACTORS

Cigarette smoking is the most common cause of COPD. However, airflow limitation is seen in nonsmokers as well though the severity of illness is less in nonsmokers. There is a complex relationship between COPD, smoking, sex, environmental exposure, and genetic predisposition. Poor socioeconomic status and longer life expectancy are also important factors.

Genetic Factors

Severe hereditary alpha 1 deficiency is an uncommon but well-known cause of emphysema, more if there is associated exposure to environmental pollutants. It should be considered in younger emphysema patients with genetic history. In the case of smokers, genetic predisposition increases the development of COPD.

Age and Gender

Age is considered as a risk factor, but it is not clear whether healthy aging leads to COPD or it is the cumulative exposure that leads to changes. Recent studies have shown that the prevalence of COPD is same in male and females, probably due to changing habits of smoking.

Lung Growth and Development

Lung growth during gestation and childhood infections are important factors in determining lung function in adulthood. This was shown in a large study and meta-analysis.

Smoke and Particles Exposure

Cigarette smoking is the most common cause for development of COPD. Passive smoking and smoking during pregnancy is also an important risk factor. Occupational exposure to organic and inorganic dust fumes are under recognized risk factors for COPD. This problem may be even higher in developing countries like India. A high level of air pollution is emerging as an important cause for COPD, especially in patients with preexisting lung and heart disease. This effect is especially important in causing impaired lung growth in children.

Preexisting Obstructive and Airway Disease

Preexisting asthma is an important risk factor for subsequent development of COPD as shown by multiple studies. Chronic bronchitis was associated with mucus hypersecretion and accelerated forced expiratory volume in one second (FEV_1) decline. Young smokers with chronic bronchitis have higher risk for developing COPD.

Infection

Recurrent childhood infections are associated with reduced lung function. Colonization with *Pseudomonas* increases the risk of exacerbation and all cause mortality. Tuberculosis is a risk factor and also an important comorbidity in COPD patients. Patients with human immunodeficiency virus (HIV) are at higher risk of COPD.

PATHOPHYSIOLOGY

It is now understood how the underlying disease process in COPD leads to characteristic symptoms and physiological abnormalities. Predominant changes include small airways, but there is involvement of lung parenchyma and pulmonary vasculature as well. The pathological changes include chronic inflammation, structural changes from repeated injury, repair, and fibrosis.

Airflow Obstruction and Gas Trapping

The reduction in the FEV_1, FEV_1/forced vital capacity (FVC) ratio, and the accelerated decline in FEV_1. Characteristic of

COPD is related to the extent of chronic inflammation, luminal exudates due to hyperplasia of mucus gland, increased number of goblet cells, and fibrosis in the small airways.

Mucus Hypersecretion

A chronic productive cough is due to an increased number of goblet cells and enlarged submucosal glands, both because of chronic airway irritation by cigarette smoke and other noxious agents.

Gas Exchange Abnormalities

Abnormalities in gas exchange result in hypoxemia and hypercapnia, and have several mechanisms in COPD.

Pulmonary Hypertension

Pulmonary hypertension may develop late in the course of COPD. It is mainly due to hypoxic vasoconstriction and chronic inflammatory changes in small pulmonary arteries which results in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure. Pulmonary artery hypertension has shown to relate to the risk of exacerbation.

Systemic Features

Chronic obstructive pulmonary disease is now defined as a systemic disease. Most patients with COPD have concomitant chronic diseases linked to the same risk factors, i.e., smoking, aging, and inactivity, which may have a major impact on health status and survival. Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange. In the circulation, these inflammatory mediators are present which may contribute to skeletal muscle wasting and cachexia, and may initiate or worsen comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, and metabolic syndrome.

INITIAL ASSESSMENT

Clinical Manifestations

The three cardinal symptoms of COPD are chronic cough, sputum production, and dyspnea. Symptoms which are less common include wheezing and chest tightness. History of decreasing level of activity or reduction in the speed of walking should be enquired. Other symptoms include weight loss or weight gain, anxiety, and depression.

History

The past history of exacerbations should be ascertained. A detailed history should include number of exacerbations in the previous year, need for emergency visits, hospitalization, intensive care admissions, need for ventilatory support, and need for glucocorticoids. History of cigarette smoking, exposure to biomass fuel, occupational exposure to organic or inorganic gases or metals should be elicited. The modified Medical Research Council (mMRC) dyspnea grading and COPD assessment test (CAT) scoring system can be used to assess the severity of symptoms. These scales should be used along with history of exacerbation and spirometry to plan management of the patients.

Physical Examination

On clinical examination findings can vary as per severity. Initial findings on chest examination may be normal, prolonged expiration, or wheezing on prolonged expiration. As the disease progresses the breath sounds are reduced, wheezing is heard, and increased anteroposterior (AP) diameter due to hyperinflation is seen. The percussion note will be hyperresonant. There may also be features of respiratory compromise such as difficulty in speaking due to respiratory effort, use of accessory respiratory muscles, and paradoxical chest wall/abdominal movements. There may be signs of right heart failure. It includes edema of the feet, ascites, and elevated jugular venous pressure (JVP). Clubbing is not seen in COPD and should search for other diseases such as lung cancer, bronchiectasis, or interstitial lung disease (ILD). If present, decreased mental status could reflect hypercapnia or hypoxemia and asterixis could indicate CO_2 narcosis.

DIAGNOSIS

Pulmonary function test, particularly spirometry, is the cornerstone for diagnosis of COPD. Besides for diagnosis, it also helps to assess the severity of airflow limitation, response to treatment, and progression of disease.

Spirometry

Chronic obstructive pulmonary disease is typically associated with $FEV_1/FVC < 0.7$ and no or partial post bronchodilator reversibility. FEV_6 obtained by stopping expiratory effort after 6 seconds rather than till complete cessation of airflow is an acceptable representative of FVC.

Lung Volume

In cases of obstructive airway disease including COPD, lung volume study is not routinely required. However, lung volumes help to differentiate the cause of FVC reduction. If reduction of FVC is due to hyperinflation, there is reduction of inspiratory capacity (IC) and vital capacity (VC) with increased total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV). If reduced FVC is due to air trapping without hyperinflation the TLC remains normal. Diffusing capacity of carbon monoxide (DLCO) is done if the symptoms are out of proportion to spirometry abnormality, hypoxemia [peripheral oxygen saturation (SpO_2) < 92%], and if there is a plan for lung reduction surgery. With increasing severity, the DLCO decreases. It is because of reduction in surface area for diffusion due to loss of alveoli in emphysema and loss of capillary bed. DLCO < 55% is an indication for assessment for home oxygen therapy.

*The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has classified COPD based on severity of airflow limitation (**Box 1**).*

Imaging

Chest X-ray

Chest X-ray clues to COPD are hyperinflated lungs, flat diaphragm, dirty lung fields, bullae, increased translucency, and tubular heart. In case of pulmonary hypertension, there is prominence of hilum and relative cardiomegaly.

Computed Tomography Scan

High-resolution computed tomography (HRCT) chest is a very useful test to evaluate the type of emphysema, especially if lung reductive surgery or medical lung reductive surgery (endobronchial valve) is planned. Both inspiratory and expiratory scan should be done to assess for nonemphysematous air trapping.

Additional tests are obtained depending on the clinical evaluation of the patient.

- Cardiac evaluation
- *Alpha-1 antitrypsin levels*: Symptomatic patients with persistent airflow limitation, especially if nonsmoker or minimally smoker, emphysema in young patients (<45 years), predominantly basal involvement, or family history of emphysema. Genotyping can also be done.
- *6-minute walk test*: It is done to assess the functional status of the COPD patients.

BOX 1: GOLD classification of COPD.

In patients with $FEV_1/FVC < 0.70$:

GOLD 1: Mild: $FEV_1 > 80\%$ predicted

GOLD 2: Moderate: $50\% \leq FEV_1 < 80\%$ predicted

GOLD 3: Severe: $30\% \leq FEV_1 < 50\%$ predicted

GOLD 4: Very severe: $FEV_1 < 30\%$ predicted

(COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease)

TREATMENT

General Measures

It is important to educate the patients about smoking cessation, avoidance of exposure to biomass and environmental pollutants, vaccination, inhaler technique, early signs of worsening status, and self-management of worsening. Regular physical therapy and pulmonary rehabilitation also play an important role in symptomatic improvement.

Pharmacologic Therapy

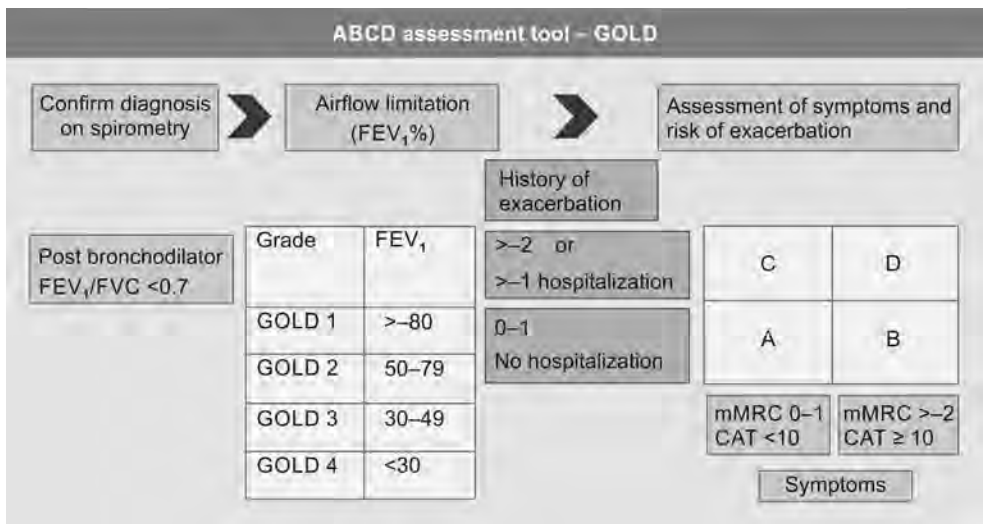
The therapy of COPD is based on risk assessment tool of GOLD guidelines (**Fig. 1**). It depends on severity of symptoms and history of exacerbation and hospitalization. Current recommendation for the management of COPD is described in **Table 1**.

Role of Bronchodilators

- Regular use of inhaled bronchodilators is required to reduce symptoms
- Long-acting beta-agonist—long-acting muscarinic antagonist (LABA-LAMA) combination improves symptoms, lung function, and reduce exacerbation rate.
- LAMA is more effective in reducing exacerbation and hospitalization than LABA
- Tiotropium improves exercise tolerance in pulmonary rehabilitation
- Theophylline has shown to improve symptoms modestly in stable COPD

Long-acting beta-agonists:

- *Salmeterol*: It is available as DPI.
- Dose is one puff (50 µg/inhalation) twice daily
- *Formoterol*: It is available as DPI
- Dose is one to two inhalations (12–24 µg total dose) twice daily
- *Indacaterol*: It is available as DPI (in capsule form)
- Dose is one to two capsule (75 µg/capsule) once daily



(COPD: chronic obstructive pulmonary disease; CAT: chronic assessment test; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council)

FIG. 1: Risk assessment tools for chronic obstructive lung disease.

TABLE 1: Recommendation of COPD treatment.

Group A	Group B	Group C	Group D
• SABA or SAMA • As per need only	• Preferred—LAMA • Alternative—LABA • As per need SABA/SAMA • Choice depends on patient's tolerance • Severe symptoms—LAMA • Can add theophylline	• LAMA • As per need SABA	• Preferred—LAMA • Severe symptoms—LAMA-LABA • LAMA-LABA-ICS • Eosinophil counts > 300/μL • LABA-ICS

(COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting beta2 agonist; SAMA: short-acting muscarinic antagonist)

Long-acting antimuscarinic agents:

- *Tiotropium*: It is available as dry powder inhaler (DPI) and metered-dose inhaler (MDI). DPI is available as 18 μg and MDI as 9 μg. Dose is 18 μg/day.
- *Glycopyrronium*: It is available as DPI or respules for nebulization. Long-term use is found to be safe. DPI is available as 25 and 50 μg and 2 mL respules—25 μg/mL. Dose is twice a day.

Methylxanthines

There is evidence of a modest bronchodilator effect of theophylline compared to placebo in stable COPD. It has a small therapeutic ratio, so the window of safety is less. Higher doses can cause life-threatening atrial or ventricular arrhythmias, seizures irrespective of past history. In therapeutic doses also, it can cause nausea, vomiting, heartburn, headache, insomnia, etc. Being a nonselective phosphodiesterase inhibitor, it has several drug interactions, important being Digitalis and Coumadin.

Oral Glucocorticoids

Long-term steroids have no role in stable COPD. Moreover, it also has a significant side effect such as infection and myopathy.

Phosphodiesterase-4 Inhibitors

They have an anti-inflammatory effect by inhibiting breakdown of cyclic adenosine monophosphate (AMP). Roflumilast has been shown to reduce exacerbation in moderate and severe COPD treated with systemic steroids, severe to very severe COPD, and a history of exacerbation.

Antibiotics

Long-term use of azithromycin has shown to reduce exacerbation as per recent studies, but also increases risk of bacterial resistance, causes prolongation of QT interval.

Role of Mucolytics and Antioxidants (N-acetyl-L-cysteine)

In COPD, patients not receiving steroids regular treatment with mucolytic and N-acetyl-L-cysteine may reduce symptoms and reduce exacerbation. Though dose is not defined due to heterogeneity of studies.

Nonpharmacological Therapy

Other than smoking cessation nonpharmacological measures include vaccination, oxygen therapy, noninvasive ventilation, regular exercise, pulmonary rehabilitation and in severe cases supportive care and end of life hospital care.

Oxygen Therapy

In patients with arterial hypoxemia, partial pressure of arterial oxygen (PaO_2) < 55 mm Hg or SpO_2 < 88% with or without hypercapnia, confirmed twice over 3 weeks period, and long-term oxygen therapy (LTOT) have shown to improve survival and quality of life. Aim should be to keep arterial oxygen saturation (SaO_2) > 89%. If PaO_2 is between 55 and 60 mm Hg or SaO_2 of 88% and evidence of pulmonary arterial hypertension (PAH), LTOT is recommended. Patients should be evaluated after 60–90 days to determine long-term oxygen requirements.

Role of Noninvasive Ventilation at Home

Noninvasive ventilation has shown to have survival benefit and reduced need for hospitalization in patients with COPD and obstructive sleep apnea. A recent multicenter prospective randomized controlled trial (RCT) involving 13 centers included 116 patients with hypercarbia showed that using NIV with oxygen prolonged the time to readmission and death within 12 months significantly.

Pulmonary Rehabilitation

Respiratory therapist or physiotherapist plays a very important role in pulmonary rehabilitation. It involves exercise training, beginning at low level and slowly increasing the intensity to improve exercise capacity and reduce dyspnea. Pursed lip breathing, diaphragmatic breathing, and yogic exercises help to reduce air trapping and reduce work of breathing.

Palliative and End-of-life Issues

Palliative care refers to symptom control and reducing suffering of the patient with minimal invasive intervention. One of the most disabling symptoms in these patients is dyspnea. Opiates chest wall vibration and fan blowing over chest may help to offer relief. NIV may also help.

Bronchoscopy Intervention and Lung Transplant Surgery

Lung volume reduction either bronchoscopic (endobronchial one-way valve, coil, or thermal ablation) or surgical method may be considered in cases of heterogeneous or homogenous emphysema with significant hyperinflation which is refractory to optimum medical treatment. Lung transplant is also recommended for severe disease in specific indications.

ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The GOLD defines an exacerbation of COPD as "an acute worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication". This generally includes an acute change in one or more of the following cardinal symptoms:

- Cough increases in frequency and severity
- Sputum production increases in volume and/or changes character
- Dyspnea increases

Triggers

Respiratory infections are estimated to trigger approximately 70% of COPD exacerbations. Viral and bacterial infections cause most exacerbations, whereas atypical bacteria are a relatively uncommon cause. The remaining 30% are due to environmental pollution, pulmonary embolism, or have an unknown etiology. Some COPD exacerbations of unknown etiology may be related to other medical conditions, such as myocardial ischemia, heart failure, aspiration, or pulmonary embolism.

Risk Factors

According to observational studies, the risk of developing an exacerbation of COPD correlates with:

- Advanced age
- Productive cough
- Long-standing COPD
- Recent history of antibiotic therapy or oral steroids
- COPD-related hospitalization within the previous year
- Need for intensive care unit (ICU) admission in previous year
- Increase in pollution levels in air
- Chronic mucus hypersecretion
- Peripheral blood eosinophil count $>0.34 \times 10^9$ cells per liter
- Comorbidities (e.g., ischemic heart disease, chronic heart failure, or diabetes mellitus)

In general, worsening airflow limitation (FEV_1) is associated with an increasing risk of COPD exacerbation, although airflow limitation alone does not provide a good assessment of exacerbation risk.

Other potential contributors to an increased risk of exacerbations include the following:

- *Severity of COPD and history of prior exacerbations*:
  - *Low risk*: Typically, GOLD 1 or 2 (mild-to-moderate airflow limitation) and/or 0–1 exacerbation per year, no hospitalization due to an exacerbation.
  - *High risk*: Typically, GOLD 3 or 4 (severe or very severe airflow limitation) and/or ≥2 exacerbations per year or ≥1 hospitalization due to an exacerbation.
- *Gastroesophageal reflux disease* (GERD) may be an additional risk factor for COPD exacerbations.
- *Pulmonary hypertension*: Secondary pulmonary hypertension may be an additional risk factor for COPD exacerbations.

Clinical Features

By definition, patients present with the acute onset or worsening of respiratory symptoms, such as dyspnea, cough, and/or sputum production, over several hours to days. For patients with a mild exacerbation (absence of resting dyspnea or respiratory distress, preserved ability to perform activities of daily living), who do not require emergency department treatment, the evaluation may be limited to clinical assessment and possibly pulse oxygen saturation.

Patients who require emergency care, the evaluation should generally include the following:

- Assessment of pulse oxygen saturation
- A chest radiograph to look for pneumonia, pneumothorax, pulmonary edema, and pleural effusion
- Laboratory studies (e.g., complete and differential blood counts, serum electrolytes, and glucose).
- *Arterial blood gas (ABG) analysis*: Pulse oximetry is checked in routine follow-up of COPD patients. However, it does not give information on partial pressure of carbon dioxide (PCO_2). If the patient is stable and SpO_2 is >88%, ABG is not routinely required. However, if acute or chronic respiratory acidosis is suspected or if ventilatory support is anticipated, ABG should be checked.
- *Microbiology*: Sputum Gram stain and culture are often not useful for identifying bacterial infection in patients with COPD exacerbations and are not obtained for most exacerbations of COPD. Sputum culture may be helpful in patients who are strongly suspected of having a bacterial infection but fail to respond to initial antibiotic therapy.

While not necessary in most patients, evaluation for possible respiratory virus infection by polymerase chain reaction (PCR) diagnostic panels have been developed that can detect multiple respiratory viruses (e.g., influenza, adenovirus, parainfluenza virus, respiratory syncytial virus, human metapneumovirus, coronavirus, and rhinovirus) if clinically indicated. Although the exact indications for their use in COPD exacerbations are not clear.

Severity of Exacerbation

- *Mild*: Mild tachypnoea [respiratory rate (RR) 20–30 breaths/min], no accessory muscle of respiration, no altered sensorium, hypoxia easily correctable with low flow oxygen, and no hypercarbia.
- *Moderate*: Tachypnea (RR > 35 breaths/min), accessory muscle of respiration active, no altered sensorium, hypoxia easily correctable with low-flow oxygen (venturi 28–40%), and rise in PCO_2 above usual PCO_2 or between 50 and 60 mm Hg.
- *Severe*: Tachypnoea (RR > 35 breaths/min), accessory muscle of respiration active, altered sensorium present, hypoxia not easily correctable with low-flow oxygen (requiring >40% venturi), rise in PCO_2 above 60 mm Hg, or respiratory acidosis (pH < 7.25).

Patients with COPD who present to the hospital with acute worsening of dyspnea should also be evaluated for potential alternative diagnoses (**Table 2**). The importance of considering alternate diagnoses was illustrated in an autopsy

TABLE 2: Differential diagnosis of the chronic obstructive pulmonary disease (COPD).	
Pneumonia	Chest radiograph, C-reactive protein (CRP), and/or procalcitonin
Pneumothorax	Chest radiograph or ultrasound
Pleural effusion	Chest radiograph or ultrasound
Pulmonary embolism	• D-dimer and/or Doppler sonogram of lower extremities • Chest tomography—pulmonary embolism protocol
Pulmonary edema due to cardiac diseases	Electrocardiogram, cardiac ultrasound, and cardiac enzymes
Arrhythmias—atrial fibrillation/flutter	Electrocardiogram
Fluid overload	Chest X-ray and ultrasound chest to look for B lines

study of 43 patients with COPD who died within 24 hours of admission for a COPD exacerbation. The primary causes of death were heart failure, pneumonia, pulmonary thromboembolism, and COPD in 37, 28, 21, and 14%, respectively. A chest radiograph will differentiate among several of these possibilities. A clear chest radiograph may be a clue to pulmonary embolism, especially when dyspnea and hypoxemia are more prominent than cough or sputum production.

MANAGEMENT OF EXACERBATION

Goals

Goals are reversing airflow limitation with inhaled short-acting bronchodilators and systemic glucocorticoids, treating infection, ensuring adequate oxygenation, and averting intubation and mechanical ventilation. Other goals of care are to prevent complications of immobility, such as thromboembolic and deconditioning, improve nutritional status, and aid patients who smoke with smoking cessation.

Oxygen Therapy

Supplemental oxygen is a critical component of acute therapy. Because of the risk of worsening hypercapnia use controlled oxygen to maintain a pulse SpO_2 of 88–92% or an arterial oxygen tension (PaO_2) of approximately 60. In two small randomized trials, titrating supplemental oxygen to SpO_2 88–92% resulted in a lower mortality compared with high-flow (nontitrated) oxygen. Venturi masks are the preferred means of oxygen delivery because they permit a precise delivered fraction of inspired oxygen (FiO_2). Venturi masks can deliver a FiO_2 of 24, 28, 31, 35, 40, or 60%.

High-flow Nasal Cannula

Provides supplemental oxygen (adjustable FiO_2) at a high-flow rate (up to 60 L/min), resulting in a low level of continuous positive airway pressure. The specific indications for high-flow nasal cannula (HFNC) remain unclear, and robust comparisons of HFNC with NIV in patients with COPD exacerbations are lacking. Requirement for high FiO_2 to correct hypoxemia (> 4 L/min by nasal cannula or 35% by mask) should prompt consideration of pulmonary emboli, acute respiratory distress syndrome, pulmonary edema, or severe pneumonia as the cause of respiratory failure. Hypercapnia is generally well tolerated in patients with chronic hypercarbia. However, mechanical ventilation may be required if hypercapnia is associated with depressed mental status, profound acidemia, hemodynamic instability, or cardiac dysrhythmias.

β-adrenergic Agonist

These medications may be administered via a nebulizer or a MDI with a spacer device and may be combined with a short-acting antimuscarinic agent (e.g., albuterol and levalbuterol). Typical doses of albuterol for this indication are 2.5 mg (diluted to a total of 3 mL) by nebulizer every 1–4 hours as needed, or four to eight puffs (90 μg per puff) by MDI with a spacer every 1–4 hours as needed. Increasing the dose has not been shown to confer an advantage in COPD and can cause side effects. The British Thoracic Society guidelines suggest using air, rather than oxygen-driven bronchodilator nebulization, or limiting oxygen-driven treatments to 6 minutes to prevent risk of hypercarbia due to high-oxygen delivery. Subcutaneous injection of short-acting beta adrenergic agonists (e.g., terbutaline and epinephrine) carries a high risk for inotropic and chronotropic adverse effects, such as arrhythmias or myocardial ischemia, and is almost never used for COPD exacerbations.

Anticholinergic Agents

These agents are typically used with SABA for patients who require hospital-based treatment of a COPD exacerbation. Typical doses of ipratropium in this situation are 500 μg by nebulizer every 4 hours as needed. Alternatively, two to four puffs (18 μg per puff) can be administered by MDI with a spacer every 4 hours as needed.

Systemic Glucocorticoids

Addition of glucocorticoids to above therapies improve symptoms, lung function, and decrease the length of hospital stay. The optimal dose of systemic glucocorticoids for treating a COPD exacerbation is unknown. The GOLD guidelines advise using the equivalent of prednisone 40 mg once daily for the majority of COPD exacerbation. Frequently used regimens range from prednisone 30–60 mg, once daily, to methylprednisolone 60–125 mg, two to four times daily, depending on the severity of the exacerbation.

Antibiotics

Most clinical practice guidelines including the GOLD guidelines recommend antibiotics for patients having a moderate-to-severe COPD exacerbation that requires hospitalization. It has shown to shorten time to recover, reduce risk of early relapse, treatment failure, and hospitalization. The initial antibiotic regimen should target likely bacterial pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in most patients) and take into account local patterns of antibiotic resistance. The choice of

antibiotics is usually a beta lactam, macrolides, or tetracycline; however, in patients with frequent exacerbation anti-*Pseudomonas* or multidrug-resistant organisms cover should be given. Antiviral therapy is recommended for patients with clinical and laboratory evidence of influenza infection. Because of the risk of acute bronchoconstriction with inhalation of zanamivir, oseltamivir is preferred unless local resistance patterns suggest a likelihood of oseltamivir-resistant influenza.

Therapy without Documented Evidence

Mucoactive agents, methylxanthines, and mechanical techniques to augment sputum clearance have not been shown to confer benefit for patients with a COPD exacerbation.

Chest Physiotherapy

Mechanical techniques to augment sputum clearance, such as directed coughing, chest physiotherapy with percussion and vibration, intermittent positive pressure breathing, and postural drainage have not been shown to be beneficial in COPD and may provoke bronchoconstriction.

Supportive Care

Supportive care for patients hospitalized with an exacerbation of COPD may include one or more of the following therapies:

- *Cigarette smoking cessation*: Hospitalization may provide an opportunity for patients to move towards cigarette smoking cessation.
- *Thromboprophylaxis*: Hospitalization for exacerbations of COPD increases the risk for deep venous thrombosis and pulmonary embolism.
- *Nutritional support*: Electrolyte balance—keep a close watch on electrolytes, especially potassium levels.

TRIAGE TO HOME OR HOSPITAL

An important step in the initial evaluation is to determine whether the patient needs hospitalization or can be safely managed at home. More than 80% of exacerbations of COPD can be managed on an outpatient basis, sometimes after initial treatment in the outpatient department (OPD) or emergency department. *Criteria that might lead to a decision to hospitalize the patient have been proposed in the GOLD guidelines and include:*

- Inadequate response to outpatient or emergency department management
- Onset of new signs (e.g., cyanosis, altered mental status, and peripheral edema)
- Marked increase in intensity of symptoms over baseline increased oxygen
- Sever hemodynamic instability
- Altered or worsening of sensorium
- Worsening hypoxemia (PaO_2 < 40 mm Hg) or (pH < 7.25) despite NIV
- Need for invasive mechanical ventilation
- Underlying COPD (e.g., $FEV_1 \leq 50\%$ of predicted)
- History of frequent exacerbations or prior hospitalization for exacerbations
- Serious comorbidities including pneumonia, cardiac arrhythmia, heart failure, diabetes mellitus, renal failure, or liver failure
- Frailty
- Insufficient home support

If the exacerbation appears life-threatening or if there are indications for ventilatory support (e.g., hypoxemic or hypercapnic respiratory failure), the patient should be admitted to the ICU as quickly as possible.

NONINVASIVE VENTILATION

Noninvasive ventilation (also known as noninvasive positive pressure ventilation or NPPV) refers to mechanical ventilation delivered through a noninvasive interface, such as a face mask, nasal mask, or nasal prongs. NIV has shown a success rate of 80–85% in acute exacerbation of COPD. NIV has shown to improve hypercarbia, hypoxemia, reduce work of breathing, and dyspnea. It has shown to reduce mortality, intubation rate, length of hospital stay, and risk of ventilator-associated pneumonia (VAP).

Position statement of the Indian Society of Critical Care Medicine (ISCCM) also recommends use of NIV in COPD patients with acute on chronic respiratory acidosis (pH 7.25–7.35) and acute exacerbation of COPD (PCO_2 > 45 and pH < 7.25) unless immediate intubation is required.

Most commonly, NIV is initiated in the emergency department, ICU, or a specialized respiratory unit to enable close monitoring.

The optimal initial mode and settings for NIV have not been established. A reasonable approach is to initiate NIV in a spontaneously triggered mode with a backup RR, an inspiratory pressure of 8–12 cmH_2O, and an expiratory pressure of 3–5 cmH_2O. The inspiratory pressure is gradually increased as needed to achieve alleviation of dyspnea and good patient-ventilator synchrony. Expiratory positive airway pressure (EPAP) is slowly increased if there is ineffective triggering. It is very important that these patients are explained the procedure properly to improve compliance with the use and monitored closely for any deterioration. It is labor intensive. In case of failure, that is if the patient is not improving in 2–4 hours or any deterioration, you should immediately intubate these patients.

MECHANICAL VENTILATION

Indications of Mechanical Ventilation

The primary objectives include supporting oxygenation and ventilation, minimizing the work of breathing, reverting muscle fatigue, and avoiding dynamic hyperinflation (DHI).

- Cardiorespiratory arrest
- Failure of NIV or unable to tolerate NIV
- Severe dyspnea with clinical signs of respiratory muscle fatigue
- Increased work of breathing, not improving with NIV
- Respiratory acidosis [arterial pH ≤ 7.35 and arterial tension of carbon dioxide ($PaCO_2$) ≥ 45 mm Hg (≥6 kPa)]
- Life-threatening hypoxemia
- Worsening sensorium
- Hemodynamic instability and life-threatening asthma
- Unable to clear secretion and recurrent vomiting

For patients who require mechanical ventilation for acute respiratory failure complicating COPD, volume-targeted modes of ventilation should be preferred over pressure

support or pressure-limited modes of ventilation. Among the volume-targeted modes, choose assist control ventilation (ACV). Synchronized intermittent mandatory ventilation with pressure support ventilation (SIMV/PSV) may be used if ACV results in hyperventilation.

Endotracheal Intubation and Ventilation

Endotracheal intubation should be performed with utmost care to avoid DHI in these patients. It is important not to overventilate during bag-mask ventilation. The rate of bag-mask should be 10–12/min with adequate time for expiration. Sometimes patients develop hypotension or bradycardia during intubation. To prevent this it is advisable to give a fluid bolus before giving sedatives and reduce the rate of bagging further. If no contraindication, give ketamine and midazolam as inducing agents.

Initiate mechanical ventilation with the following initial settings for each mode:

- *Assist control mode:* For patients in whom ACV is chosen as the initial mode of ventilation, use the following settings:
  - FiO_2 to maintain the oxygen saturation of hemoglobin (SO_2) >92%
  - *Tidal volume*: 6–8 mL/kg
  - *Ventilator rate*: 10–16 breaths/min (target minute ventilation 115 mL/kg)
  - *Positive end-expiratory pressure (PEEP)*: 5–10 cmH_2O
  - *Inspiratory flow: 60 L/min. Aim inspiratory*: expiratory (I:E) 1:3 or more
  - *Trigger sensitivity*: –1 to –2 cmH_2O when pressure triggering is used or 2 L/min when flow triggering is used
- *Synchronized intermittent mandatory ventilation/ pressure support ventilation*: Usually less used for short-term ventilation. If chosen, use similar settings to ACV with the addition of pressure support (5–10 cmH_2O) for spontaneous breaths taken by the patient above the set rate. The pressure support can be subsequently increased as needed for patient comfort.
- *Pressure-limited ventilation*: Although rarely chosen as an initial mode of ventilation. Set the inspiratory pressure to target a tidal volume of 4–8 mL/kg and an I:E ratio of no less than 1:3. The FiO_2, ventilator rate, applied PEEP, flow settings, and trigger sensitivity are similar to those of ACV.
- *Pressure support volume*: Usually used as a weaning mode. Titrate pressure support to keep RR < 30 breaths/min.

Patients with COPD will often have higher than expected minute ventilation requirements and increased carbon dioxide retention, which typically improves over the patient's course.

Subsequent adjustments should be made based upon the patient's clinical status, comfort level, gas exchange, and propensity for developing *DHI. Intrinsic PEEP (also known as auto-PEEP)* is common in patients with COPD who are mechanically ventilated, due to a high prevalence of spontaneous or ventilator-induced DHI. Auto-PEEP can result in patient-ventilator dyssynchrony, increased work of breathing, barotrauma, cardiovascular collapse, and even death. The prevention and treatment of DHI is primarily achieved through a reduction in RR and/or or tidal volume, raising the inspiratory flow rate, the application of extrinsic PEEP, and treating underlying airflow obstruction (if present) with bronchodilators and glucocorticoids. Patients should receive adequate sedation and analgesia during ventilation. Narcotic (morphine or fentanyl) infusion plus midazolam infusion should be given. There is some data on use of midazolam causing delirium and some advice to use dexmedetomidine instead. Use of muscle relaxants should be minimized.

Patients should be aggressively treated with bronchodilators, glucocorticoids, and antibiotics. Major complications of mechanical ventilation include barotrauma, volutrauma, risk of VAP, and prolonged ventilation. It is recommended that the patient should be ventilated for 48 hours and if there is no major pneumonia and hemodynamic instability, the patient can be extubated to NIV. NIV has shown to improve the success of extubation and reduce the need for reintubation.

CRITERIA FOR DISCHARGE AND ADVICE

- Check all clinical and laboratory data
- Plan treatment advice and explain the plan
- Check inhaler technique. Assess need for oxygen and NIV
- Remember to give treatment for comorbid conditions
- Advice for early (4 weeks) and late (12 weeks) follow-up
- Reinforce smoking quitting

FOLLOW-UP ASSESSMENT

- Take detailed history including smoking history and examination
- On each follow-up check inhaler technique
- Perform spirometry with post bronchodilator study at least yearly
- Assess exercise tolerance. 6-minute walk test is useful to assess prognosis
- Assess health status
- Assessment of muscle strength and lower limb strength
- Check for vaccination
- Self-management plan for worsening symptoms and exacerbation should be given

PREVENTION

Smoking Cessation

Smoking cessation is the key to prevent progression of COPD. If effective resources and time is given, success rate is high approaching 25%. Use of nicotine replacement products such as nicotine gum, chewing gum, inhaler, transdermal patch, and pharmacotherapy may help to achieve long-term abstinence. However in case of recent myocardial infarction or stroke, nicotine replacement should only be started after 2 weeks. Use of E-cigarettes to aid cessation of smoking is controversial.

Vaccination

- *Influenza vaccine*: It is shown to reduce serious illness and death in COPD patients. Risk of reduced exacerbation

was seen by some studies. Either killed or live inactivated vaccines can be given.

- *Pneumococcal vaccine*: The 23-valent pneumococcal polysaccharide vaccine (PPSV23) and conjugate 13-valent pneumococcal conjugate vaccine (PCV13) has been recommended for all patients > 65 years of age. PPSV23 is also recommended for younger COPD with comorbidities like chronic heart or lung disease. PPSV23 has been shown to reduce the incidence of community-acquired pneumonia (CAP) in COPD patients < 65 years, FEV_1 < 40% predicted and associated comorbidities. PCV13 was shown to reduce vaccine-type CAP (45.6%) and vaccine-type pneumococcal disease by 75%.

PROGNOSIS

Exacerbations of COPD are associated with increased mortality. Even if the COPD exacerbation resolves, many patients never return to their baseline level of health.

Palliative Care

Given the high 1-year mortality rate after hospitalization for a COPD exacerbation, it may be appropriate to consider a palliative care referral during or shortly after a hospitalization for COPD. Palliative care assessment can help explore the patient's understanding of their illness and prognosis, assess and manage symptoms, discuss the patient's goals of care and advance care planning, and help plan end-of-life care.

SUMMARY

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that makes it difficult to empty air out of the lungs. This difficulty in emptying air out of the lungs (airflow obstruction) can lead to shortness of breath or feeling tired because patient working harder to breathe. COPD is a term that is used to include chronic bronchitis, emphysema, or a combination of both conditions. Asthma is also a disease where it is difficult to empty the air out of the lungs, but asthma is not included in the definition of COPD. It is not uncommon, however, for a patient with COPD to also have some degree of asthma. The first and most important aspect of management in smokers is to stop smoking. Medications are usually prescribed to widen the airways (bronchodilators), reduce swelling in the airways (anti-inflammatory drugs, such as steroids), and/or treat infection (antibiotics). Surgical procedures such as lung volume reduction surgery or lung transplantation may be helpful for some cases of COPD. Pulmonary rehabilitation programs offer supervised exercise and education for those with breathing problems.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Pneumonia

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INTRODUCTION

The word "pneumonia" almost always refers to a syndrome which is due to acute infection usually bacterial (may also be other microorganism), characterized by clinical and/or radiographic signs of consolidation of a part or parts of one or both lungs. Pneumonitis is sometimes used as a synonym for pneumonia, particularly when inflammation of lung has noninfectious etiology such as chemical, radiation, or interstitial. Pneumonia can be classified as anatomical and etiological given in (**Table 1**). Here we will provide a glimpse of acute pneumonia in adults. The most common causes of pneumonia with acute presentation are viruses, pneumococcus, and mycoplasma. In India, apart from those we can also get *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, or others as a causative agent for community-acquired pneumonia (CAP).

TABLE 1: Classification of pneumonia.

Basis	*Types*
Anatomical location	• Lobar • Multilobar • Segmental • Subsegmental • Bronchopneumonia
Etiological (microbiological)	• Bacterial • Viral • Fungal • Parasitic • Chemical (e.g., lipoid) • Physical (ionizing)
Empiricist's	• Community-acquired pneumonia (CAP) • Hospital-acquired pneumonia (HAP) or nosocomial pneumonia • Ventilator-associated pneumonia (VAP) • Aspiration pneumonia • Immunocompromised host pneumonia
Behaviorist's	• Easy pneumonia (responds to early treatment) • Difficult pneumonia (fails to do so)
Clinician's perspective	• Typical pneumonia • Atypical pneumonia

CLASSIFICATION OF PNEUMONIA

The main challenge in the emergency department (ED) for emergency physician is identifying the cause of the infection for pneumonia so that appropriate antibiotic treatment can be started at earliest apart from making the diagnosis of pneumonia. Patients with higher risk of mortality (i.e., hospitalized inpatients) are most beneficial with this strategy. At the time of the ED assessment, the initial therapy with antibiotics is empiric because microbiological testing results are not available. Thus, it is important to classify pneumonia to facilitate the decision-making process with regard to the institution of empiric antibiotics. *The traditional classification of pneumonia expressed as the terminology of typical or atypical pneumonia*. The *typical pneumonia* most commonly caused by *Streptococcus pneumoniae*, and clinically presents as high fever, rigors, cough with rust-colored sputum, and laboratory findings of leukocytosis. Microbiology revealed gram-positive encapsulated diplococci. The classic chest radiograph [chest X-ray (CXR)] appearance in this setting is lobar consolidation. *Streptococcus pneumoniae* is responsible for approximately 60% of CAP. The clinical presentation of *atypical pneumonia* is more gradual onset, dry cough, in healthy and ambulatory individuals. Often no organisms identified on microbiology on Gram stain because most commonly they did not have cell walls. The CXR appearance, more often an interstitial pattern. *Mycoplasma, Legionella,* and *Chlamydophila* are the most commonly described atypical organisms. The main challenge in classifying the pneumonia in typical and atypical is that in clinical practice the overlapping of presentations of these infections whereby a pneumococcal infection may present with an interstitial pattern on CXR and atypical clinical symptoms and vice versa.

So, in ED a more practical classification of pneumonia is needed to implement in which environmental contact combined with host factors is considered, so that likely offending agent can be identified. The pneumonia can be

classified broadly into four categories: CAP; hospital-acquired pneumonia (HAP); healthcare-associated pneumonia (HCAP); and ventilator-associated pneumonia (VAP). This practical classification of pneumonia is helpful for the emergency physician in implementing the appropriate empiric treatment. Thus, emergency physician should focus not only on the symptoms of pneumonia but also take history about setting in which the pneumonia is acquired, any recent travel or animal exposures along with any host risk factors that could predispose to certain types of infection and also predict patient outcome.

Community-acquired pneumonia is defined as an acute infection of the pulmonary parenchyma, contracted outside the hospital, with clinical symptoms of pneumonia along with the presence of an infiltrate on CXR. The diagnosis of CAP requires that a patient should not be hospitalized or in a nursing home in the previous 14 days. *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydophila* species, and viruses are the most common pathogens implicated in the development of CAP. A new respiratory infection that develops after >48 hours of hospital admission is HAP. Another group of patients in which repeated or multiple hospitalization is required includes patients undergoing dialysis or chemotherapy, chronic wound care or home intravenous antibiotics care, the immunocompromised patient population, and patients from nursing home facilities, so parenchymal infections in these patients hospitalized for 2 or more days in the previous 90 days is termed as HCAP. If pneumonia that is diagnosed >48 hours of patient intubation and mechanical ventilation in the intensive care unit (ICU) is termed as VAP. Schematic view of this classification of pneumonia and the most common pathogenic organisms associated with infection is provided in **Figure 1**. Predominately gram-negative bacteria are responsible for the latter three classes (HAP, VAP, and HCAP). Acinetobacter is a pathogen associated with VAP specifically, and particularly higher morbidity and mortality is seen with the three encapsulated bacteria (*S. pneumoniae*, *Klebsiella*, and *H. influenzae*) infections.

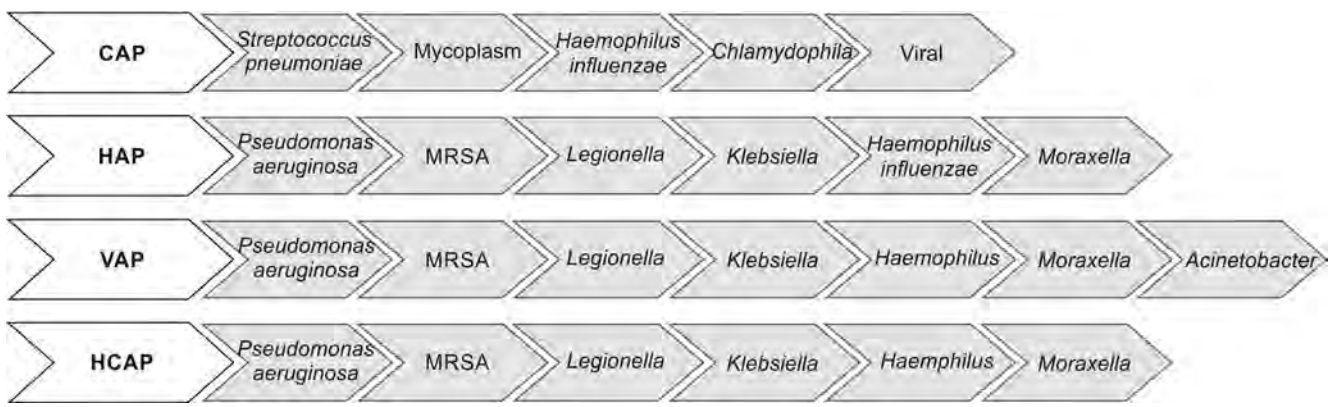
Patient suffering from chronic illness such as lung, heart, or kidney disease, sickle cell anemia, or diabetes having greatest risk of pneumococcal pneumonia. *Klebsiella*, *Legionella*, and *methicillin-resistant Staphylococcus aureus* (MRSA) infections are associated with high mortality. The clinical symptoms of pneumonia caused by various agents are often overlap so approach of antibiotic treatment of pneumonia in the ED is mostly empiric. The typical cardiovascular reaction to fever is tachycardia. Certain pneumonias due to *Legionella*, *Mycoplasma*, and tularemia may be associated with fever and relative bradycardia (Faget sign). Yellow fever, typhoid fever, brucellosis, and Colorado tick fever are the other infections associated with this clinical sign.

PATHOPHYSIOLOGY

Pneumonia is an alveolar infection that occurs due to defective and compromise innate immune system, and lower airway and alveoli unable to clear a pathogen from the respiratory tract. Lung parenchyma further damaged by local inflammatory factors and cytokines and lead to systemic inflammation, which causes secondary symptoms such as fever, chills, and fatigue. Due to the inflammatory response at histologic level, red and grey hepatization of lung tissues and congestion occurs and may resolve with minimal fibrosis. Mechanics and physiology of the lung also altered, decreased compliance of the lung and shunt occurs due to pus in the parenchyma, which increases the work of breathing and worsens hypoxemia and tachypnea—the most important bedside clinical features of severe pneumonia for emergency physicians. All ages group across the spectrum of health are affected by CAP. Specific patient subgroups are affected by certain organisms. Any condition like cigarette smoking causes risk of decreased mucociliary clearance and cough, conditions such as cerebral vascular accidents, esophageal disorders, and neuromuscular disorders lead to aspiration. Pneumonia is difficult to recognize in old age and dehydration, underlying cardiopulmonary disease, or structural lung disease.

CLINICAL EVALUATION

For typical pneumonias, cough, fever, and chest pain are the common presentation with which the patients come to the ED. Cough may be with expectoration whitish to greenish; rarely patients can have hemoptysis. Mucopurulent sputum



(CAP: community-acquired pneumonia; ED: emergency department; HAP: hospital-acquired pneumonia; HCAP: healthcare-associated pneumonia; MRSA: methicillin-resistant *Staphylococcus aureus*; VAP: ventilator-associated pneumonia)

FIG. 1: Practical classification of pneumonia for ED. (Viral includes influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza).

is mostly found with bacterial pneumonia. Patients may present only with high-grade sudden onset of fever, which is continuous, but many a times patients have already taken antipyretics for that. Chest pain can be pleuritic or dull aching in nature. Atypical presentation may also occur such as poor oral uptake, nausea, vomiting, diarrhea, change of mental status, or disorientation. This is more common in elderly patients. For clinician's perspective and management point of view in emergency it is very important to distinguish between atypical and atypical pneumonia (**Table 2**). Most of the time it is radiologically decided in Triage whether, it is typical and or atypical pneumonia. This is very important to differentiate between them and to decide about antibiotics and to add other supportive medicine. On general physical examination the patients are febrile with tachycardia and tachypnea. Sometimes relative bradycardia is also found in atypical pneumonia with *Mycoplasma, Legionella, Chlamydia psittaci, Francisella tularensis,* and *Mycoplasma pneumoniae*.

There are a few signs which can indicate serious illness or severe pneumonia such as cyanosis, nasal flaring, use of accessory muscles of respiration leading to intercostal or supraclavicular indrawing, respiratory rate >30 breaths/minute, heart rate >125 bpm, hypotension, and altered level of consciousness. In emergency, it is very important to detect pneumonia clinically and till X-ray and CT chest is done. Antibiotics first dose (to hit early and hard) can be given empirically. Though in modern era the medical science is more and more inclined towards investigations, but clinical examination and history taking is always very important either in emergency or in outpatient department (OPD). The important clinical signs the can give clue for consolidation in lung (may be absent):

- *Inspection*: While examining the respiratory system properly we may get decreased movement and tachypnea.
- *Palpation*: Tactile vocal fremitus (TVF) which is basically an increased vibration felt from the examining clinician's hand when patient is asked to say repeatedly sound like "*ek-do-teen*". It is very important to compare symmetrical areas on both side of chest. This is due to increased sound conduction at the consolidation side/lobe.
- *Percussion*: Dull note can be elicited if there is large lobar consolidation.
- *Auscultation*: Crackles or crepitation are most common findings in pneumonia. If lobar consolidation is there on auscultation with stethoscope, we may get:
  - Bronchial breath sound—harsh high-pitched inspiratory and expiratory sounds with a clear pause between them and has distinctive character
  - Vocal fremitus—audible TVF
  - Whispering pectoriloquy—whispered voice clearly transmitted to chest wall
  - Bronchophony—spoken voice is unduly loud and intense
  - Egophony—spoken voice has nasal quality like "bleating of goat"

TABLE 2: Differentiating features of typical and atypical pneumonia.

	Typical pneumonia	***Atypical pneumonia***
Microorganism	Mostly bacterial may be virus	Viral bacterial fungal protozoal
Signs and symptoms	Fever cough may be present and bulk sputum with productive cough	Fever, headache, sore throat, and upper respiratory tract also involved. Sweating and myalgia are common. Sputum is mild or absent produces nonproductive cough
Lab parameters	Raised WBC, ESR, CRP, and procalcitonin	ESR and CRP may be raised rest may be normal
Aggravating factors	Nonspecific	Air-conditioned environment, especially air-condition are not maintained
Presence of extrapulmonary symptoms and hypoxia	Rare	Yes
Treatment	Mainly antibiotics	To be given as per cause and other supportive management

(CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell)

DIAGNOSTIC APPROACH

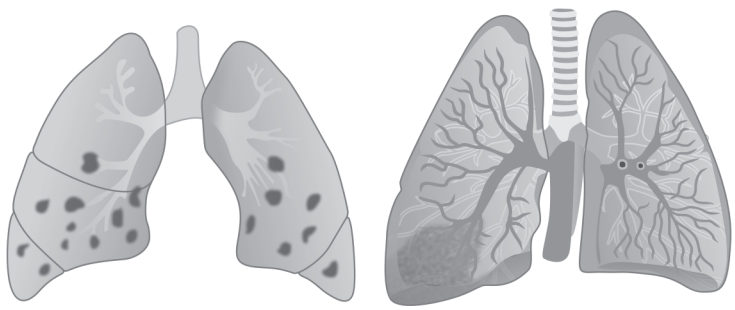
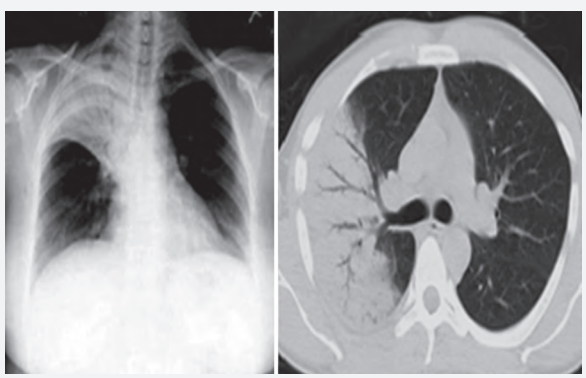
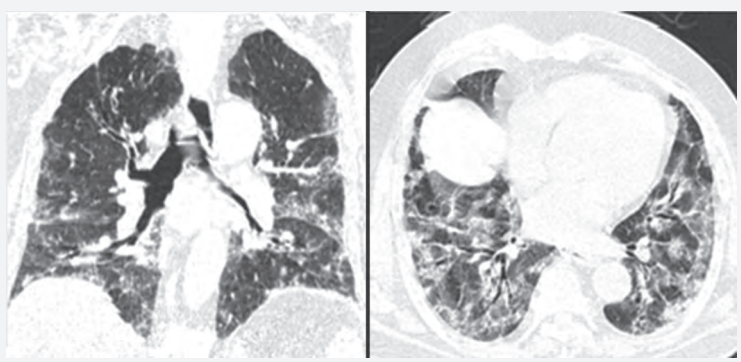
Radiology

Chest X-ray is always advisable for patients with clinical suspicion of pneumonia. We most commonly see the patchy consolidation mainly confined to the lobes with air bronchogram or interstitial infiltrates as nonhomogeneous opacity and or cavity. If CXR is not informative, then we may have to ask for chest CT to rule out mass, effusion, cavity, etc. Computed tomography, i.e., CT chest is only advisable in case of nonresolving pneumonia or clinical worsening. Radiology either CT or X-ray may be helpful in differentiating between typical and atypical pneumonia (**Table 3**). Ultrasound of chest is also useful for detection of pleural effusion or pneumonia with parapneumonic effusion.

Microbiology

Sputum Gram stain and cultures are advice for all admitted patients. The sputum Gram stain is very useful for directing the choice of initial therapy but needs to be performed on a good quality sample and by a skilled microbiologist. The Infectious Diseases Society of America (IDSA) now recommends sputum and blood culture in patients with severe disease as well as in all inpatients who is on empirically treatment for MRSA or *Pseudomonas aeruginosa*. Sputum for acid-fast bacilli (AFB) should be obtained for nonresponders as per Revised National Tuberculosis Control Programme (RNTCP) guidelines. US Food and Drug Administration (FDA) has also approved some newer test that include polymerase chain reaction (PCR) (multiplex PCR) for detecting atypical organism such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* as well as 14 respiratory tract viruses. We can use it for sputum as well

TABLE 3: Radiologic differentiating features of typical and atypical pneumonia.

	Radiologic features of typical pneumonia	***Radiologic features of atypical pneumonia***
Features	• Consolidation • Typical air bronchogram • Bronchopulmonary segment. • May be lobar or multilobar infiltration not seen in perihilar region and localized centrally within the lobes and not toward the periphery. Any lobes can be affected	Often reflects a primary infection before features of atypical pneumonia develops. This phase is also called occult pneumonia. Infiltration begins in peripheral region and spread to periphery and not restricted to lobes. Lower lobes are predominantly affected. However other lobes are also involved. There may be ground glass opacities and interstitial shadow
Schematic presentation		
X-ray/CT		

as for other respiratory samples such as bronchial washings and endotracheal secretions. These tests are rapid, sensitive, and specific.

Hematological

Total and differential leukocyte count (TLC and DLC) is of great value in dealing with pneumonia patients. In bacterial pneumonia, it is usually raised with neutrophilic predominance. It is also used for monitoring treatment response. Other important hematological tests apart from routine liver and renal function test are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum procalcitonin. CRP and ESR has good prognostic role and serum procalcitonin is of diagnostic value for bacterial pneumonia. Procalcitonin guidance for antibiotic had a great impact and it was found that there was reduction in antibiotic exposure without an increase in mortality or treatment failure. Most of the time procalcitonin is able to differentiate between viral and bacterial infection and is very useful. But the sensitivity of procalcitonin for detection of bacterial infection ranges from 38 to 91%. There is a need of clinicoradiological correlation of this test to justify withholding antibiotics from patients with CAP having normal procalcitonin value. The role of procalcitonin to determine for initial antibacterial therapy is not recommended. Apart from these tests, urinary pneumococcal antigen and blood cultures are also of good diagnostic utility. Blood culture is only recommended for hospitalized patients (severe and patient on empiric treatment for MRSA or *Pseudomonas aeruginosa*) and not for patients who need treatment on OPD basis.

Serologic Testing

In the ED serologic testing for CAP, e.g., for *Chlamydia* species, *Legionella*, and some fungi are useful only from a retrospective perspective because they usually require both acute and convalescent serum titters. For influenza and respiratory syncytial virus (RSV) rapid antigen tests are also available. These serological tests may be useful as an adjunctive ED test for infection control purposes for hospital inpatients and as an aid in decision making regarding family and contact prophylaxis. For *Streptococcus pneumoniae* and *Legionella pneumophila* urinary antigen tests (UATs) are commercially available. In patients with more severe illness, these tests have the highest diagnostic yield. These antigen tests are rapid, simple to use, and have high specificity in adults.

Ultrasonography

Bedside ultrasonography has been used extensively in the ED for diagnosis of pulmonary conditions including pneumonia. In the diagnosis of radio-occult (negative CXR) pleural-pulmonary lesions bedside lung ultrasonography has been shown to be 96% sensitive and 96% specific. For the diagnosis of emergency pulmonary conditions, bedside lung ultrasonography is an ideal tool, with the benefit of the absence of radiation.

HOSPITAL ADMISSION DECISIONS

Assessment of the severity of illness is important for diagnostic and treatment decisions for pneumonia. These assessments of illness by scoring system affect the decision between inpatient and outpatient treatment and ICU admission versus admission to a general ward.

Scoring Systems

Two scoring systems can assist the emergency physician in the identification of patients who may be candidates for outpatient treatment: CURB-65 is a severity of illness score and the pneumonia severity index (PSI) is a prognostic model (**Table 4**). These objective criteria should be used along with physician judgment in clinical decision making. Patient compliance to oral medication and outpatient social support systems should be considered. The PSI uses a two-step approach to risk assessment. Patients who are considered as low risk, recommended for outpatient management. Patient's age 50 years, without significant comorbid conditions, and who have no red flags on physical examination are considered as low-risk patient. Patients are classified into categories based on age, comorbid illness, abnormal physical examination findings, and laboratory abnormalities who do not meet these low-risk criteria.

These scores are helpful in decreasing the admission rates and healthcare costs. However, the scoring system does not consider dynamic observation of patients over time, the ability to take oral medications, home supports, and access to follow-up.

CURB-65 is a more simplified tool that uses five criteria to determine patients at lower risk for adverse events. These criteria are confusion; uremia [blood urea nitrogen (BUN) >7 mmol/L]; respiratory rate (>30 breaths/minute); blood pressure (60 mm Hg diastolic); age of 65 years or greater.

Direct admission to an ICU or high-level monitoring unit is recommended for patients with either of the major criteria

TABLE 4: Comparison of CURB-65 and PSI scoring system.

CURB-65	*PSI (pneumonia severity index)*
• Confusion +1 • Blood urea nitrogen >7 mmol/L +1 • Respiratory rate >30 +1 • Systolic blood pressure <90 mm Hg • Diastolic blood pressure <60 mm Hg +1 • Age >65 +1	• Age • Female -10 • Nursing home resident +10 • Neoplastic disease history +30 • Liver disease +20 • Congestive heart failure +10 • Cerebrovascular disease +10 • Renal disease +10 • Altered mental status +20 • Respiratory rate >29 +20 • Systolic blood pressure <90 +20 • Temperature <35.5°C or >39.9°C +15 • Pulse >124 +10 • pH <7.35 +30 • Blood urea nitrogen (BUN) <29 +20 • Sodium <130+20 • Glucose <13.8 +10 • Hematocrit <30% +10 • Partial pressure of oxygen <60 +10 • Pleural effusion on X-ray +10

or with three of the minor criteria. *Major criteria are invasive mechanical ventilation or septic shock with the need for vasopressors*. **Table 5** shows the minor criteria for sever CAP.

TREATMENT OF PNEUMONIA

The initial approach to the pneumonia patient by a clinician either in emergency or in OPD is to access the severity, send the investigations (radiology and microbiology as discussed), and start the empirical treatment (**Table 6**). As per Indian guidelines the approach for pneumonia as depicted in algorithm (**Flowchart 1**). To assess the severity of pneumonia there are various scoring systems [CURB-65, CRB-65, SMART-COP, SMRT-CO, and American Thoracic Society-Infectious Diseases Society of America (ATS-IDSA) criteria] which can help us to decide regarding admission (ICU or ward) and OPD management. The most used is CURB-65 (**C**onfusion, **U**rea >7 mmol/L, **R**espiratory rate >30 breaths/minute, **B**lood pressure (systolic <90 mm Hg or diastolic <60 mm Hg), age >**65** years).

After empiric therapy we must follow-up the patients and if there is no response to the therapy within after 48–72 hours they should be re-evaluated. Once the culture report is available, the pathogen targeted therapy, if not started earlier can be started. To chase the culture report is very important for escalation or de-escalation of antibiotics. The first and foremost treatment of pneumonia is antibiotic but other supportive care also needs to be addressed like:

- Antipyretics
- Clear the airway
- Oxygen therapy, if needed
- Adequate hydration and nutrition
- Evaluate for ICU care
- Need to be seen for requirement of ventilator (noninvasive or invasive)

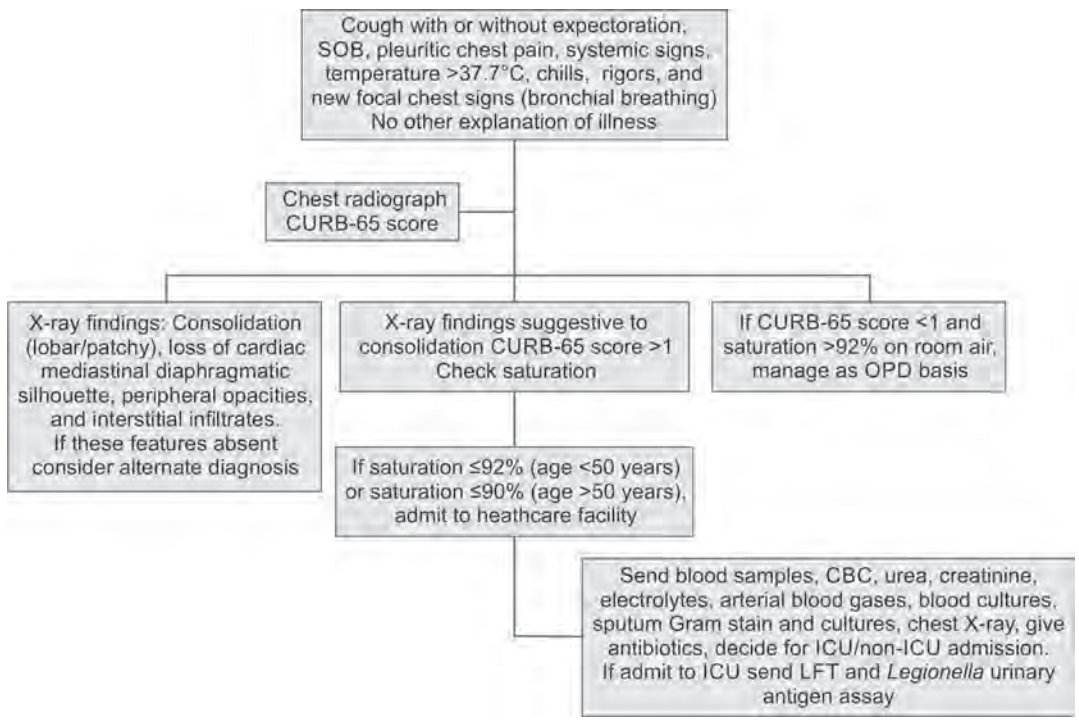
In emergency, oxygen supplement has very important role when respiratory failure (RF) is there. RF may range from mild to severe and is of different types. It is very important to understand and diagnose [on basis of arterial blood gas (ABG), oxygen saturation (SpO_2), etc.] the type of RF that would help in management.

- *Type 1 (hypoxemic)*: Arterial partial pressure of oxygen (PaO_2) < 60: Failure of oxygenation
- *Type 2 (hypoxia with hypercapnic)*: Arterial partial pressure of carbon dioxide ($PaCO_2$) >45: Failure to exchange or remove carbon dioxide and decreased alveolar minute ventilation, which is often accompanied by hypoxemia.
- *Type 3 (perioperative)*: Which is because of increased atelectasis due to low functional residual capacity (FRC) in the setting of abnormal abdominal wall mechanics that may results in type I or type II RF and can be ameliorated by anesthetic or operative technique, posture, incentive

TABLE 5: Minor criteria for severe CAP.

Physical examination	*CXR*	*Laboratory*
• Respiratory rates • Blood pressures require aggressive fluid and vasopressors • Hypoxemia PaO_2/FiO_2 ratio <250 • Mental status-confusion • Hypothermia temperature <36°C	Multilobar infiltrates	• Leukopenia: WBC <4,000 cells/mm^3 • Thrombocytopenia platelets counts <100,000 cells/mm^3

(CAP: community-acquired pneumonia; FiO_2: fraction of inspired oxygen; PaO_2: arterial partial pressure of oxygen; WBC: white blood cell)


Cough with or without expectoration, SOB, pleuritic chest pain, systemic signs, temperature >37.7°C, chills, rigors, and new focal chest signs (bronchial breathing) No other explanation of illness
Chest radiograph CURB-65 score
X-ray findings: Consolidation (lobar/patchy), loss of cardiac mediastinal diaphragmatic silhouette, peripheral opacities, and interstitial infiltrates. If these features absent consider alternate diagnosis
X-ray findings suggestive to consolidation CURB-65 score >1 Check saturation
If CURB-65 score <1 and saturation >92% on room air, manage as OPD basis
If saturation ≤92% (age <50 years) or saturation ≤90% (age >50 years), admit to heathcare facility
Send blood samples, CBC, urea, creatinine, electrolytes, arterial blood gases, blood cultures, sputum Gram stain and cultures, chest X-ray, give antibiotics, decide for ICU/non-ICU admission. If admit to ICU send LFT and *Legionella* urinary antigen assay

(CBC: complete blood count; ICU: intensive care unit; LFT: liver function test; OPD: outpatient department; SOB: shortness of breath)

FLOWCHART 1: Algorithm for approach to pneumonia in emergency department.

spirometry, postoperative analgesia, and attempts to lower intra-abdominal pressure.

- *Type 4 (shock)*: It is basically due to cardiovascular instability, among patients who are intubated and ventilated in the process of resuscitation for shock. Goal of ventilation is to stabilize gas exchange and to unload the respiratory muscles, lowering their oxygen consumption.

Mostly type 1 RF is managed by oxygen supplement or high-flow nasal cannula (HFNC) and patients with type 2 RF will require positive pressure ventilation support [continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and noninvasive ventilation (NIV)]. Failure to respond to any of this supportive management will lead to intubation and mechanical ventilation regardless of type of RF.

Oxygen supplement ⇔ HFNC ⇔ NIV ⇔ Mechanical ventilator

The treatment of RF is oxygen supplement. There are different modalities for oxygen supplement for managing hypoxia in pneumonia (**Table 7**) and various new emerging oxygen supplement equipment are coming to help patients of hypoxia in emergency and delivering FiO_2 in different rate (**Table 8**). Following are the modalities:

- *Nasal cannula*: It is an open device to deliver oxygen, but has low-flow and low-oxygen concentration. It is the simplest and cheapest way to deliver oxygen in hypoxic patients. Domiciliary oxygen can be provided and not much technical speciality is required. The FiO_2 delivery depends upon minute ventilation and amount of entrained room air, hence difficult to control its oxygen delivery accurately. The other limitation is that it does not increase the FiO_2 significantly in severe RF patients demanding more oxygen. High oxygen flow through nasal cannula rather leads to drying of the nasal mucosa and patient discomfort. Nasal prong is mainly used for relatively stable patients.
- *Venturi masks*: This device is used to deliver controlled and accurate amount of FiO_2. To deliver precise fraction of oxygen, variable oxygen concentration with color coding is there (aperture of different sizes). These masks supply oxygen through a jet-mixing device which causes a controlled entrainment of air and precise oxygen concentrations from 24 to 50% is delivered. This may be helpful in chronic obstructive pulmonary disease (COPD) patients who require controlled oxygen to prevent CO_2 narcosis.

TABLE 6: Initial empiric antimicrobial therapy for CAP.

Outpatient	*No comorbidities or risk factors for MRSA or Pseudomonas aeruginosa*: Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is 25%)
	With comorbidities: Combination therapy with amoxicillin/clavulanate or cephalosporin and macrolide or doxycycline OR monotherapy with respiratory fluoroquinolone
In Patient	*Non-ICU (nonsevere)*: A beta-lactam + macrolide OR respiratory fluoroquinolone
	ICU (severe): Pseudomonas not suspected: A beta-lactam plus either azithromycin or a fluoroquinolone
	Pseudomonas not suspected but patient allergic to beta-lactam: A fluoroquinolone and aztreonam
	Pseudomonas suspected: An antipneumococcal, antipseudomonal beta-lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem plus ciprofloxacin or levofloxacin 750 mg; or the above beta-lactam plus aminoglycoside and azithromycin. Or the above beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (in penicillin-allergic patients use aztreonam instead of the beta-lactam)
	If MRSA is suspected, add vancomycin or linezolid
	India being a TB prevalent country fluoroquinolone are not recommended for empiric treatment
	Add MRSA or *P. aeruginosa* coverage and obtain cultures/nasal PCR to allow de-escalation or confirmation of need for continued therapy (if prior respiratory isolation of same)

(CAP: community-acquired pneumonia; MRSA: methicillin-resistant *Staphylococcus aureus*; PCR: polymerase chain reaction; TB: tuberculosis)

TABLE 7: Modalities to manage respiratory failure in pneumonia.

Modalities	***O_2 supplement***	***HFNC***	***Positive pressure***	***Mechanical ventilation***
Delivery methods	• Nasal cannula • Facemask • Venturi mask	Optiflow	• BiPAP • CPAP • AVAP • NIV	Mechanical ventilator
Intubation requirement	Noninvasive	Noninvasive	Noninvasive	Invasive
Respiratory failure	Type 1	Mainly type 1	Mainly type 2	Any type
Given at	Domiciliary, emergency, IPD, HDU, and ICU	Emergency, IPD, HDU, and ICU	Emergency, IPD, HDU, and ICU	ICU only
Contraindication	Can be given under strict monitoring particularly in COPD patients (may cause CO_2 narcosis)	Noncooperative patients	• Noncooperative patients • Copious secretion • Neck fracture	Not such

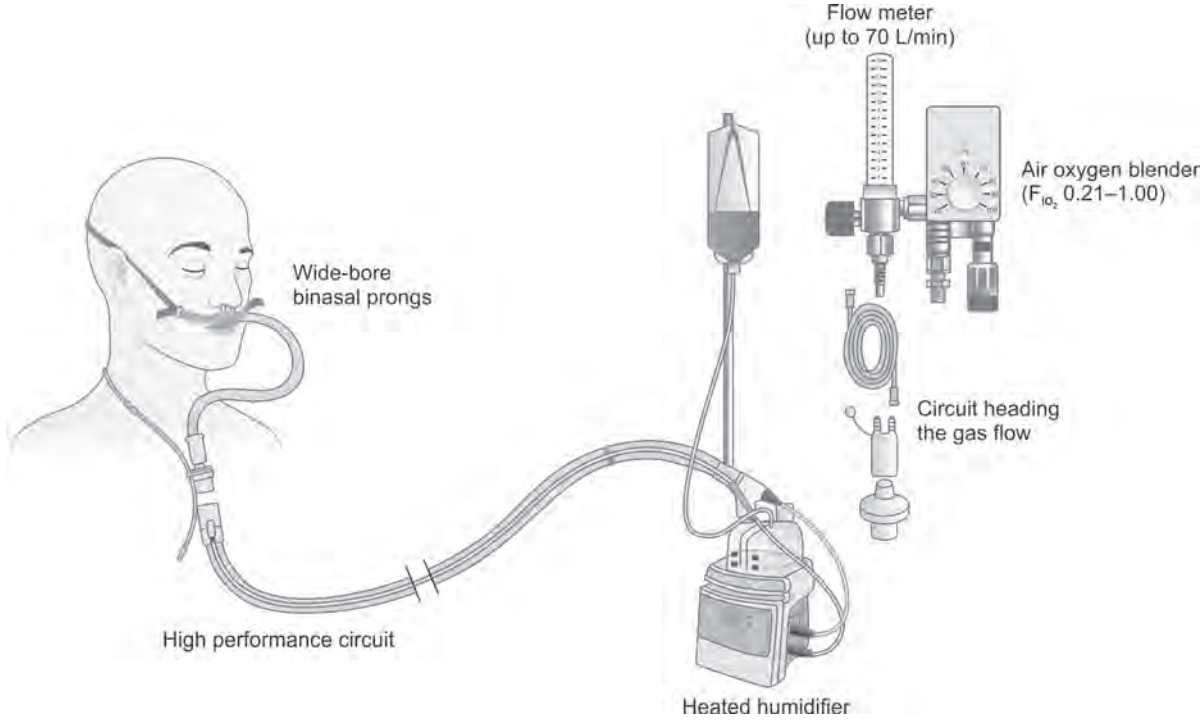
(AVAP: average volume assured pressure; BiPAP: bilevel positive airway pressure; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; HDU: high dependency unit; HFNC: high-flow nasal cannula; ICU: intensive care unit; IPD: inpatient department; NIV: noninvasive ventilation)

- *Reservoir face masks*: It is high flow, high oxygen concentration, open device designed to minimize entrainment of air in patients with high inspiratory flow demand. These masks include a reservoir bag that is full of 100% oxygen. When the patient take breathe, effort generating a flow higher than the wall circuit can deliver, the reservoir of oxygen will be emptied to minimize entrainment of room air. The bag should be partially inflated throughout the respiratory cycle. It is used in severely sick patients with high oxygen demand.
- *Resuscitation bag-mask-valve unit*: It is used when patients required high oxygen. It needs high oxygen flow of around 15 L/min. Because of high oxygen demand, it is difficult to apply domiciliary (mostly used in hospitalized and sick patients with high oxygen demand). It causes minimized entrainment of room air when used with good facemask seal.
- *Noninvasive positive pressure ventilation (NPPV)*: Positive pressure ventilation to increase the tidal volume is used here. It gives ventilatory assistance along with controlled oxygen using a tight-fitting facemask called interface. Here the interface between the patient and the ventilator is used without intubating the patient, hence called noninvasive. It is very useful device in order to avoid or prevent intubation in selected patients.
- *High-flow nasal cannula*: Basic principle is depicted in **Figure 2**. The physiological effect of HFNC is:
  - Increased fraction of inspired oxygen (FiO_2)
  - Gas inlet flow prevents secondary room air entrainment
  - Provides anatomic oxygen reservoirs using nasopharynx and oropharynx
  - Washing out of airway dead space
  - Development of a CPAP effect
  - Decreases atelectasis
  - Improvement in pulmonary ventilation perfusion
  - Decreases work of breathing: Counteracts intrinsic positive end-expiratory pressure (PEEP)

TABLE 8: Various oxygen delivery system and delivered fraction of inspired oxygen (FiO_2).

100% oxygen flow rate (L/min)		*Delivered FiO_2 (%)*
Nasal cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Oxygen mask	5–6	40
	6–7	50
	7–8	60
Mask with reservoir bag	6	60
	7	70
	8	80
	9	90
	10	>99
Nonrebreathing mask	4–10	60–100
Venturi mask	3 (80)	24
	6 (68)	28
	9 (50)	35
	12 (50)	40
	15 (41)	50

Numbers in parentheses indicates total flow of entrained room air with venturi mixture.



(FiO_2: fraction of inspired oxygen)

FIG. 2: Basic principle—high-flow nasal cannula (HFNC).

- Greater patient comfort
- Warmed and humidified nasal oxygen can be better tolerated, especially with flows >6 L/min.

SPECIAL TREATMENT CONSIDERATIONS

Timing of Antibiotics

This is the traditional teaching for ED physician that the first antibiotic dose should be administered while the patient is still in the ED, especially in the special population. For patients admitted through the ED, studies suggested early antibiotic timing improves the outcomes. Early antibiotic treatment has been shown to decrease length of hospital stay but does not seem to shorten the time to clinical stability. However, there is insufficient evidence to establish an overall benefit for patients with CAP without severe sepsis in mortality or morbidity from antibiotics administered in <8 hours from ED arrival.

Transition from Parenteral Antibiotics to Oral Antibiotics

Parenteral antibiotics are started initially for treatment in most hospitalized patients. Once the patient has become clinically stable and has shown clinical improvement, oral antibiotics can be started. Criteria for clinical stability include temperature <37.8°C, heart rate <100 bpm, respiratory rate <24 breaths/min, systolic blood pressure >90 mm Hg, room air oxygen saturation of >90%, and normal mental status. Oral antibiotics should be started after assessing the patient for ability to ingest oral medications, with normal functioning gastrointestinal tracts.

Duration of Treatment

As per evaluation of few controlled trials the optimum duration of antibiotic therapy in either inpatients or outpatients with CAP are for 7–10 days or longer. Duration of treatment should be a minimum of 5 days and before discontinuation of treatment patient should be afebrile for 48–72 hours. The patient should not have any signs of clinical instability at the time of discontinuation of treatment.

Noninvasive Positive Pressure Ventilation

In patients with pneumonia, NPPV does not decrease overall duration of overall hospitalization or in-hospital mortality, except in the patients with pneumonia and underlying COPD. NPPV associated with a significant reduction in respiratory rate, need for endotracheal intubation, and duration of ICU stay, generally well-tolerated and safe. However, other studies have failed to show benefit of NPPV, patients eventually requiring intubation in patients with hypoxic RF. Hence, the routine use of NPPV in patients with severe pneumonia, with the exception of patients with underlying COPD is not recommended because of these conflicting data. Cautious trial of NPPV for refractory hypoxemia in patients with severe pneumonia is recommended by ATS and the IDSA.

Role of Steroid: Hypotensive and Fluid-resuscitated Patients with Severe Pneumonia

In addition to antimicrobials and symptomatic care, corticosteroids being the most important and widely debated as CAP treatment adjuncts and should be considered. Steroids may reduce the frequency of acute respiratory distress syndrome (ARDS) and decrease the length of illness by attenuating the inflammatory response. Steroids reduce the need for mechanical ventilation and rate of ARDS by 5% as per systematic review and meta-analysis. Despite this evidence in favor of steroids, there are many high-quality studies showing no benefit. The case for adjunctive steroids is stronger in severe CAP. Steroids trial should be given in patients with vasopressor-dependent shock and selectively in patients with severe CAP and evidence of inadequate cortisol response. Another important treatment adjunct in hospitalized patients is early induction of physical therapy.

Diffuse Bilateral Pneumonia and Acute Respiratory Distress Syndrome

Mortality is extremely high for patients with severe diffuse bilateral pneumonia or ARDS. Significant reduction in mortality with the use of low tidal volume ventilation (6 mL/kg ideal body weight) is revealed by ARDS net trial, known as lung protective ventilation strategy. The ATS therefore has made a level 1 recommendation that patients with diffuse bilateral pneumonia or ARDS should be mechanically ventilated with low tidal volumes.

Nonresponding Pneumonia

A clinical syndrome in which clinical symptoms of pneumonia do not improve or worsen despite an initial 10 days of antibiotic therapy or in which radiographic opacities fail to resolve within 12 weeks considered as nonresolving pneumonia. Mortality is greatly increased among nonresponding patients as compared with patients who initially respond to treatment. Overall mortality as high as 49% has been reported for nonresponding hospitalized patients with pneumonia. Nonresponse to antibiotics in pneumonia requires either a transfer to a tertiary level of care, further diagnostic testing, or a change in treatment. Most common cause of apparent treatment failure is inadequate host response. Patient who are most likely to be nonresponders are older than 65 years, those with COPD, diabetes, alcoholism, or those who are undergoing immunosuppressive therapy.

Long-term Host Effects

Patients should be informed about the usual course of illness in CAP on discharge. Fevers typically resolve within 3 days of initiating antibiotics. In previously healthy adults with pneumococcal pneumonia, 80% of patients will still have fatigue and 50% will have dyspnea 1 week after presentation. Overall, patients improve clinically much faster than radiographs clear. Primary care providers should ensure that after a pneumonia diagnosis, patient should receive aspirin and statin if they are eligible as excess cardiovascular risk has been observed for 5–10 years after infection likely due to the fact that systemic inflammation destabilizes coronary plaques and produces a procoagulant effect.

PREVENTION

Smoking cessation is the most important measure to reduce a patient's risk of CAP in the primary care setting because

tobacco use interferes with immune system and lung function. Children and all healthy adults over the age of 65 years should receive vaccination against *S. pneumoniae* and *H. influenzae*. Adults 65 years and older should be given 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be given at least 1 year later, important for patients with COPD in whom pneumococcal vaccine has been shown to reduce the likelihood of CAP and exacerbations of COPD. Influenza vaccines should be given yearly to all eligible patients. Finally, frequent hand washing should be encouraged to patients and providers alike, primarily to prevent spread of respiratory viruses.

SUMMARY

The challenge for the emergency physician is to recognize and diagnosis pneumonia which is a common disease presentation to the ED, initiate early and appropriate empiric antibiotic therapy, risk stratify patients with respect to severity of illness, and recognize indications for admission. Apart from initiating the empiric antibiotics in ED for pneumonia he should be vigilant regarding respiratory isolation and droplet precautions, but also the environment in which the pneumonia was contracted and the host factors that may implicate risk for a particular microorganism. Bacterial and viral pathogens both are responsible for CAP. Essential information to clinically diagnose CAP is obtained by history, physical examination including vital signs and saturation of peripheral oxygen, and chest radiographs results. Past medical history for risk factors that predispose to drug-resistant pneumonia is essential to take from the patient. Emergency physician need to be aware of risk factors for pneumonia and also the nonresponding pneumonia, in order to use the appropriate empiric broad spectrum antibiotics. Blood cultures should be collected before administering antibiotics and sputum cultures in ED in severe CAP when applicable. To determine the most appropriate disposition for a patient of CAP, PSI, and CURB-65 risk stratification tools should be used routinely. Underlying comorbidities of the patient, the clinical likelihood of deterioration, and the access to outpatient follow-up should also be taken in the account during the disposition, apart from the severity of the presenting symptoms. In ED, careful severity assessment includes screening for occult sepsis with a serum lactate is a crucial step of CAP management and should be followed by early antibiotics and fluid resuscitation when indicated. Emergency physician should know latest antimicrobial treatment guidelines for both outpatient and inpatient CAP, which will continue to change as resistance patterns in respiratory pathogens evolve. To prevent the respiratory infections in children and adults hand washing, mask, social distancing, and vaccination must be encouraged.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Pneumothorax

Bhawana Sharma, Devendra Richhariya

INTRODUCTION

A pneumothorax is defined as the accumulation of air in the pleural space with secondary collapse of the surrounding lung. It must be distinguished from bulla or air cysts within the lung. Pneumothoraces can be divided into spontaneous pneumothorax and traumatic pneumothorax. Spontaneous pneumothorax is subclassified as either primary spontaneous pneumothorax (PSP) or secondary spontaneous pneumothorax (SSP) (**Table 1**). PSP occurs without a precipitating event in a person with no clinical evidence of lung disease. Many of these individuals have occult lung disease with subpleural blebs on computed tomography (CT) scans. Complication of underlying lung disease, most often chronic obstructive lung disease (COPD) gives rise to SSP. Blunt (nonpenetrating) or penetrating trauma disrupting the lung, bronchus, or esophagus causes traumatic (or nonspontaneous) pneumothorax. A subcategory of traumatic pneumothorax is iatrogenic pneumothorax, which occurs as a consequence of diagnostic or therapeutic maneuvers (i.e., thoracentesis, insertion of a central venous catheter, surgery, or mechanical ventilation).

TABLE 1: Etiological classification of pneumothorax.

Primary spontaneous: No underlying lung disease	Subpleural bullae formation → smoking causes elastic fiber dysfunction → influx of neutrophils and macrophages, inflammation induced → obstruction of small airway → rise in alveolar pressure and air leak into lung interstitium
Secondary spontaneous: Underlying lung disease	• Chronic obstructive pulmonary disease (COPD) • Asthma • Cystic fibrosis • Interstitial lung diseases and connective tissue disease • Carcinoma • Catamenial: Female 30–40 years, history of pelvic endometriosis, and thoracic endometriosis related to menstruation
Traumatic: Due to blunt and traumatic chest injuries	• Due to blunt and traumatic chest injuries • Fall from height • Dashboard injury and steering wheel injury • Road traffic accident
Iatrogenic: Due to diagnostic and therapeutic procedure	• Transthoracic needle aspiration or biopsy • Thoracentesis • Closed pleural biopsy • Transbronchial biopsy • Subclavian or jugular vein catheterization • Mechanical ventilation • Cardiopulmonary resuscitation • Nasogastric tube placement • Tracheostomy • Liver biopsy

PATHOPHYSIOLOGY

The pleural space has negative pressure during the entire respiratory cycle. This negative pressure is due to elastic recoil capacity of lung (collapsing nature) and the tendency of chest wall to expand. The negative pressure at the apex is more than the base, and this pressure difference keep the alveoli more distended in this region. Whenever a communication develops between an alveolus and the pleural space, air will move from the alveolus into the pleural space (due negative pressure difference) until there is equalization of pressure or the communication is sealed. As a consequence pneumothorax enlarges and lung becomes smaller resulting in reduction of vital capacity of the lung and partial pressure of oxygen (PaO_2). Total lung capacity, functional residual capacity, and diffusing capacity are also reduced. The reduction in arterial PaO_2 appears to be caused by low ventilation perfusion (Va/Q) ratios, anatomic shunts, and, occasionally, alveolar hypoventilation. If perfusion to the collapsed lung is preserved, there is an increase in pulmonary shunt and substantial hypoxemia. If perfusion to the collapsed lung is reduced by hypoxic vasoconstriction, hypoxemia may be minimal. In general, pneumothoraces occupying <25% of the hemithorax are not usually associated with significant shunts. Under normal circumstances, despite

the degree of pneumothorax; hypoxemia tends to abate within 24 hours, presumably because of redistribution of pulmonary blood flow. In tension pneumothorax (mechanical ventilation, resuscitation, and trauma), the intrapleural pressure is more than the atmospheric pressure during entire expiration and inspiration. The collapsed lung produces hypoxia and reduced venous return due to compression of atria decreases the cardiac output and resulting in hypotension.

CLINICAL FEATURES

The clinical presentation depends on degree of lung collapse and underlying lung pathology. Patient of pneumothorax may be asymptomatic or may be critically ill. Clinical manifestations are unreliable indicators of the size of the pneumothorax. The patients may present with chest pain, dyspnea, cyanosis, sweating, and tachycardia. Clinical examination may reveal pulsus paradoxus, respiratory distress, and tracheal deviation (to opposite side). There may be hyperresonance on percussion and auscultation may reveal ipsilateral decreased/absent breath sounds. Presence of chest pain and respiratory distress accompanied by tachycardia, tachypnea, and hypotension indicates tension pneumothorax. Rarely there may be cyanosis and altered level of consciousness. In emergency department, clinical evaluation should be the main determinant of the management strategy.

PRIMARY SPONTANEOUS PNEUMOTHORAX

Primary spontaneous pneumothorax is a primary process that occurs in the absence of underlying clinical or radiological lung disease. However, unrecognized lung disease may be present in most patients with a PSP and rupture of a subpleural bleb may result in the pneumothorax. The peak incidence is between the second and the third decade of life. Smokers are more likely to develop PSP. PSP develops secondary to a visceral pleural tear, which results from rupture of pleural blebs and bullae which usually located in apical area and partially communicated with the tracheobronchial tree. Several theories exist regarding the development of blebs and bullae in patients with PSP. The pathogenesis of bleb can be explained with alveolus air ruptured into the thin fibrous layer of visceral pleura where it accumulates forming cysts. Blebs may be congenital, acquired, or develop as a result of local inflammation, e.g., smoking or secondary to disturbed collateral ventilation. The formation of blebs may be associated with the weakening of the elastic fibers of the lung. Such process is caused by the imbalance between protease and antiprotease and oxidants and antioxidants, in which inflammatory cells (mainly neutrophils and macrophages) play a major role. This is supported by the fact that duration of smoking is associated with an increase in the risk of developing pneumothorax as compared to nonsmokers. There are various inflammatory changes in the distal airways occur in smokers which may lead to endobronchial obstruction of the small airways leading to over pressure in alveolar tissue and rupture of pulmonary parenchyma. The mechanisms of the formation of bullae are less clear than those of blebs, but the current evidence suggests possibility of regional damage to the apical portion of the lung. This damage is probably related either to ischemia or to the greater distensile forces of apical alveoli caused by more negative pleural pressure at the apices. Abrupt swings in atmospheric pressure also associated with high frequency of PSP.

SECONDARY SPONTANEOUS PNEUMOTHORAX

Secondary spontaneous pneumothorax associated with a wide variety of pulmonary diseases of either a focal or a diffuse variety of pulmonary diseases. Chronic obstructive pulmonary disease (COPD) is the most common cause associated with pneumothorax among all pulmonary diseases. Secondary to appropriate prophylaxis, the role of acquired immunodeficiency syndrome (AIDS) and *pneumocystis carinii* pneumonia infection is declining as a major etiology of SSP. The peak incidence is at 60–65 years of age. Development of SSP depends on two mechanisms: (1) Hyperexpansion of the distal airspace due to the obstruction of inflamed airways, or (2) Visceral pleural tear due to underlying inflammatory parenchymal process such as necrotizing pneumonia.

CATAMENIAL PNEUMOTHORAX

This is a SSP. It is a rare syndrome of recurrent pneumothorax in women occurring within 72 hours of the onset of the menses. It is important to recognize the catamenial pneumothorax since the management is distinct from other forms of spontaneous pneumothorax. The peak incidence is 30–40 years of age. The pathogenesis of catamenial pneumothorax remains obscure. The first hypothesis is that air enters through a diaphragmatic defect to the peritoneal cavity then escapes into the thoracic cavity during menstruation (though not demonstrated in majority of cases). Diaphragmatic defect may present as congenital defect or may be acquired by breakdown of diaphragmatic endometrial implants. The second hypothesis is the presence of focal implant of endometrial tissue on pleural surface,and pneumothorax occurs due to swelling of this focal implant during hormonal changes of menses. The third hypothesis is increased serum level of prostaglandin F2 (PGF2), known to exist in menstruating women, causes vascular and bronchial damage.

TENSION PNEUMOTHORAX

This is a pneumothorax in which intrapleural pressure more than the atmospheric pressure during most of the respiratory cycle. It is considered as a medical emergency since acute deterioration in cardiopulmonary functions occurs.

Incidence

Tension pneumothorax develops in association with a spontaneous pneumothorax in 1–2% of cases, mainly with traumatic penetrating lung injury and barotrauma secondary to mechanical ventilation.

Pathogenesis

The basis of tension pneumothorax depends on the development of a condition of a unidirectional flow of air from injured pulmonary parenchyma into the pleural space in such a way that a “check-valve” mechanism result. Initially during

expiration only, pleural pressure is positive but later pressure becomes positive throughout the entire respiratory cycle with increasing accumulation of air. Circulatory collapse may follow, mainly as a result of the reduction in oxygen delivery due to severe hypoxemia secondary to the development of a large shunt in the involved collapsed lung. Reduction in cardiac output and systemic blood pressure will follow later.

Pneumothorax and Air Travel

The exact incidence of pneumothorax during commercial air travel is unknown, but seems to be exceedingly rare. The main factor that might predispose patients to pneumothorax during air travel is the expansion of the trapped air due to the reduction of barometric pressure according to Boyle's law. Noncommunicating pulmonary blebs and bullae will enlarge as the air expands and could rupture. Aircraft maintain a "cabin altitude" <8,000 feet at the highest operating altitude (usually 22,000–44,000 feet), which is achieved by pressurizing the cabin. Such pressurization will not only maintain an acceptable PaO_2 in the cabin, but it will also reduce the risk of spontaneous pneumothorax, as trapped gas within the lungs expands by only 38% at a cabin altitude of 8,000 feet compared to 400% at 35,000 feet. Based on the current available data, air travel may be contraindicated in patients with severe bullous emphysema, large congenital pulmonary cysts, or a prior spontaneous pneumothorax in the preceding 30 days.

RADIOLOGICAL EVALUATION OF PNEUMOTHORAX

Chest X-ray, an expiratory film, is more sensitive method in diagnosing the pneumothorax (**Fig. 1A**). Confirmation can be done by demonstrating the thin (<1 mm thick) visceral pleural line displaced away from the chest wall. Lateral decubitus film is also helpful in identifying a small pneumothorax. Large, thin-walled, and air-containing bulla should be differentiated from pneumothorax. Generally, in pneumothorax, pleural line is oriented in convex fashion towards the lateral chest wall, whereas in large bulla, pleural line is usually concave. In doubtful conditions, CT scan of the chest is helpful in differentiating the two conditions. An estimation of the percentage of lung volume lost due to pneumothorax is also the part of radiological evaluation of pneumothorax. **Accurate pneumothorax size calculations are best achieved by CT scanning.** For clinical purposes, an approximation of the % collapse can be made from the following equation:

% Collapse = [(D-d)/D × 100] When (D and d) are the average diameter of the chest wall and lung.

% Collapse = 4.2 + [4.7 × (A + B + C) another formula can also be used for estimation of % collapse **(Fig. 1B).**

MANAGEMENT OF PNEUMOTHORAX

Management of pneumothorax mainly consists of: (1) Remove the air from the pleural space to allow re-expansion of the collapsed lung, (2) Reduce the likelihood of recurrence.

General Physiology

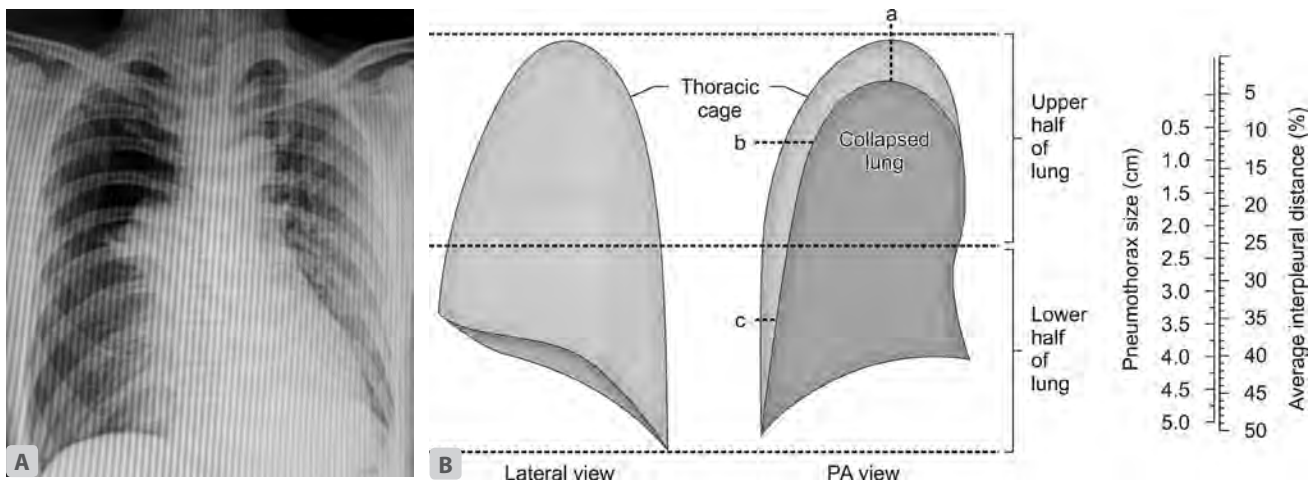
Air in the pleural space nitrogen (N_2), oxygen (O_2), carbon dioxide (CO_2), and water (H_2O) will slowly equilibrate with tissue gases. Oxygen and CO_2 will be absorbed and the remaining N_2 will have a small pressure gradient between pleural gas and tissue gas, mainly capillary blood. Nitrogen in the pleural space will then be absorbed slowly (secondary to pressure gradient) at a rate of approximately 1.25% per 24 hours, and so lung expansion will take place gradually. This means that a 30% pneumothorax will need 24 days to resolve spontaneously.

Simple Observation

A simple observation is a reasonable option when the following criteria are met: (1) Small PSP (<15–20%), (2) Healthy and asymptomatic patient, and (3) No evidence of progression of the pneumothorax.

Oxygen Supplementation

A high concentration of fraction of inspired oxygen (FiO_2) will simply widen the nitrogen gradient between the pleural space and the capillary blood thus allowing the rapid absorption of the pleural gas. This is achieved by getting a higher O_2 tension in the blood, leading to a reduction in the blood nitrogen



FIGS. 1A AND B: (A) Showing right side pneumothorax; (B) Quantification of pneumothorax size on chest radiograph using intrapleural distances at three locations: (a) the apex of collapsed lung to cupola, (b) the midpoint of the upper half of collapsed lung to chest wall, and (c) the midpoint of the lower half of collapsed lung to chest wall.

tension, and so widening the nitrogen gradient between the blood and pleural space. Based on this simple physics, pleural space air absorption can be increased by fourfold to sixfold. Oxygen administration should be considered for any patient admitted for observation and treatment of pneumothorax.

Catheter Aspiration

Catheter aspiration should always be considered for the initial treatment if PSP is exceeding 15–20% of the value of the hemithorax. It is successful in avoiding tube thoracostomy in 65% of such cases. If the catheter aspiration method is chosen, air should be aspirated using a 50 mL syringe attached to a stopcock, until a resistance is felt, which indicates lung expansion. If no resistance is felt after 4 L of air has been aspirated, a persistent leak is present and tube thoracostomy is indicated. Catheter aspiration does not reduce the incidence of recurrence of spontaneous pneumothorax.

Tube Thoracostomy

Tube thoracostomy is indicated for patients with SSP of >15–20% of the hemithorax value. It is also indicated for patients with PSP who have severe shortness of breath or chest pain, are hypoxic, or failed catheter aspiration. Finally,it is also indicated for traumatic as well as mechanical ventilation induced pneumothorax. Following placement, the thoracostomy tube is connected to a one-way valve or a chest drainage system, which has two basic components. A water seal chamber, which functions as a one-way valve, consists of a tube submersed under water to prevent air entry into the negative-pressured pleural cavity. When pleural pressure becomes positive and exceeds the height of the submersed tube (usually 2 cm), air can escape. The second component is the suction control chamber, which provides a controlled amount of suction. Generally speaking, suction should be reserved for patients in whom expansion does not take place within 24 hours. The tube is left in place until lung expansion is complete and the air leak is closed. At this point, the tube is clamped for 12–24 hours and the patient is observed for recurrence by chest X-ray. If the lung remains expanded, the tube is removed. Failure of tube thoracostomy is considered to be the inability to expand the lung fully or the presence of a persistent air leak after 7 days of tube placement (in the absence of positive pressure mechanical ventilation). The thoracostomy tube (without pleurodesis) does not reduce the incidence of recurrent spontaneous pneumothorax.

Chemical Pleurodesis

Intrapleural administration of a chemical to produce adhesion of the visceral and parietal pleura is a therapeutic option in selected cases of pneumothorax. Properly applied, it can decrease the recurrence rate of spontaneous pneumothorax. Chemical pleurodesis, however, is not effective for the closure of bronchopleural fistula. Tetracycline was considered as the sclerosing agent of choice due to its efficacy, ease of administration, low cost, and lack of significant side effects. In a prospective randomized trial, tetracycline reduced the recurrence rate to 25% compared to the tube thoracostomy rate of 41%. In several other studies, tetracycline reduced the recurrence rate further to 9–16%. Different studies have documented a dose response relationship. The proposed mechanism of action is the release of cytokines [interleukin 6-8 (IL 6-8) and tumor necrosis factor], which are markers of inflammatory response that attract neutrophils to the pleural space causing pleural symphysis. Tetracycline is no longer available for clinical practice and doxycycline has been used as an alternative. A number of other sclerosing agents have also been utilized including bleomycin, aerosolized talc, and talc slurry. Aerosolized talc has the lowest reported recurrence rate (4–6%) and is highly efficacious in achieving pleurodesis in both persistent SSP and recurrent PSP. Despite its efficacy, its application needs a thoracoscopic procedure under local or general anesthesia and special surgical skill. Talc slurry has recently gained much interest, and it might be proven to be the sclerosing agent of choice. Preliminary data indicates that talc slurry has a high success rate. In a randomized prospective trial of 96 patients, pleurodesis with talc slurry resulted in the lowest recurrence rate of 8%, compared to 13% with tetracycline and 31% with simple tube drainage. The major concern with talc slurry is the reported association with acute respiratory distress syndrome (ARDS). This complication is probably dose related and occurred when high doses (>10 g) of talc were used. Liberal use of analgesia is usually indicated for severe pain, which is the most common side effect of chemical pleurodesis.

Thoracotomy

Thoracotomy is the most effective treatment modality for preventing recurrent pneumothorax, with a recurrence rate of 0.6–2%. The advantages of surgical management are controlling the air leak, decreasing the recurrence rate, and addressing any underlying lung pathology that may have contributed to the pneumothorax. Surgical pleurodesis can also be performed, if indicated. The indications for thoracotomy and surgical management of pneumothorax are as following: (1) Large (>50% minute ventilation) air leak for over 24 hours with proper drainage. (2) Continued symptoms due to persistent air leak. (3) Recurrence of pneumothorax with failure or contraindication to chemical pleurodesis. (4) Pneumothorax accompanied by hemorrhage, loculated effusion, or empyema. (5) Recurrent contralateral pneumothorax. (6) Simultaneous bilateral pneumothorax (single-side procedure). (7) Pneumothorax following previous pneumonectomy. (8) Treatment of initial episode in patients with high-risk occupation (for example, pilots). Recently, video-assisted thoracic surgery (VATS) has been introduced as a possible alternate to thoracotomy. A recurrence rate of 5% has been reported for VATS compared to conservative therapy either by observation or tube thoracostomy. Recent data has shown that, irrespective of the presence of blebs or bullae, drainage and hospitalization time are shorter and complications and recurrence are much lower in patients treated with VATS when compared to conservative therapy with either first time or recurrent spontaneous pneumothorax.

INTERCOSTAL CHEST DRAIN INSERTION

Intercostal chest drains are inserted into the pleural or mediastinal spaces to remove abnormal collections of air, blood, pus or fluid and in many acute and chronic conditions, especially when respiratory function is compromised. The procedure is usually performed by surgeons and chest physicians, but every emergency physician should be well versed with the technique of insertion of chest drain. Insertion of an intercostal chest drain are indicated for appropriate lung re-

expansion in pneumothoraces, complicated parapneumonic effusions or empyema, hemothoraces, bedside pleurodesis, and following cardiothoracic surgery or thoracoscopic procedures (**Table 2**). Absence of informed consent or patient cooperation is the only absolute contraindication for tube thoracostomy. Relative contraindications include uncorrected coagulopathy (e.g., patients with international normalized ratio >1.5–2 or with a platelet count <50,000/μL). Chest tube insertion should be avoided over an infected skin area. Once the indication is ascertained, follow the preparation and equipment checklist to arrange all necessary requirements at the bedside (**Table 3**).

TABLE 2: Indications and contraindications for intercostal chest drain insertion.

Indications	• Pneumothorax (in any ventilated patient, tension pneumothorax, persistent or recurrent pneumothorax, large secondary pneumothorax, and malignant pleural effusion) • Empyema and complicated pleural effusion • Traumatic hemopneumothorax • Post-chest surgery
Contraindication	• Coagulopathy • Dense lung adhesions • Diaphragmatic hernia

TABLE 3: Checklist—Preparation and equipment for intercostal chest drain.

Preparation	• Identify the correct patient and side of insertion • Review the radiology and indication for procedure • Explain the procedure and obtain informed consent • Arrange for equipment • Secure intravenous line • Mild sedation may be required if patient is apprehensive • Monitoring of vitals and oxygen saturation during the procedure
Equipment required	• Sterile gown and gloves • Sterile drapes • Suture set • Sterile gauze swabs • Syringes and needles of various sizes • Local anesthetic • Scalpel and blade (No. 11) • Betadine • Local anesthetic—lignocaine 1% or 2% • Suture—silk No. 1 on cutting needle • Instrument for blunt dissection (e.g., curved clamp) • Chest drains • Connecting tubing • Closed drainage system (including sterile water for underwater seal) • Dressing material (Tegaderm)

Chest Tube Types and Sizes

The chest tubes or catheters are basically classified according to size and method of insertion. Various materials such as polyvinyl chloride, polyethylene, and silicone are used for making the chest tubes, and commercially available in straight, angled, or coiled at the end ("pig-tail") with numbers of holes on the sides and tip and with radiopaque strip. According to the Poiseuille's law (liquids) and the Fanning equation (gases), internal diameter and length of chest tubes determine the air or liquid flow rate through the drain. The size of a chest tube means its outer diameter and is displayed in "French" (F) and 1 F corresponding to one-third millimeter. Thus, a 12 F tube is 4 mm in diameter. Chest tube sizes usually range between 8 F and 36 F. A general distinction is made between small-bore chest tube (SBCT) and large-bore chest tube (LBCT). SBCT can be defined as 14 F or less, and LBCT as >14 F, some authors also prefer to consider a group of medium-bore tubes (16–24 F). Based upon expert opinion, use of chest tubes ≥20 F is recommended in the following situations: (1) there is significant risk of air leak, as in traumatic pneumothorax or bronchial dehiscence; (2) iatrogenic pneumothorax from barotrauma (mechanical ventilation); (3) hemothoraces; and (4) postoperative drainage of the chest cavity. Estimation of size of chest tube according to the age can be estimated with the help of **Table 4**.

- Spontaneous uncomplicated pneumothorax: 16–22 Fr (small bore)
- Unstable patient, bronchopleural fistula, or mechanical ventilation: 24–28 Fr
- Complicated pneumothorax or hemothorax (trauma): 32 Fr (large bore) or larger
- Pediatric: 4 X (age/4 + 4)
- For Seldinger technique of insertion: 14 Fr

Techniques for Chest Tube Placement

Small-bore chest tube (14 F or less) or medium-bore chest tubes (MBCT) are typically placed using the Seldinger technique, whereas LBCT (>24 F) can be inserted by blunt dissection or the trocar technique (**Figs. 2A** and **B**). Because of the ease of insertion and increased patient comfort, the Seldinger technique has become the most widespread method of tube placement. Conversely, the trocar technique is obsolete and should be avoided. It significantly increases the risk of misplaced drains and organ perforation. Advantages and possible complications of the procedure should be explained to the patients, written informed consent should be obtained, except in emergency situations. A recent chest radiograph should be obtained and evaluated before starting the procedure.

The first step involves positioning the patient according to the location chosen for drain insertion.

Most comfortable position for chest tube insertion is supine position with arm abducted and placed by side. If patient is breathless or can not lie supine, upright position leaning over pillow/cardiac table or lateral decubitus position is preferred (**Fig. 3A**). Chest drains are usually inserted in the triangle of safety, which is defined anteriorly by the fold of pectoralis major, posteriorly fold of latissimus dorsi, and inferiorly by a line drawn downward from nipple, which usually corresponds to 5th or 6th intercostal space in the midaxillary line. Clean a large area appropriately with Betadine and drape with sterile

TABLE 4: Chest tube size for age.

		Pneumothorax	*Pleural fluid*	*Empyema*	*Hemothorax*
Neonate/newborn	<5 kg	8–14 Fr	8–14 Fr	8–14 Fr	14–20 Fr
Infants/children	5–10 kg	8–14 Fr	8–14 Fr	12–18 Fr	18–24 Fr
	10–15 kg	8–14 Fr	8–14 Fr	18–24 Fr	18–24 Fr
	15–20 kg	8–14 Fr	8–14 Fr	18–24 Fr	18–24 Fr
	20–30 kg	8–14 Fr	8–14 Fr	18–24 Fr	18–24 Fr
Preteen-adult	>30 kg	24 Fr	24 Fr	24–32 Fr	24–36 Fr
Calculating pediatric tube size for age—pediatric= 4 X (age/4 + 4)					

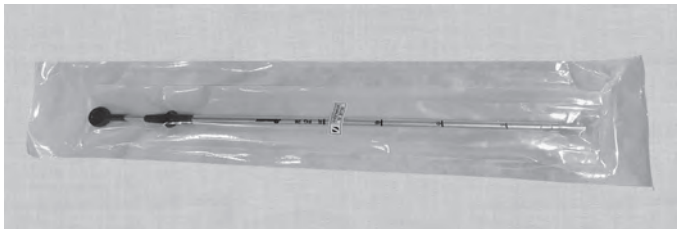


FIG. 2A: Intercostal drain with trocar.

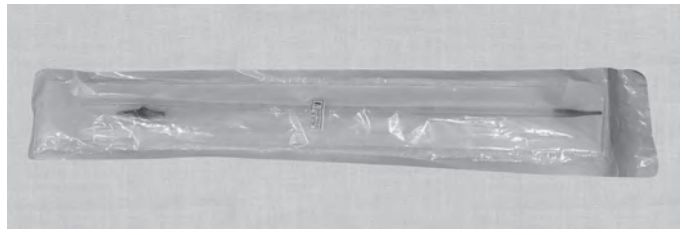


FIG. 2B: Intercostal drain without trocar drain.

sheets. Aspirate and identify if air or fluid/blood can be aspirated. In case of loculated collections, ultrasonography is helpful to identify the site of insertion of drain. In cases of severe cardiomegaly and distorted thoracic anatomy, blind insertion of a chest tube through the *"triangle of safety"* is not safe. If air or fluid is not found, the insertion site should be changed. Infiltration of skin, subcutaneous tissue, chest wall muscles, and pleura are performed using generous amount of diluted local anesthetic. Up to 7 mg/kg of locally injected 1% lidocaine with epinephrine (1:100,000) can be used (up to 5 mg/kg if not using epinephrine). Stepwise approach is as follows (**Fig. 3B**). Skin incision is made parallel to the intercostal space (size 1–2 cm) at the marked site. Blunt dissection of subcutaneous tissues is done with a blunt artery forceps up to intercostal muscles. Insert the finger to explore the tract created and feel for the intercostal space. Enter the pleural cavity using a blunt artery forceps (guarded by fingers) at the upper border of the lower rib (this avoids injury to the neurovascular bundle running at the lower border of each rib). One may encounter gush of air coming out (pneumothorax) or blood (hemothorax) or pleural fluid (effusion). Keep the blades of the artery forceps open so as to create the tract for chest drain. Insert the finger through the wound into the intercostal space to feel inside the pleural cavity and rule out underlying dense lung adhesions. This maneuver also allows the surgeon to feel for the tract which facilitates in the insertion of chest tube. The chest tube is held by blunt artery forceps just proximal to its tip and is inserted into the pleural cavity. Drain is directed toward apex in case of pneumothorax and toward base in case of fluids and then pushed into the pleural cavity for appropriate length. Successful drainage of pleural cavity can be achieved even if the tube is not placed at the ideal position. Drain manipulation and reposition should not be performed until the drain is functioning and draining the pleural cavity. The drain is then connected to closed underwater seal drainage system (**Fig. 4**). Look for the bubbling of air or column swing in the tubing. This confirms the presence of functioning tube in the pleural cavity. Fix the drain with the help of vertical mattress suture taken near the drain. The whole length of string is wrapped around the drain tightly and then tied (the same suture would be utilized to close the wound after drain removal). Extra stitch may be applied to avoid leakage from insertion site. Dressing is applied and drapes are removed. Check for any kink or leakage in the tubing. Provide adequate length of the tubing and avoid loop of tube on the floor.

Postprocedure Intercostal Drain Care

Not >1 L of fluid should be allowed to drain in case of massive pleural effusion, to avoid re-expansion pulmonary edema. The drain should be clamped and fluid drained intermittently (500 mL every few hours by releasing the clamp). Chest X-ray must be done following the procedure to ensure the correct position of the drain (**Fig. 5**). All holes of the drain should be inside the pleural cavity. The dressing should remain clean and dry, change if it gets soaked or spoiled. Adequate analgesia should be given to promote chest physiotherapy. The underwater seal bottle should be kept below the level of chest. Universal sterile precautions should be taken while changing the underwater seal bottle and should be done by a trained person. Chest drains should never be clamped, especially in patients with pneumothorax (clamping of drains in patients with air leaks can cause tension pneumothorax). Daily drainage chart should be maintained and hourly drainage should be recorded in patients of hemothorax

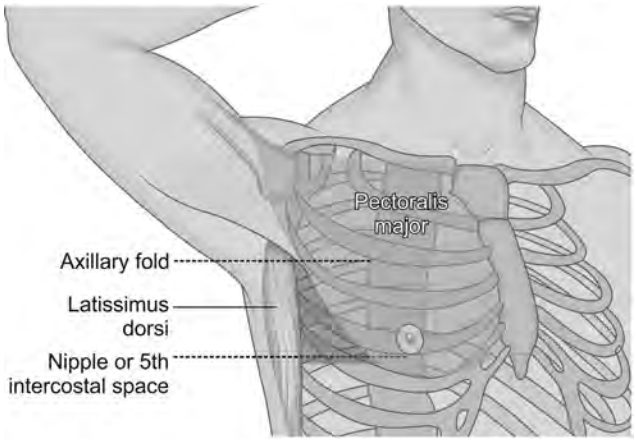


FIG. 3A: Position of the patient for chest drain insertion.

Underwater Seal Chest Drain System

Once a chest tube is in place, a chest drainage system is attached.

Single-chamber underwater seal chest drains (**Fig. 6A**), as the name suggests, single chamber/bottle is used in this system. The patient chest tube is submerged in the water about 2 cm which act as one-way valve. The air in the tube will bubble out and escape into the atmosphere when the patient's pleural pressure exceeds the level of water (i.e., >2 cm H_2O). With inhalation of the patient the negative intrapleural pressure will suck drain water up the tube, but no additional air can enter. Advantages of single-bottle drains are it is simple, cheap, and easily improvised from unrelated equipment, it is very useful for simple pneumothorax, there is usually no need for anything more sophisticated, and the fluid level (i.e., valve pressure) is

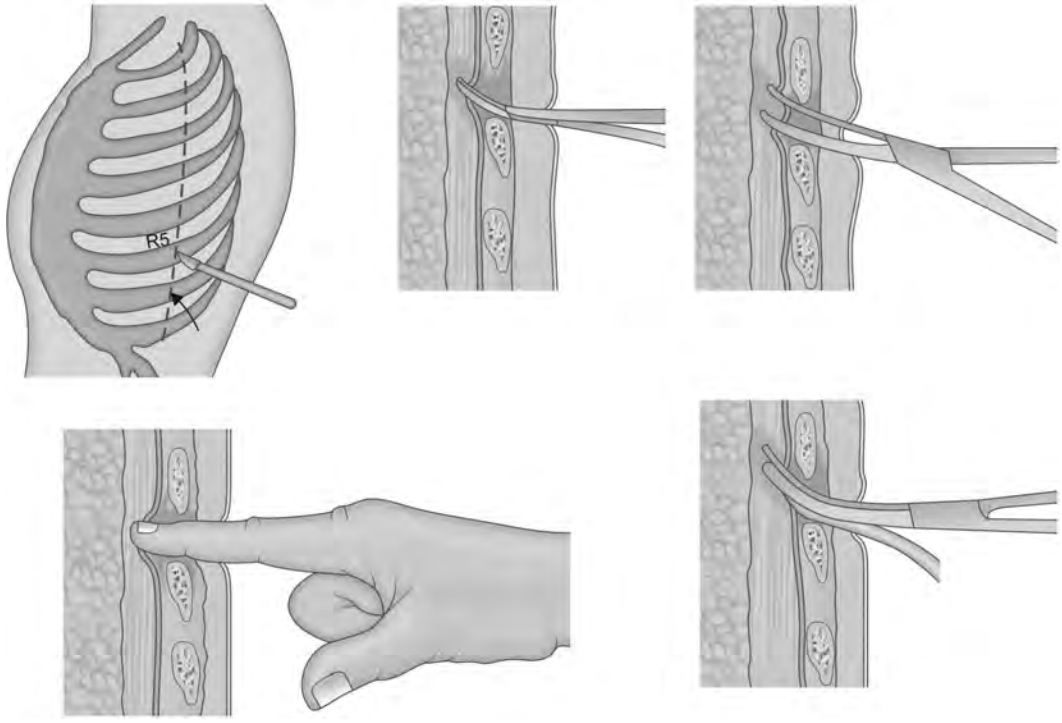


FIG. 3B: Stepwise approach.

FIG. 4: Underwater seal drainage system.

FIG. 5: Postintercostal drain procedure X-ray.

adjustable. The disadvantage of single-bottle system is that it is not suitable for pleural fluid drainage. Second, if pleural fluid goes enter the bottle, froth will form. Third, fluid may reflux into the patient's chest cavity. To remove the disadvantages of the single-bottle system another bottle or chamber is added in the system to make it *two-chamber underwater seal chest drains* (**Fig. 6B**). Fluid collection chamber is separated from the water seal chamber in this system. Pleural fluid can be collected in separate bottle without affecting the underwater seal to prevent the re-entrainment of air. Advantages of two-bottle system are consistent (low) resistance to air expulsion because of fixed underwater seal level, no development of froth as pleural fluid and water seal are separate. So, two-bottle system is used in pneumothoraces as well as drainage of pleural fluid. Two-bottle system has disadvantages of being less efficient in draining the air cavities, and without suction the drainage is less efficient. To overcome this problem *three-chamber underwater seal drain* (**Fig. 6C**) is developed which is similar to two-bottle seal but another chamber is added to help regulate the suction pressure. Advantages of the three-chamber drain: Pressure of the suction can be adjustable which protects the pleural cavity from the unmoderated effects of wall suction. Three-bottle system is effective for both pneumothorax and pleural fluid. There is virtually no chance that pleural drain fluid will reenter the chest cavity with a sudden decrease in intrathoracic pressure. Disadvantages of three-bottle system includes continuous frothing, its complexity, and in case of suction failure or occlusion two-chamber system will be blocked and chances of re-expansion of the pneumothorax. To overcome this situation one may add forth bottle for safety to make it *four-chamber underwater seal drain* (**Fig. 6D**). This system is different with addition of *another* underwater

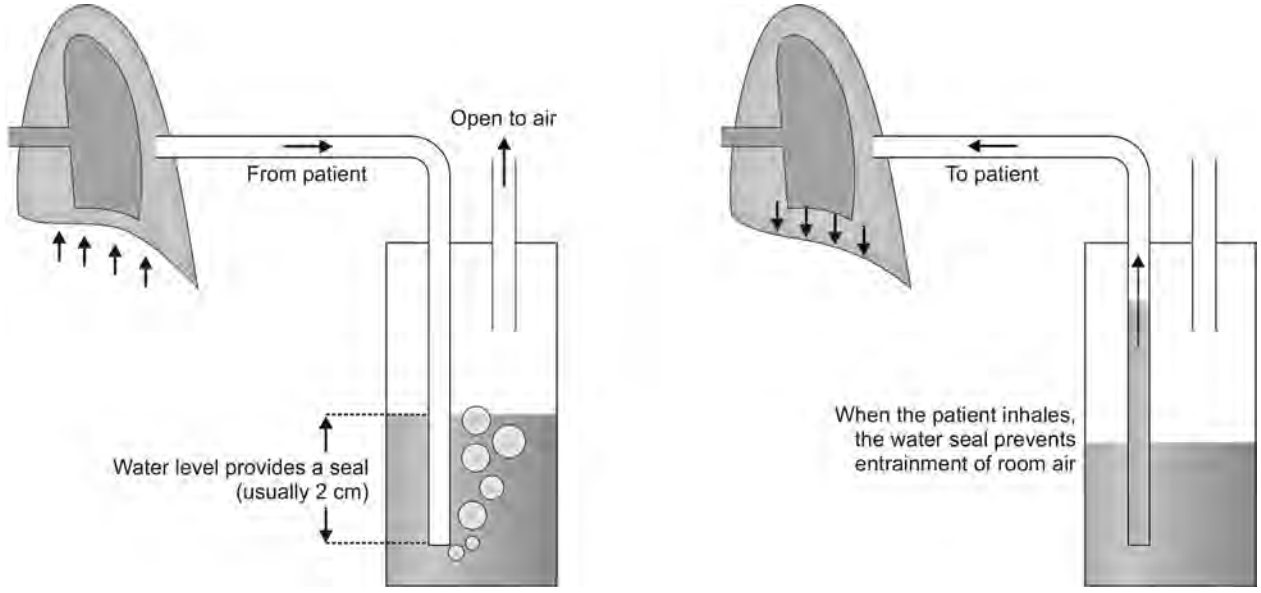


FIG. 6A: Single-chamber underwater seal drain.

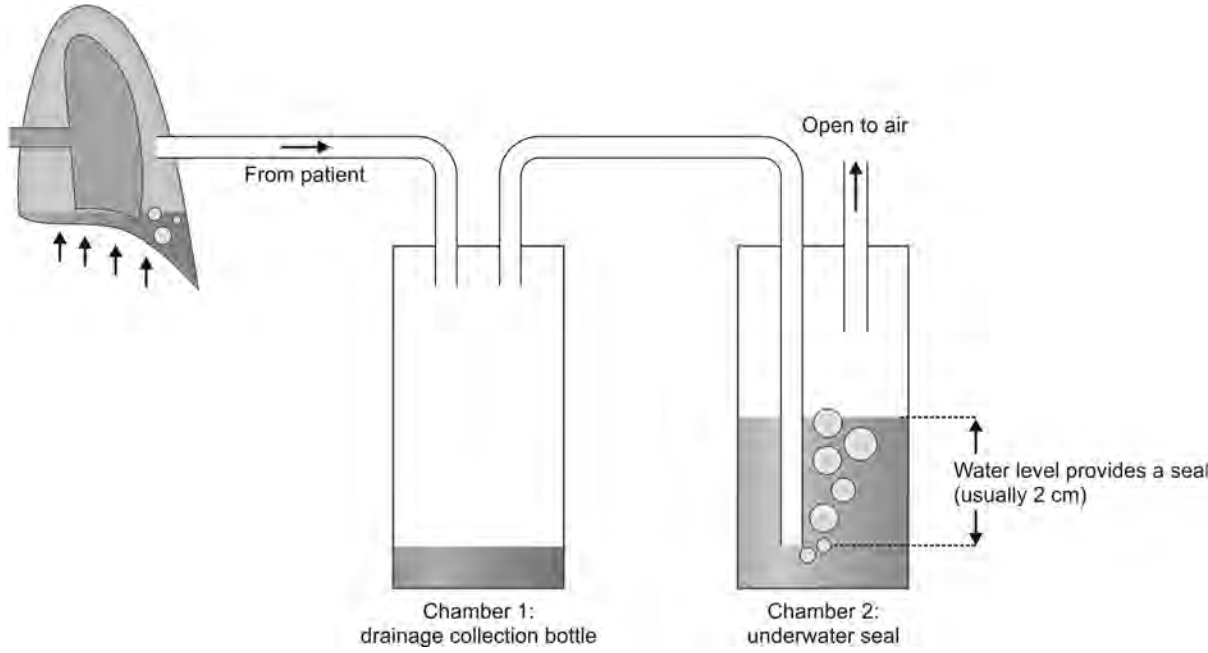


FIG. 6B: Two-chamber underwater seal drain.

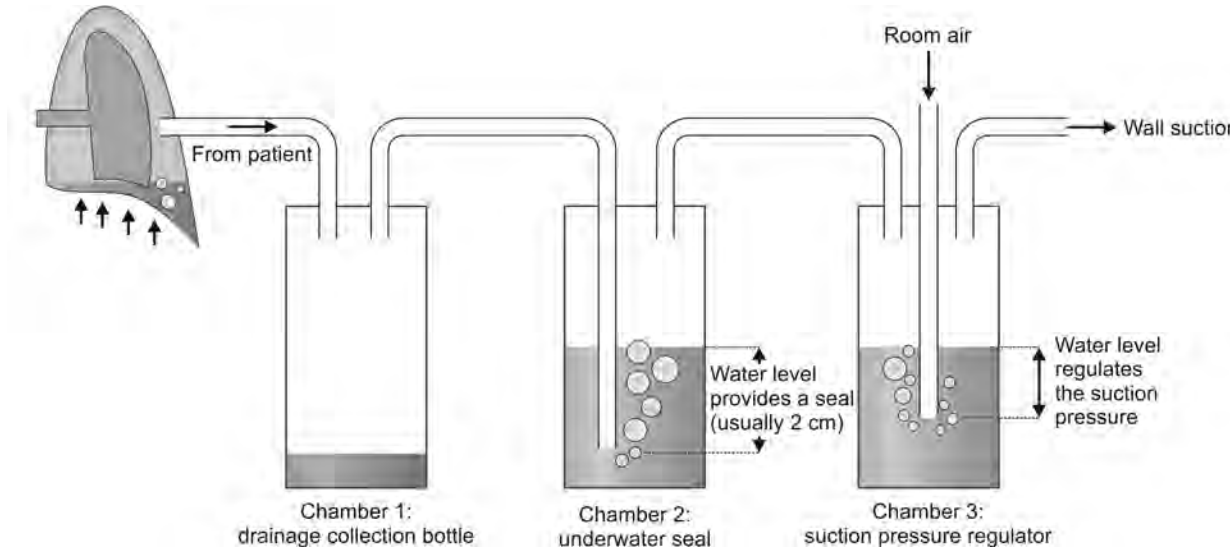


FIG. 6C: Three-chamber underwater seal drain.

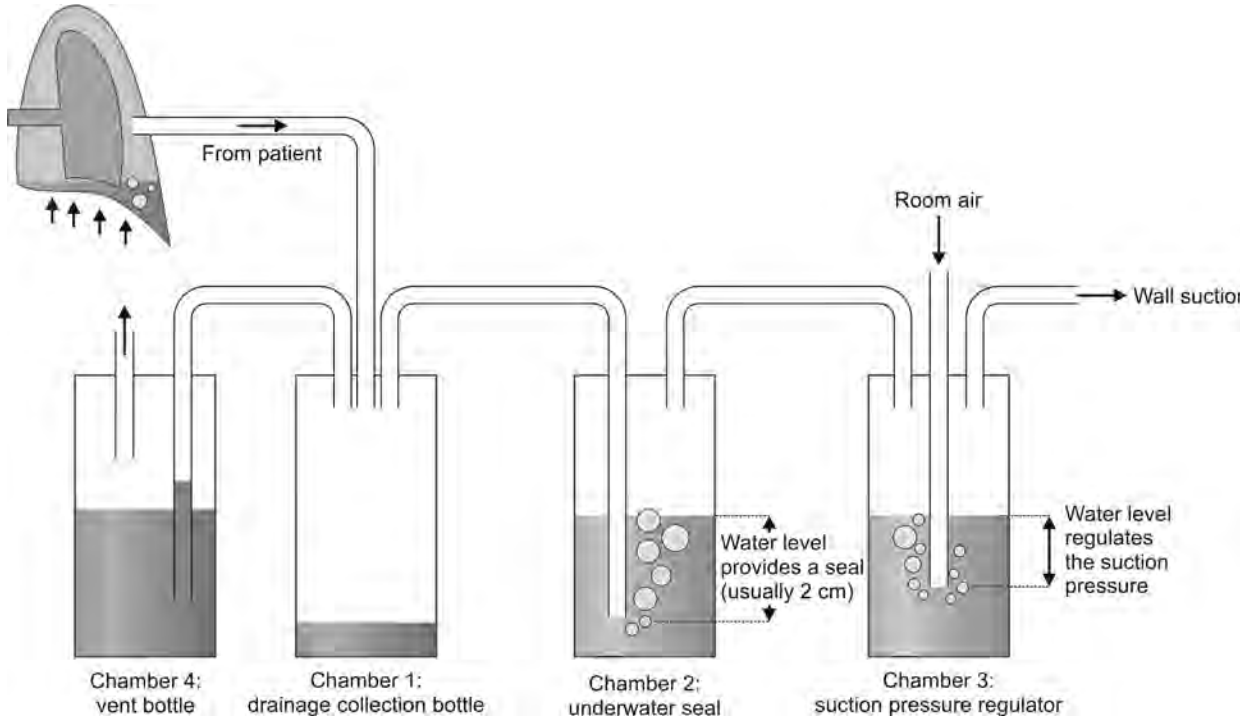


FIG. 6D: Four-chamber underwater seal drain.

seal, and not connected from the wall suction and vented to the room air. In case of sudden suction failure, it protects the patient from pneumothorax. In normal circumstances, with adequate suction, the underwater seal prevents the air from the fourth chamber from entering the rest of the system.

Intercostal Chest Drain removal

Chest drain can be removed, if: (1) Chest X-ray shows complete lung expansion (resolution of pneumothorax/hemothorax or pleural effusion). (2) No air leak (ask the patient to cough and look for air bubbling at the underwater seal). (3) Daily drainage should be <200 mL/day (should not be blood). Once the decision for drain removal is taken, take the help of an assistant and maintain aseptic precautions while removing the drain. Clean the wound and tubing with Betadine. Cut the distal end of the suture and untie. Explain the procedure to the patient and ask the patient to do inspiration and expiration on instruction. Ask the assistant to hold the ends of suture. Ask the patient to hold the breath at the peak of expiration and pull the drain out while the assistant pull the ends of suture

to tighten the knot thereby sealing the wound as soon as the drain is pulled out. Ask the patient to resume breathing as the knot is tied. Extrastitch may be applied to secure an air tight closure. Sterile dressing is applied. Check the integrity of the removed drain (especially for pigtail catheters). Chest X-ray is done 2 hours after drain removal to rule out pneumothorax. Symptomatic large pneumothorax needs drain reinsertion otherwise observation with serial chest X-rays is required for small asymptomatic pneumothorax which resolves spontaneously. For drain reinsertion always make a separate incision. Never use the previous drain site for drain reinsertion even if the drain is inadvertently pulled out.

Complications Related to Intercostal Chest Drain Insertion

The complications rate mainly depends on operator experience, the size of the tube, and use of imaging to guide insertion. Fewer complications appear when experienced operators insert under image guidance. The most frequent immediate complications include pain, inability to place the drain, and vasovagal syncope, while delayed complications included pain, blockage of drain, dislodgment of tube, and subcutaneous emphysema. With large-bore chest drain (LBCT ≥20 F) commonly reported complications are malposition, drain blockage, organ injuries, and empyema. Re-expansion pulmonary edema is a rare, but potentially serious complication of the treatment of pneumothorax by pleural drainage. The major risk factors are the duration of collapse prior to the attempts of re-expansion (>3 days) and the rapidity of the re-expansion, especially if suction is applied. The pathogenesis of re-expansion pulmonary edema is not clear, but may be related to increased pulmonary capillary permeability secondary to the vascular damage following prolonged collapse, perhaps compounded by increased capillary blood flow due to re-expansion. Re-expansion pulmonary edema is usually self-limited and management is supportive. In high-risk patients, staged lung expansion and avoidance of active suction, if possible, should be considered in order to minimize the risk of this complication. Complications related to chest drain insertion are summarized in (**Table 5**).

TABLE 5: Complications of intercostal chest drain insertion.

Insertion-related complications	• Malposition of the chest tube • Hemothorax, lung injury (laceration and bronchopleural fistula) • Diaphragm injury • Cardiac and great vessel injuries • Esophageal injury • Thoracic duct injury (chylothorax) • Injury to abdominal organs (stomach, liver, spleen, and bowel)
Infectious complications	• Chest tube site infection • Empyema • Necrotizing chest wall infection
Mechanical complications	• Tube dislodgment • Tube kinking • Tube occlusion • Arrhythmias • Phrenic nerve palsy • Horner's syndrome
Miscellaneous complications	• Pain • Inadvertent drain removal (inadequately secured chest tube) • Subcutaneous emphysema • Re-expansion pulmonary edema • Retained catheter fragment • Chest wall arteriovenous fistula • Procedure tract metastases (mesothelioma)

PNEUMOMEDIASTINUM (MEDIASTINAL EMPHYSEMA)

Presence of air in the mediastinum is termed as pneumomediastinum and also known as mediastinal emphysema. Presence of air into the mediastinum without an obvious causative factor is termed as spontaneous pneumomediastinum and secondary pneumomediastinum when a causative factor is identified, e.g., operative procedure, viscous perforation, infection, or trauma. Pneumomediastinum can be observed in a significant percent of patients in whom no causative factor is identified. Acute exacerbation of asthma and COPD with excessive coughing may lead to pneumomediastinum.

Pathophysiology

Laenek in 1827 first described the pneumomediastinum. Possible explanation for pneumomediastinum is the abnormal sudden increase of pressure in the mediastinum, creating low and negative pressure in the pleural cavity, causing air to dissect in between the mediastinal structures, which support the mediastinal organs. The situation can also be arisen by a dramatic decrease in intravascular pressure and that further create relative pressure gradient in the perivascular spaces. Subcutaneous emphysema may also occur as the air may dissect to the neck, upper abdomen, or the skin via the loose alveolar fat tissue. Pneumothorax or pneumoperitoneum can also occur once air passes the pleura or peritoneum.

Incidence

The pneumomediastinum is not a common entity, but many authors believe that the occurrence of pneumomediastinum is more frequent than initially thought due to underdiagnosis. Infrequently the pathology may not be identified on the chest radiograph and consequently related symptoms may be attributed to musculoskeletal pain or other insignificant causes.

Clinical Presentation

The main presenting symptom is chest pain, usually retrosternal, radiating to the neck or the back. The pain is acute and sudden onset, or follows exacerbations of underlying pathology such as asthma. Other frequent symptoms include dyspnea, coughing spells, neck pain, emesis, or dysphagia, which however may

be attributed to the possible underlying disease. In cases of spontaneous pneumomediastinum no complain is usually reported and no inducing factor may be found. With diagnosed pneumomediastinum, subcutaneous emphysema can be detected in 70% of patients. Other clinical features depending on underlying pathology include rhinolalia (nasally sounding voice), hoarseness of voice, and swelling of neck. Most patients generally remain well appearing, but in some patient clinical evaluation may reveal tachycardia, tachypnea, or anxiety. A specific sign with an infrequent appearance should be sought for, known as the Hamman's sign. It is the presence of mediastinal crunch or click present on auscultation over the cardiac apex and the left sternal border synchronous with the heartbeat. Accumulation of a significant amount of air in the mediastinum, causing vessel or tracheal obstruction is considered as malignant pneumomediastinum and gives rise to features suggestive of tamponade and decreased venous return.

Diagnosis

Plain anterior chest film is helpful in diagnosing the pneumomediastinum, showing lucent streaks, bubbles of air outlining mediastinal structures, and visible mediastinal pleura (**Fig. 7**). If chest X-ray is inconclusive, chest CT scan should be considered to confirm the diagnosis, also helpful in assessing the extent of the pneumomediastinum (i.e., mild, moderate, or severe). CT chest can also be performed in suspicious cases and to identify causative factors or pathologies as routine diagnostic modality. CT chest can also differentiate pneumomediastinum and pneumopericardium (air within the pericardium and not on the prepericardial fat). CT chest can also reveals presence of pneumothorax which can be missed on a plain chest X-ray in cases with severe subcutaneous emphysema. Bronchoscopy, esophagoscopy, or esophagography are not routinely required.

Management

Pneumomediastinum is generally known as a benign clinical condition with good prognosis. Once the significant pathology is excluded, the pneumomediastinum treatment is directed toward symptom relief. After diagnosis patient can be hospitalized for next 24 hours for observation. Strict bed rest is advised with symptomatic treatment for pain. Antianxiety drugs and coughing suppressant, antitussives can be added. Oxygen administration should be added as this increases the gas absorption. Any underlying pathology such as asthma or COPD should be treated and controlled adequately. In the rare instances of missed esophageal/pulmonary trauma, significant amount of air accumulated in the mediastinum which can cause important air leak and the simple pneumomediastinum may progress to a tamponade and airway compression. In such cases, decompression, VATS, or even thoracotomy may require. Extensive subcutaneous emphysema or pneumothorax is the other complication of pneumomediastinum which may require skin incisions and chest tube drainage. Respiratory compromise may occur if air can dissect in the retropharyngeal and retroperitoneal space. Rarely air can dissect between the mediastinum and the upper spine causing free air in the spinal canal and the condition is called pneumorrhachis.

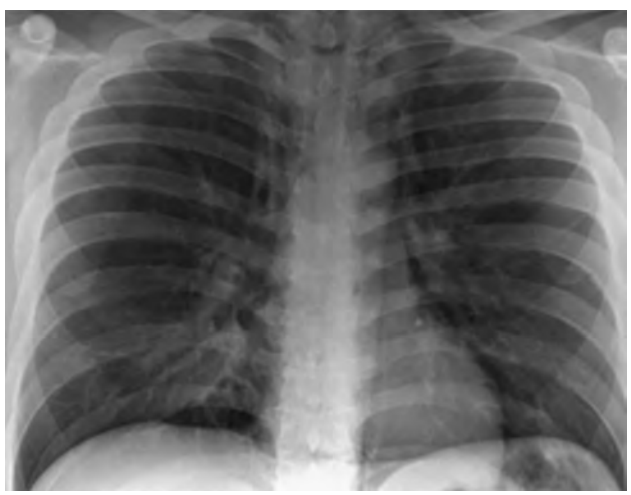


FIG. 7: Chest X-ray showing mediastinal emphysema.

SUBCUTANEOUS EMPHYSEMA

Subcutaneous emphysema is a condition when air gets into the tissues, accumulated under the skin and in the soft tissues, and on palpation gives crepitus. This frequently seen in the soft tissues of the chest wall or neck, but other parts of the body can also involve. Various diseases process can give rise to subcutaneous emphysema such as blunt or penetrating trauma, pneumothorax, barotrauma, infection, malignancy, or can develops as a complication of surgical procedures. The most common and visible sign and symptom of subcutaneous emphysema is swelling around the neck accompanied with pain in the chest. Other clinical features include mild sore throat, neck pain, swallowing difficulties, dyspnea, wheezing, and feeling of distension. Most of the cases present with minimal symptoms, no specific treatment is required. Condition becomes severe, stressful, and life-threatening if it involves the deeper tissues of the thoracic outlet, chest, and abdominal wall, can lead to high airway pressure, severe respiratory acidosis, ventilator failure, pacemaker malfunction, airway compromise, and tension phenomena due to restriction of full lung re-expansion. Subcutaneous emphysema can be diagnosed by physical examination (crepitation on palpation) and radiological studies indicating air in the involved area. Subcutaneous emphysema often presents a management dilemma. Management of subcutaneous emphysema includes identifying and removal of the offending cause of the subcutaneous dissection of air. Subcutaneous incisions, needles, drains, or cervical mediastinotomy are the modalities of treatment used in clinical practice. Two infraclavicular incisions may be an option when these interventions do not relieve increasing respiratory distress.

SUMMARY

Pneumothorax can occur in various clinical settings. It is classified as primary and secondary pneumothorax. Small PSP often requires no intervention, while a SSP almost always

requires drainage because of the high risk of recurrence and complications. In an emergency situation, one should believe more on clinical findings rather than waiting for X-ray, and immediate treatment is required. Management of pneumothorax is summarized in **Table 6**. Pneumomediastinum is considered as uncommon condition when air leaks into the mediastinum as a result of physical trauma or other pathologic situations and detected in mediastinum on chest X-ray. Clinical features may include breathlessness, hoarseness of voice, and subcutaneous emphysema mostly affecting neck, face, and chest. On auscultation "crunching" sound can be heard timed with the cardiac cycle (Hamman's crunch). The diagnosis can be confirmed by doing CT scan of the thorax. Pneumomediastinum may also present with cardiac tamponade like symptoms due to increased intrapulmonary pressure on venous flow to the heart. Most of the pneumomediastinum are treated conservatively as the tissues in the mediastinum will slowly resorb the air of the cavity.

TABLE 6: Summary—treatment of pneumothorax.

Primary spontaneous pneumothorax	***Secondary spontaneous pneumothorax***
Small pneumothorax: • Provide oxygen and observation in emergency department • Repeat chest X-ray after 24 hours if no further increase in size, then no further management only follow-up in outpatient department (OPD) *Large pneumothorax*: • Hospitalization • Chest tube insertion • If expansion of lung and no air leak • Remove chest tube and repeat chest X-ray after 24 hours • If stable then no further management • If large pneumothorax or air leak then surgical intervention needed	*Small/large pneumothorax*: • Hospitalization • Oxygen inhalation • Chest tube insertion *Surgery*: In patients with persistent air leak, recurrent pneumothorax, spontaneous hemothorax professions such as pilots and divers *Chemical pleurodesis*: Only be used if a patient is either unwilling or unable to undergo surgery. Rate of success is low with chemical pleurodesis

MULTIPLE CHOICE QUESTIONS

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89 CHAPTER

Pleural Effusion, Lung Empyema, and Cavitary Lung Lesions

Laxman Bhusal, Rabin Bom

PLEURAL EFFUSION

The term effusion means escape of a fluid from anatomical vessels by rupture or exudation. Pleural effusion means presence of excessive amount of fluid in the potential space between the visceral and parietal pleura. There are many causes that results in pleural effusion (**Table 1**), e.g., congestive heart failure (CHF), malignancy, pneumonia, and pulmonary embolism. Tuberculosis is most common cause in the developing world. Other causes that can lead to pleural effusion include viral infections, cirrhosis, nephrotic syndrome, uremia, ovarian hyperstimulation syndrome, collagen vascular diseases, myxedema, and intra-abdominal conditions.

Pathophysiology of Condition

Pleural fluid is secreted from parietal pleura and absorbed by visceral pleural microcirculation and lymphatics of parietal pleura. When there is excessive production of pleural fluid or decreased reabsorption then pleural effusion occurs. Normally there is 0.1–0.2 mL/kg body weight fluid present in pleural space which is clinically insignificant. Pleural effusions are mainly divided into two groups— (i) transudates and (ii) exudates—according to composition of the pleural fluid. Transudate is ultrafiltrate of plasma, containing low amount of protein. A transudative effusion develops due to an increase in hydrostatic pressure or decrease in oncotic pressure within the pleural microvessels. This results from imbalance between hydrostatic and oncotic pressure between pleural microvessels. Most common cause of transudate is CHF. Exudates contains relatively high amount of protein. Any pulmonary or pleural process leading inflammation can cause exudative effusion. Most common cause for exudative effusion is parapneumonic effusion. Parapneumonic effusion is caused due to intense pleural inflammatory reaction to infection of adjacent lung. Exudative effusion can also occur due to malignant conditions, inflammatory conditions in the abdomen like pancreatitis or subphrenic abscess. Pleural adhesion may occur due to fibrinous tissue left behind after reabsorption of exudative effusion.

Massive effusion (>1.5–2 L) is usually caused by malignancy but also can occur in heart failure and other volume load conditions. Pleural fluid is considered as an exudate if one or more of the following conditions are met (Light's Criteria):

- Pleural fluid protein level/serum protein level exceeds 0.5.
- Pleural fluid lactate dehydrogenase (LDH) level/serum LDH level exceeds 0.6.
- Pleural fluid LDH level exceeds two-thirds of the upper limit of normal for the serum LDH level.

Clinical Presentation

Most of small pleural effusions are asymptomatic. Patient complains of pleuritic pain, pain over shoulder. Dyspnea usually does not occur until the volume of pleural fluid is at least 500 mL in adults. Physical finding varies depending on amount of pleural effusion. Pleural frictional rub may be only finding in isolated pleurisy. Signs of cardiopulmonary compromise may be present in massive effusions.

Red Flags (Concerning Features)

- Respiratory rate >30 breaths/min
- Heart rate >120 beats/min
- Blood pressure <90/60 mm Hg
- Hemorrhagic pleural effusion

Evaluation

History: Patient complains of fever, pleuritic chest pain, and dyspnea.

Physical examination: Oxygen saturation may be decreased in moderate-to-severe pleural effusion. Patient may feel difficulty in speaking or completing sentences. High respiratory rate in moderate-to-severe pleural effusion. Unequal movement of chest wall may be noticed in severe pleural effusion. Decreased breath sounds or bronchial breathing sound on auscultation. Dullness on percussion over pleural effusion side. Orthopnea is present; patient can be seen seated with tripod position. Tachycardia is seen in

TABLE 1: Causes of pleural effusion.

Transudates	• Congestive heart failure • Cirrhosis with ascites • Nephrotic syndrome • Hypoalbuminemia • Myxedema • Peritoneal dialysis • Glomerulonephritis • Superior vena cava obstruction • Pulmonary embolism
Exudates	*Infections:* • Bacterial pneumonia • Bronchiectasis • Lung abscess • Tuberculosis • Viral illness • Fungal infection • Parasitic infections
	Neoplasms: • Primary lung cancer • Mesothelioma • Pulmonary or pleural metastasis • Lymphoma
	Connective tissue diseases: • Rheumatoid arthritis • Systemic lupus erythematosus • Drug-induced lupus • Immunoblastic lymphadenopathy • Sjögren's syndrome • Wegener's granulomatosis • Churg–Strauss syndrome
	Abdominal or gastrointestinal disorders: • Pancreatitis • Subphrenic abscess • Esophageal rupture • Abdominal surgery • Diaphragmatic hernia • After liver transplant • Endoscopic variceal sclerotherapy
	Other conditions: • Pulmonary infarction • Uremia • Drug reactions • Postpartum • Chylothorax • Meigs' syndrome

moderate-to-severe cases of pleural effusion. Hypotension may be seen in severe pleural effusion. Pedal edema present in cases of fluid overload conditions such as CHF, nephrotic syndrome, cirrhosis, and malnutrition.

Investigations

Tests routinely performed on pleural fluid include the cell count and cell differential, pH, protein, LDH, and glucose. Additional commonly performed tests in selected patients include amylase, cholesterol, triglycerides, N-terminal pro-brain natriuretic peptide (BNP), creatinine, adenosine deaminase (ADA), gram and acid-fast bacillus (AFB) stain, bacterial and AFB culture, and cytology. Suspected patients with pleural effusion should undergo chest X-ray (**Figs. 1A** and **B**). Minimum of 200 mL of pleural effusion is required to be seen in upright chest radiograph. Less than 200 mL of pleural effusion can be noted in posterior costophrenic gutter on lateral projections. Chest ultrasound has replaced the lateral decubitus X-ray in the evaluation of suspected pleural effusions and as a guide to thoracentesis (**Fig. 2**). Sonographically, pleural effusion appears hypoechoic fluid above the diaphragm. Curvilinear probe is used to visualize pleural effusion in mid axillary line. Hemothorax and pyothorax appears heterogeneous in ultrasound. A significant pleural effusion is large enough to produce a pleural fluid strip >10 mm wide on lateral decubitus radiographic views or by ultrasound. CT scan is gold standard for pleural effusion, it can detect as little as 3–5 mL of pleural effusion (**Figs. 3A** and **B**). CT scan helps in differentiating between pleural and parenchymal cause for pleural effusion.

Diagnostic thoracentesis is done if available with help of ultrasound to reduce the complications. This fluid should be sent for culture and biochemical analysis. Light's criteria to identify exudative pleural effusion are 98–99% sensitive wile specificity is 65–86%. Most transudates have absolute total protein concentrations below 3.0 g/dL (30 g/L). Tuberculous pleural effusions virtually always have total protein concentrations above 4.0 g/dL (40 g/L). Pleural fluid LDH levels above 1,000 IU/L (with upper limit of normal for serum of 200 IU/L) are characteristically found in empyema, rheumatoid pleurisy, and pleural paragonimiasis, and are sometimes observed with malignancy. A pleural fluid of pH < 7.3 is associated with parapneumonic effusions, malignancies, rheumatoid effusions, tuberculosis, and systemic acidosis. A pH < 7.0 strongly suggests empyema or esophageal rupture and is generally taken to be an indication for tube thoracostomy. A low pleural fluid glucose concentration [<60 mg/dL (3.33 mmol/L), or a pleural fluid/serum glucose ratio < 0.5] narrows the differential diagnosis of the exudate. If there is neutrophil predominance then it suggests parapneumonic, pulmonary embolism, or pancreatitis in origin. If there is lymphocytic predominance then it favors towards cancer, tuberculosis, or postcardiac surgery.

Measurement of ADA may be helpful to distinguish between malignant and tuberculous pleurisy when an exudative effusion is lymphocytic, but initial cytology and smear and culture for tuberculosis are negative. The level of ADA is typically >35–50 U/L in tuberculous pleural effusions.

In case of nonbloody tap, bloody fluid suggests trauma, neoplasm, or pulmonary infarction. If the hematocrit of the pleural fluid exceeds that of the peripheral blood by 50%, the effusion is, by definition, a hemothorax. In case of suspicion of malignancy fluid should be submitted for cytologic examination.

FIGS. 1A AND B: (A) X-ray suggestive of mild pleural effusion on left side of chest indicated by arrow; (B) X-ray suggestive of massive pleural effusion on left side of lung.

Treatment

Treatment is started with systematic approach starting from airway-breathing-circulation. If dyspnea is present oxygen is supplemented. Most pleural effusions do not require emergent drainage. Indications of therapeutic thoracentesis in emergency are: (1) Massive effusions (>1.5 L), (2) Respiratory and circulatory collapse in which condition draining the pleural effusion stabilizes the patient, (3) Pyothorax, (4) Recurrent pleural effusion in oncology patient where patient gets symptomatically better after thoracentesis. Relative contraindications of thoracentesis include coagulopathy and bleeding disorders. For risk of potential pneumothorax ultrasound-guided thoracentesis can be performed.

Following thoracentesis, a chest radiograph should be obtained to evaluate for iatrogenic pneumothorax. Depending on laboratory result of thoracentesis antibiotics are used. In developing countries, tuberculosis is common so antitubercular medicine are initiated as per national tuberculosis guidelines. In case of pyothorax, broad-spectrum antibiotics are initiated until culture and sensitivity results and then narrowed down. If pleural effusion is due to systemic cause such as cardiac, liver, and renal causes, then those are treated first.

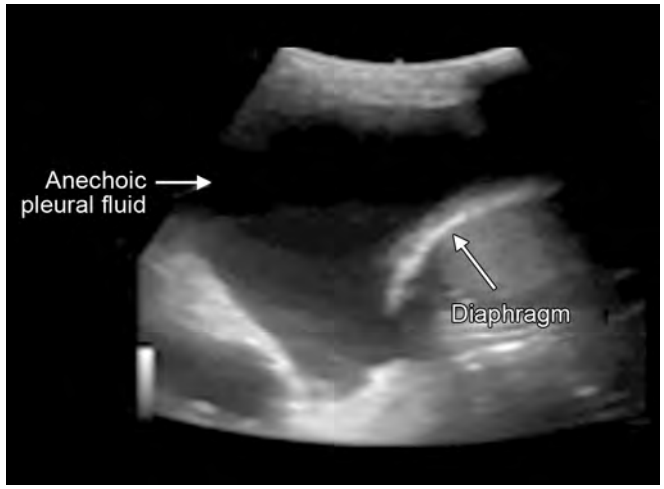
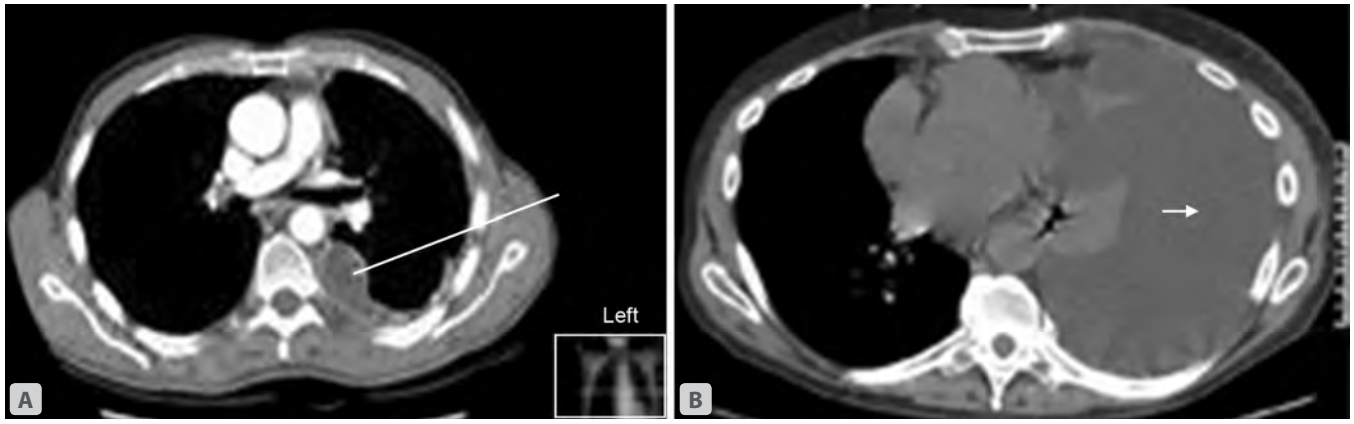


FIG. 2: Ultrasound suggestive of pleural effusion above diaphragm.

Disposition

Patients with pleural effusion who are having unstable respiratory and hemodynamic condition are admitted to hospital. Viral pleuritic or pleural effusion, minimal effusion after surgery or postpartum resolves spontaneously within few days. Pleural effusion that develops on background of cardiac failure responds well to diuretics. Patients with parapneumonic



FIGS. 3A AND B: (A) CT scan suggestive of left-sided mild pleural effusion; (B) CT scan suggestive of massive pleural effusion of left side of lung.

effusion due to community-acquired pneumonia should be admitted to hospital as it increases morbidity and mortality. Empyema develops in 5–10% of parapneumonic effusion. Early surgical drainage is treatment of choice. Malignant pleural effusion indicates disseminated stage of cancer. Recurrent drainage may be required for symptomatic relief. These patients may get relieved by pleurodesis or pleuroperitoneal shunts.

LUNG EMPYEMA

An empyema refers to a collection of pus within the pleural space, which can develop when pyogenic bacteria, fungi, parasites, or mycobacteria invade the pleural space, either from an adjacent pneumonia or from direct inoculation (e.g., from blunt trauma) or other source. Empyema that develops from an adjacent pneumonia is a subclass of a complicated parapneumonic effusion. Empyema is pus in pleural cavity (**Figs. 4A** and **B**).

Causes

Bacterial pneumonia with a parapneumonic effusion is the most common precursor, seen in about 60% of empyema patients (**Table 2**). Other causes of empyema up to 40% may be secondary to a nonpneumonic process, such as systemic infection with hematogenous spread or abdominal etiology (**Table 3**).

Pathophysiology of Condition

Most empyema is due to underlying pneumonia. They develop in three stages. Patient can present at any stage of development.

1. *Simple or uncomplicated parapneumonic effusion*: Pleural effusion with exudative nature without evidence of microorganisms or infection.
2. *Complicated parapneumonic effusion and empyema:* When bacterial invasion across the damaged pleural mesothelium stimulates an inflammatory response resulting in fibrin deposition and loculations within the pleural space. Here exudative fluid with high white cell counts is noted. If frank pus is noted then it is termed as empyema. Empyema can present independently of pneumonia (e.g., empyema due to esophageal rupture, blunt or penetrating chest trauma, and hematogenous spreads).
3. *Chronic organization:* Pleural fluid begins to organize. Fibrinous pleural covering starts to form and may encase the lungs impairing lung functions.

Clinical Presentation

Patient is suspected for empyema if symptoms of pneumonia do not resolve with the therapy. Symptoms of pneumonia are fever, cough, dyspnea, chest pain, and malaise. Onset may be insidious, patient appears chronically ill, weight loss, anemia, and night sweats.

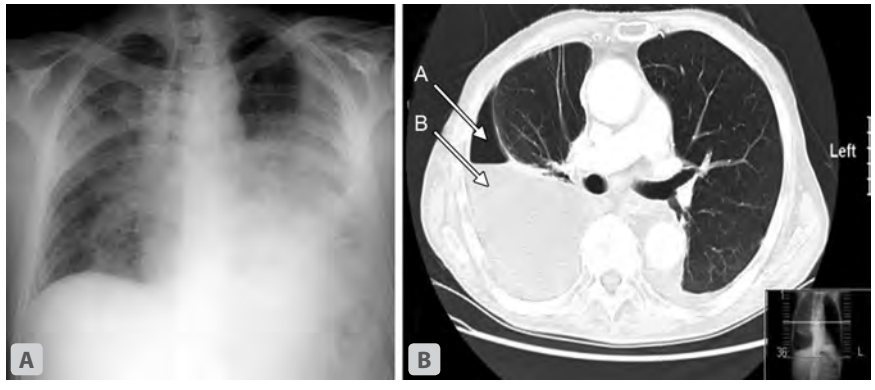
Physical examination includes decreased breath sounds, dullness to percussion, decreased tactile fremitus, and occasionally frictional rub. Patient with pneumonia deteriorating or not getting better with antibiotic is feature of concerns.

Diagnosis

Diagnosis is done by aspiration of pleural fluid by thoracentesis preferably with ultrasound guidance. At least one of following finding should be present: Positive Gram stain or culture, pleural fluid glucose < 40 mg/dL, pH <7.2, and LDH > 1,000 IU/L. Patients need to have following investigations: Chest X-ray and ultrasound of lungs, if loculated effusion CT scan of chest may be required. Complete blood count (CBC), serology, pleural fluid analysis (protein and LDH), Gram stain, AFB stain, culture, and sensitivity are done.

Treatment

Main treatment of empyema is drainage and antibiotics. Analgesics like nonsteroidal anti-inflammatory drugs (NSAIDs) should be used for pleuritic pain. Ultrasound-guided drainage of small empyema and chest tube thoracentesis relieves symptoms. Antibiotics should be used on background of clinical presentation and results of diagnostic studies. Antibiotics should cover both aerobic and anaerobic pathogens. Antibiotic with beta-lactamase activity like piperacillin-tazobactam or ampicillin-sulbactam, a carbapenem, or clindamycin should be used. For anaerobic pathogens, second- or third-generation cephalosporin plus metronidazole, a carbapenem, or a beta-lactam aminopenicillin with beta-lactamase activity should be used. For methicillin-resistant *Staphylococcus aureus* (MRSA)



FIGS. 4A AND B: (A) Empyema on left side of lung; (B) CT scan suggestive of pleural empyema.

TABLE 2: Causative agents of empyema.	
Bacteria	• *Streptococcus pneumoniae*, microaerophilic streptococci (e.g., *S. anginosus and S. intermedius)* • Anaerobes*: Fusobacterium* species, *Prevotella* species, *Peptostreptococcus* species, and *Bacteroides* species • *S. aureus* • Atypical bacteria: *Legionella, Mycoplasma,* and *Chlamydia* species • Mycobacteria
Fungal	Rare <1% mostly *Candida*

TABLE 3: Common organism in empyema and associated pathology.	
Pathology	***Organism***
Pneumonia	• *Streptococcus pneumoniae* • *Staphylococcus aureus*
Pneumonia (unimmunized with Haemophilus influenzae type B vaccine)	*H. influenzae*
Lung abscess	Mixed oropharyngeal anaerobes
Aspiration pneumonia	*S. aureus*
Recent thoracotomy	Gram-negative bacilli
Chest trauma	• *S. aureus* • Gram-negative bacilli
Contiguous abdominal infection	• Gram-negative bacilli • Anaerobes
Esophageal rupture	Mixed oropharyngeal organisms
Postprocedure	• Methicillin-resistant *S. aureus* • *Pseudomonas*
Hospital-acquired empyema	• Methicillin-resistant *S. aureus* • *Pseudomonas*
Pneumonia in the setting of human immunodeficiency virus	• Tuberculosis • Fungal infections

vancomycin is used. Intravenous antibiotic should be used until clinical and radiological improvement then switched to oral agents. Fibrinolytics (streptokinase, urokinase, etc.) helps to drain better in loculated empyema. One-third of patients treated with antibiotics and chest tube drainage need surgical drainage.

Disposition

Patients are admitted to hospital until clinical and radiological improvement is noted. Chest tube should be removed when the lung is fully reinflated and there is <200–300 mL of noninfected fluid output in 2 hours.

CAVITARY LUNG LESIONS

When there is confined space within lung which contains air, fluid, solid material, or combination of the three then it is known as cavitary lesion. These lesions are surrounded by a wall, usually of varied thickness. Some authors have tried to make this distinction by defining cysts as being air-containing spaces surrounded by a thin (4 mm or less) wall and cavities at least 5 mm thick. Cavitary lesions may be single or multiple and may be accompanied by multiple nodules, parenchymal scarring, and loss of volume (as in tuberculosis), pneumonia (as in lung abscess), or pleural disease.

Causes

Cavities are frequent manifestations of a wide variety of pathological processes involving the lung. Presence of a cavity helps the clinician to focus the diagnostic evaluation (**Table 4**). Viral infection like coronavirus disease-2019 (COVID-19) can also cause cavitary lesions in lung.

Pathophysiology of Condition

Most lung abscesses arise as a complication of aspiration pneumonia and are caused by species of anaerobes that are normally present in the gingival crevices. Pneumonitis arises first but, based upon the usual mixture of organisms, progresses to tissue necrosis after 7–14 days. This necrosis results in lung abscess and/or an empyema in the form of suppurative necrosis (pyogenic lung abscess), caseous necrosis (tuberculosis), ischemic necrosis (pulmonary infarction. In case of infectious diseases, cavitation represents the outcome of complex interactions between host and pathogen. Lung abscesses are usually polymicrobial infections. Malignant processes may cavitate because of treatment-related necrosis, internal cyst formation, or internal desquamation of tumor cells with subsequent liquefaction. Fluid within a cavitary lesion may be thin and serous (resembling pleural fluid), thick and purulent, or bloody, and it may contain necrotic lung tissue, blood cloths, or foreign material (e.g., fungal hyphae).

TABLE 4: Causes of cavitary lung lesions.		
Infectious	Bacterial	• Anaerobic abscess • Aerobic abscess • Infected bullae • Tuberculosis • Actinomycosis • Pleural empyema
	Fungal	• Coccidioidomycosis • Histoplasmosis • Blastomycosis • Aspergillosis • *Cryptococcus*
	Parasitic	*Echinococcus*, *Entamoeba histolytica, amebiasis,* and *Paragonimus westermani*
Neoplastic	• Bronchogenic carcinoma (squamous cell carcinoma or adenocarcinoma) • Metastatic cancer (colorectal or renal) • Lymphoma or Hodgkin's disease	
Inflammatory	• Sarcoidosis • Wegener's granulomatosis	
Other	Foreign body aspiration	

Clinical Presentation

Patient presents with fever, cough with purulent sputum, and shortness of breath, malaise, pleuritic chest pain, anorexia, nausea, and vomiting. At later stages hemoptysis and weight loss.

Differential Diagnosis of Cavitary Lung Lesions

Many different diseases present as cavitary pulmonary nodules. The spectrum of diseases ranges from acute to chronic infections, chronic systemic diseases, and malignancies. Knowledge of common and uncommon radiological findings in correlation with relevant clinical history and findings is necessary to make the right diagnosis and recommend the correct follow-up. Infections which may be caused by several groups of microorganisms, e.g., *S. pneumoniae, S. aureus, and Klebsiella,* include pulmonary abscess, septic emboli, *Mycobacterium tuberculosis* infection, nontuberculous mycobacterial infections, aspergillosis, systemic disease such as granulomatosis and polyangiitis, rheumatic nodules, sarcoidosis, and malignancies are considered among differential diagnosis.

Investigations

Once history and physical examination is done following investigations should be sent:

Complete blood count and chest X-ray (**Fig. 5**) initially help to come to conclusion. Chest CT scan helps to delineate the lesions (**Figs. 6A** and **B**). Routine Gram stain and aerobic culture of expectorated sputum for aerobes should be performed, ideally before antibiotics have been started. Serology if not done prior. Baseline of liver function test (LFT) and renal function test (RFT) will guide during course of treatment. Sputum culture and AFB stain for tuberculosis. Blood cultures in case of bacterial infection. Tumor markers may be necessary if malignancy is suspected. Examiner must be vigilant to look for primary source of tumor.

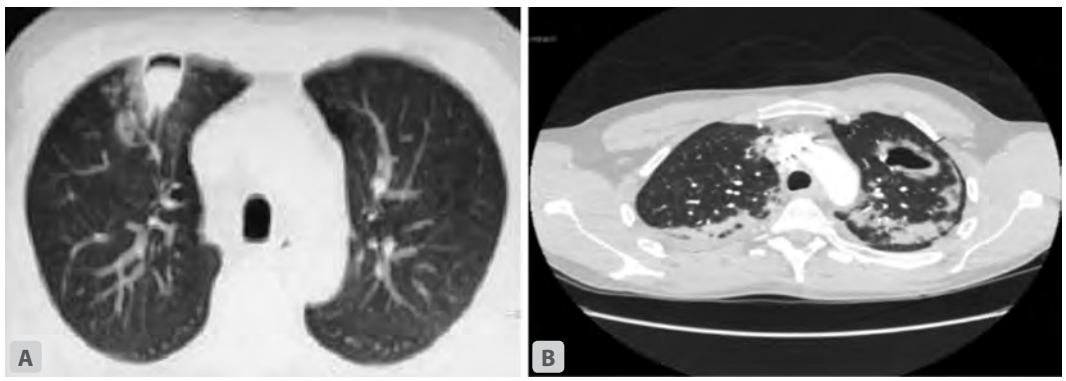
Treatment

Treatment modality depends on clinical presentation of patient to health center. If patient is in respiratory and hemodynamic distress then patient is managed in emergency. Airway, breathing, and circulation problems are addressed and managed. Patient is started on broad-spectrum antibiotics till culture report arrives. Empiric regimens should penetrate the lung parenchyma and target both strict anaerobes and facultatively anaerobic streptococci. Drugs that are reasonable to use are any combination of a beta-lactam–beta-lactamase inhibitor [e.g., ampicillin-sulbactam 3 g intravenously (IV) every 6 h] or a carbapenem (e.g., imipenem and meropenem). The duration of the antibiotic should be prolonged until the chest radiograph shows a small and stable residual lesion or is clear. If infection is due to tuberculosis then antitubercular medication are started according to national tuberculosis guidelines. Surgical drainage is must if there is cyst along with pus in thoracic cavity (empyema thoracis). The usual indications are failure to respond to medical management suspected neoplasm or hemorrhage. If infection is due to fungal etiology then antifungal are initiated. Antiparasitic medications for cavitary lesions caused by parasites. Cardiovascular and thoracic surgery and oncological consultation for cavitary lesions caused by malignancy.

Disposition

Patients with cavitary lung lesions who appear sick must be admitted to hospital. They must be managed with intravenous

FIG. 5: Chest X-ray of patient with cavitating staphylococcal pneumonia.



FIGS. 6A AND B: (A) Computed tomography (CT) of immunocompromised patient with invasive aspergillosis; (B) CT scan of the chest with contrast opacity in the left upper lobe with cavitation.

medications. Patients who are stable and ambulatory without comorbid conditions can be managed on outpatient basis.

SUMMARY

Tuberculosis is the most common cause of pleural effusion in developing countries. Chest radiograph will detect pleural effusion >200 mL. Ultrasound is more sensitive in detecting small amount (as much 50 mL) of pleural effusion. Chest CT is gold standard for minimal pleural effusion. Therapeutic thoracentesis is indicated for relief in acute respiratory and cardiovascular compromise. Diagnostic thoracentesis helps to distinguish between transudative and exudative nature of effusion.

Lung empyema required drainage for proper treatment along with management of underlying cause like pneumonia with antibiotics. Antibiotics with both aerobic and anaerobic coverage should be used. Intravenous antibiotics should be used until clinical and radiological improvement is seen.

Cavitary lesions of lungs are caused by diverse group of pathological agents. Knowledge about causative agents of cavitary lesions, clinical features, and radiological patterns helps in coming to diagnosis and management.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

90 CHAPTER

Devendra Richhariya, Bhawana Sharma

INTRODUCTION

Humans and animals are affected by large group of virus family—coronaviruses. In rare instances, animal coronavirus infect people and spread between them such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). The outbreak of coronavirus was first noticed in Wuhan city in Hubei province of China in mid-December, 2019. The World Health Organization (WHO) (under International Health Regulations) has declared this outbreak as a "Public Health Emergency of International Concern (PHEIC)" on 30th January 2020. The WHO subsequently declared coronavirus disease-2019 (COVID-19) as a pandemic on 11th March, 2020. About 213 countries and the territories are affected due to COVID-19. More than 90% of COVID-19 cases are outside China.

Available evidence shows that coronavirus [SARS coronavirus 2 (SARS-CoV-2)] is a zoonotic source (bat origin). Coronavirus is related to the SARS virus. It is an enveloped ribonucleic acid (RNA) and probably uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry. ACE2 mostly present in the lung alveolar epithelial cells, cardiac myocytes, and vascular endothelial cells

Person-to-person transmission is the main source and cause of spreading of infection. Respiratory droplets are released when infected person sneeze, cough, or speaks. These droplets contain viable viruses and infect surface also, and when any person comes in to contact of infected surface and touches his/her nose/eyes/face infections spreads. As per current evidence infectivity period starts 2 days prior to onset of symptoms and remain up to 8 days. Median incubation period is of 5 days. Various issues such as period of infectivity of a person and role of preclinical and asymptomatic period in transmission are still under research.

The SARS-CoV-2 infection (COVID-19) is primarily an upper respiratory tract infection and small proportion of cases can progress to severe systemic involvement such as acute respiratory distress syndrome (ARDS), sepsis and septic shock, and multi-organ failure including acute kidney injury and cardiac injury.

Autopsy studies done mostly in European countries and China reveal endothelial damage of pulmonary vasculature followed by extensive alveolar and interstitial inflammation due to SARS-CoV-2 infection. These changes result in COVID-19 vasculopathy, pulmonary intravascular coagulopathy, hypercoagulability, ventilation perfusion mismatch, and refractory ARDS. ARDS-induced hypoxemia may also activate the coagulation cascade.

DEFINITION OF CASES AND CLINICAL FEATURES

Suspected Cases

- Patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough and shortness of breath), a travel history/residence in a location of endemic area during the 14 days prior to symptom onset
- A patient with any acute respiratory illness who comes in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset
- A patient with severe acute respiratory illness need hospitalization and clinical presentation not fully explain the alternative diagnosis

Probable Cases

Coronavirus disease 2019 testing is inconclusive or could not be done for any reason in any suspected cases.

Confirmed Cases

Irrespective of signs and symptoms laboratory confirmation of the COVID-19 cases.

CLINICAL FEATURES

Common Generalized Features

Fever, cough, fatigue, shortness of breath, expectoration, myalgia, rhinorrhea, sore throat, and diarrhea are common generalized features. Before onset of symptoms, loss of smell and taste also reported by some patient.

Atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, and absence of fever are reported in elderly and immuno-compromised individuals.

Children may have fewer/mild symptom (fever and cough) than adult. Few cases may progress to severe disease, especially in individual who are elderly and associated with risk factors such as diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immune suppression, and cancer.

Pulmonary Features

Mild cold like symptom is seen in majority of the COVID-19 infected patient. Symptoms appear 2–14 days of exposure, mostly dry cough, fever, and sore throat. The most common complications seen in COVID-19 patients are pneumonia (15%), shortness of breath, and desaturation of blood oxygen level which needs hospitalization. About 5% of severely symptomatic patient may need advanced organ support therapy including intubation and mechanical ventilation in intensive care unit. Extrapulmonary manifestations are summarized in **Table 1**.

TABLE 1: Extrapulmonary features of COVID-19.

Cardiac manifestation	• Coronary artery disease • Acute cardiac injuries • Arrhythmias (atrial arrhythmia is common) • Heart failure • Cardiogenic shock • Cardiac tamponade • Myopericarditis
Neuromuscular manifestation	• CNS—headache, dizziness, confusion, delirium, stroke ataxia, and seizures • PNS—taste, smell, vision impairment, and neuropathy • Skeletal muscle—myopathy and raised CPK level
GI manifestation	• Anorexia • Nausea and vomiting • Abdominal pain • Abnormal liver function test • Detection of virus in stool
Renal manifestation	• Raised blood urea nitrogen • Proteinuria • Hematuria • Acute kidney injury
Ocular manifestations	• Watery eyes, increased secretions, chemosis, and conjunctivitis
Hematologic manifestation	• COVID-19 is considered as hypercoagulable state and increase risk of venous thromboembolism • Pulmonary embolism • Deep vein thrombosis and catheter-related thrombosis • Thrombocytopenia
Psychiatric manifestation	Anxiety, depression, panic/somatic attack, post-traumatic stress, and suicidal tendency
Skin manifestations	Maculopapular exanthem, papulovesicular rash, urticaria, and painful papule petechiae

(CNS: central nervous system; COVID-19: coronavirus disease-2019; PNS: peripheral nervous system)

SEVERITY CLASSIFICATION OF SARS-CoV-2, INVESTIGATIONS AND SUGGESTED TREATMENT

Progression of illness due to SARS-CoV-2 is classified in to three categories (**Table 2**) which corresponds to distinct clinical findings, treatment response, and complications. Initial stage is categorized as mild at the time of inoculation with asymptomatic or mild clinical features. Diagnosis at this stage includes respiratory sample, polymerase chain reaction, serum testing for SARS-CoV-2 immunoglobulin G (IgG) and immunoglobulin M (IgM), chest imaging, complete blood count, and liver function tests. Complete blood count may reveal a lymphopenia and neutrophilia without other significant abnormalities. Treatment at this stage is primarily targeted toward symptomatic relief. Antiviral therapy, such as remdesivir, may prove beneficial, may reduce duration of symptoms, minimize contagiousness, and prevent progression of severity. Prognosis and recovery is excellent if disease is in this stage. Next progressive stage is moderate category in which virus multiply, localized inflammation in the lung, and established pulmonary disease. Clinical features are fever, cough, and breathlessness associated with pulmonary infiltrates and ground-glass appearance in X-ray and CT scan of the chest. Markers of systemic inflammation may be elevated. Patient should be admitted in hospital and observed closely. Judicious use of anti-inflammatory therapy and corticosteroids may be beneficial if hypoxia persists or requirement of oxygen therapy increases. Few patients may progress into severe categories with extensive pulmonary involvement and extrapulmonary manifestation. Systemic inflammatory markers are elevated in moderately sever/severe categories. Inflammatory cytokines and biomarkers such as interleukin-2 (IL-2), IL-6, IL-7, granulocyte colony-stimulating factor, macrophage inflammatory protein-1α, tumor necrosis factor-α, C-reactive protein, ferritin, and D-dimer are significantly elevated in severe category patients. Troponin and N-terminal pro B-type natriuretic peptide can also be elevated. Severe COVID-19 patients are at higher risk of thrombosis due to low blood flow (induced by both vasoconstriction and stasis) together with endothelial injury and hypercoagulability. The incidence of venous thromboembolism [deep vein thrombosis (DVT) and pulmonary embolism (PE)] is more due to excessive thrombin generation and imbalance of pro- and anticoagulant factors. Stroke is also common in critically ill COVID-19 patient. Disseminated intravascular coagulation (DIC) is not a common complication of COVID-19. Pathophysiology for COVID-19-related systemic microthrombosis is summarized in **Figure 1**. Experimental therapies such as favipiravir, remdesivir, tocilizumab (TCZ) (targeting cytokine storm), and plasma therapy can be offered. Suggested investigations in each category are summarized in **Table 3**. Suggestive treatment options which are under research are summarized in **Tables 4** and **5**.

CT CHEST IN SARS-CoV-2—CORRELATION WITH DISEASE SEVERITY

Reverse transcription-polymerase chain reaction (RT-PCR) assay is used for definitive diagnosis of COVID-19. Though this is accurate laboratory test while in clinical practice sensitivity range from 42% to 83% and depend on symptom duration,

TABLE 2: Classification of clinical severity of SARS-CoV-2.

Categories	*Clinical presentation*	*Clinical parameters*
Mild	• Mild upper or lower respiratory tract infection with mild symptoms of fever, cough, sore throat, nasal congestions, malaise, headache, loss of taste or smell, mild gastrointestinal symptoms (nausea, vomiting, and diarrhea) • Clear sensorium	• No oxygen dependency • No respiratory distress • Room air SpO_2 >95% • No hypotension • No multi-organ involvement
Moderate	• Moderate lower respiratory symptoms • Dyspnea • Worsening vomiting/diarrhea • Fever confusion/drowsiness • Unusual symptoms: Febrile encephalopathy, CVA, and MI	• Oxygen dependency/±respiratory distress • Tachypnea, RR >24 breaths/min • SpO_2 <93% on room air • No hypotension • No multi-organ involvement
Severe	• Severe lower respiratory infection • Sever pneumonia • Dyspnea • Worsening nausea vomiting • Fever confusion drowsiness • Unusual symptoms: Febrile encephalopathy, CVA, and MI	• Oxygen dependency/±respiratory distress • Tachypnea, RR >30 breaths/min • SpO_2 <95% on supplemental oxygen on 10 L/min, HFNC (FiO_2 50%), NIV (FiO_2 50%, and EPAP 6) • Presence of hypotension • Shock and multi-organ involvement • Septic shock persisting hypotension in spite of volume resuscitation requiring vasopressor to maintain MAP > 65

(CVA: cerebrovascular accident; EPAP: expiratory positive airway pressure; FiO_2: fraction of inspired oxygen; MAP: mean arterial pressure; MI: myocardial infarction; NIV: noninvasive ventilation; RR: respiratory rate; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: oxygen saturation)

TABLE 3: Baseline laboratory investigations for SARS-CoV-2.

• Real-time or conventional RT-PCR test is recommended for diagnosis. • SARS-CoV-2 antibody tests are not recommended for diagnosis of current infection with COVID-19.	
Mild cases	• Complete blood count, electrolytes and ECG • If risk factors present other tests should be included e.g., LFT, KFT, PT/INR, CRP, LDH, D-dimer, lactate, blood group, arterial blood gas, ECHO, Trop I
Moderate and severe cases	Arterial blood gases, complete blood count, ferritin, fibrinogen, LFT, KFT, PT/INR, CRP, LDH, D-dimer, lactate, blood group, ECHO, ECG, Trop I, X-ray chest, HRCT chest, and collect blood culture (prior to antibiotics)
Investigations which have prognostic value and indicative of risk of progression • *CRP > 100 • LDH > 245 • Trop I > ULN • D-dimer > 1,000 ng/mL* • *Ferritin > 300 µg/L • IL-6 > 70 (10 times of ULN)*	
Baseline investigations to be repeated 48–72 hours in moderate and severe cases	

(COVID-19: coronavirus disease-2019; CRP: C-reactive protein; CT: computed tomography; ECG: electrocardiogram; ECHO: echocardiogram; HRCT: high-resolution computed tomography; IL: interleukin-1; KFT: kidney function test; LDH: lactic dehydrogenase; LFT: liver function test; PT/INR: prothrombin time/international normalized ratio; RT-PCR: reverse transcription-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; Trop I: troponin I; ULN: upper limit of normal)

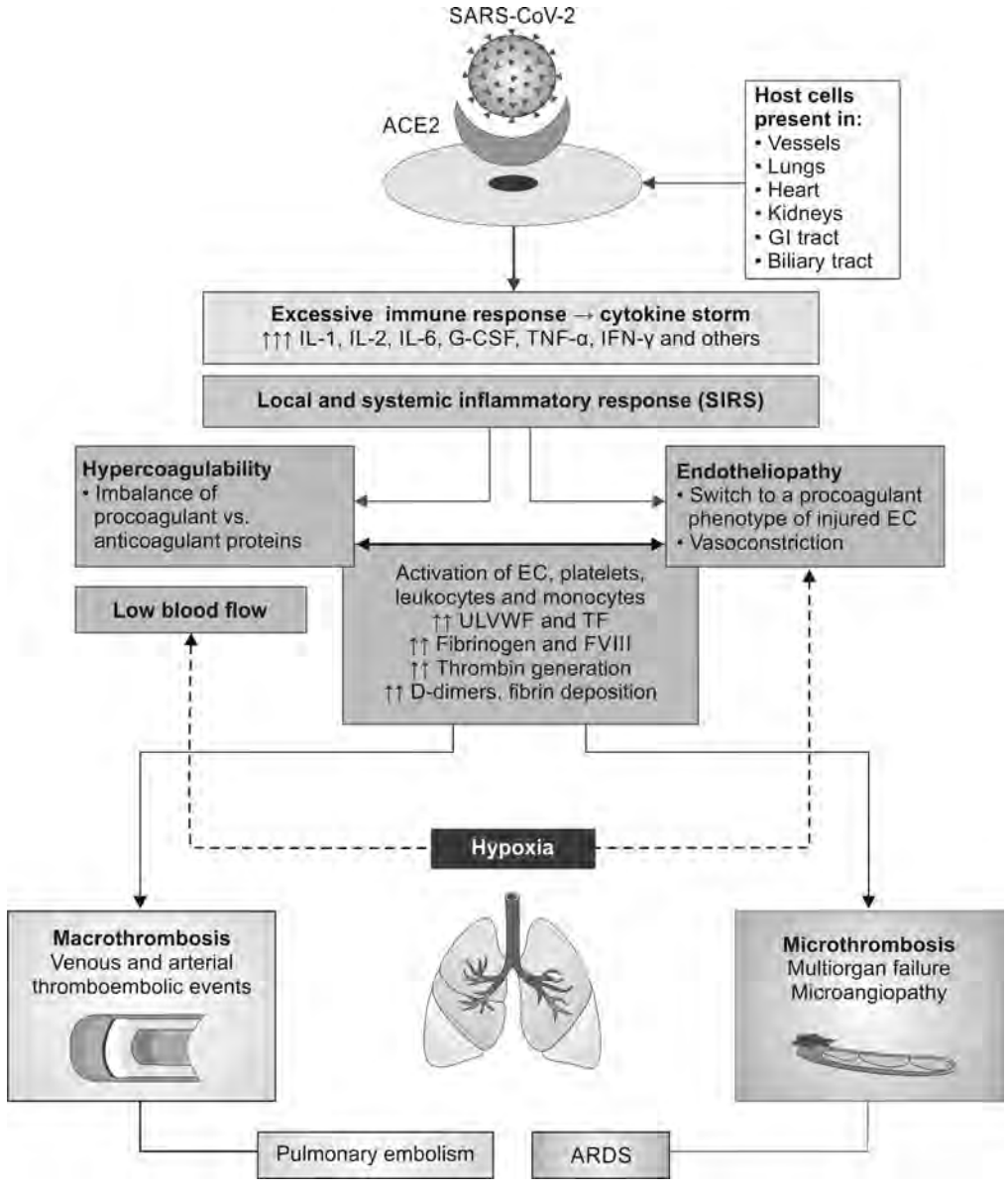
viral load, and test sample quality. RT-PCR assay results takes hours or days to come which causes pressure on observation or holding area where patient are observed before being sent to COVID ward. In view of this role, CT chest is evolving in COVID-19 for clinical workup and decision making.

The main hallmark of COVID-19 pneumonia manifests as bilateral ground glass opacities with or without consolidative areas, with a predominant peripheral, lower lobe, and posterior anatomic distribution. Some CT findings of COVID-19 overlap with some other viral disease but have some specific findings which are not seen in other disease. COVID-19 Standardized Reporting Working Group of the Dutch Radiological Society chose the term COVID-19 Reporting and Data System (CO-RADS) to standardized assessment scheme for pulmonary involvement of COVID-19. The CO-RADS provides suspicion of pulmonary involvement (category-1 very low to category 5 very high) in SARS-CoV-2 infection (**Table 6**).

Computed tomography has a reported high sensitivity in patients infected by SARS-CoV-2, thus it is largely used to help patient management. In the current public health emergency, a highly sensitive test like CT allows to speed-up diagnostic workflow and establishes isolation at admission.

REMDESIVIR

Several potential treatments for coronavirus SARS-CoV-2 infection have emerged during the COVID-19 pandemic. Remdesivir is an antiviral prodrug and originally investigated for the treatment of Ebola virus infection and considered a treatment for COVID-19 because it was known to have activity against coronaviruses that undergoes intracellular metabolism to form a pharmacologically active nucleoside triphosphate metabolite. This competes with adenosine triphosphate (ATP) for incorporation into nascent RNA chains by SARS-CoV-2 RNA-dependent RNA polymerase, delaying chain termination during replication of viral RNA. It is used for the treatment of COVID-19 pneumonia requiring supplemental oxygen in adults and adolescents (aged ≥12 years with body weight



(ACE2: angiotensin-converting enzyme 2; ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease-2019; EC: endothelial cell; FVIII: factor VIII; G-CSF: granulocyte colony-stimulating factor; GI: gastrointestinal; IFN: interferon; IL: interleukin; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SIRS: systemic inflammatory response syndrome; TF: tissue factor; TNF: tumor necrosis factor; ULVWF: ultralarge von Willebrand factor)

FIG. 1: Pathophysiology for thrombosis in critically ill patients with COVID-19. SARS-CoV-2 aggression on the host cells through ACE2 receptors, the excessive immune response-induced cytokine storm, the local and systemic inflammatory response responsible for an endothelial damage and a hypercoagulability state, leading to both systemic and macro- and microthrombosis.

≥40 kg). The recommended dose regimen comprises a loading dose of 200 mg by intravenous infusion, followed the next day by 100 mg once daily by intravenous infusion for a total of at least 5 days and maximum for 10 days (similar dose recommended for older people). Remdesivir should not be prescribed for patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min]. Its pharmacokinetics has not been evaluated in patients with renal or hepatic impairment. Its safety during pregnancy and in women who are breastfeeding is unknown.

Two clinical trials of remdesivir in COVID-19 have been published—one small study from China and the second is an international clinical trial [the Adaptive COVID-19 Treatment Trial (ACTT)]. The National Institute for Health and Clinical Excellence (NICE) review included these and an observational study (n = 53). Remdesivir significantly reduced the median time to recovery compared with placebo. In the China trial, serious adverse events were reported in 18% of patients treated with remdesivir and 26% assigned to placebo, but discontinuation was more frequent with remdesivir (12% vs. 5%). Adverse events resulted in treatment discontinuation in 9% of patients treated with remdesivir and 10% of those assigned to placebo.

TABLE 4: Suggested treatment guidelines for mild SARS-CoV-2.	
Mild cases	*(Asymptomatic to mild symptoms no oxygen therapy no X-ray/CT findings no rise of inflammatory markers, no risk factors)*
General measures in mild cases	1. Balanced diet 2. Adequate sleep 3. Breathing exercises 4. Remain physically active 5. Hot water gargles three times a day 6. Positive mood and outlook 7. In case of symptoms seek medical advice 8. Monitor saturation with pulse oximeter 9. Temperature monitoring and paracetamol as needed 10. Multivitamins, zinc, vitamin C, and vitamin D
When to seek medical attention	Immediate medical attention must be taken if serious signs or symptoms develop. These could include: 1. Difficulty in breathing and saturation <94% 2. Persistent pain/pressure in the chest 3. Mental confusion or inability to arouse 4. Developing bluish discolorations of lips/face 5. As advised by treating medical officer
When to discontinue home isolation	Patient under home isolation will end home isolation after 17 days of onset of symptoms (or date of sampling, for presymptomatic cases) and no fever for 10 days. There is no need for testing after the home isolation period is over.
During initial phase of pandemic various repurposed drugs are used in combination or alone, though their efficacy is not established: Hydroxychloroquine + azithromycin (in age <50 and no cardiac comorbidities) OR Hydroxychloroquine + doxycycline (in age >50 and no cardiac comorbidities) OR Doxycycline + ivermectin (any age with cardiac comorbidities) OR Only doxycycline (after 7 days of onset of symptoms) OR Favipiravir (contraindicated in hepatic/renal comorbidities and in pregnancy • *Tablet hydroxychloroquine 400 mg BD × 1 day followed by 200 mg BD × 9 days* • *Tablet azithromycin 500 mg OD × 1 day followed by 250 mg OD × 4 days* • *Capsule doxycycline 100 mg BD after food × 5 days* • *Tablet ivermectin 12 mg OD × 3 days* • *Tablet favipiravir 1,800 mg BD on day 1 followed by 800 mg BD × 8–14 days* • *In all regimen add antacid zinc, vitamin C, and vitamin D* • Strong recommendations against the use of chloroquine hydroxychloroquine with or without azithromycin in hospitalized or nonhospitalized patient • Strong recommendations against the use of lopinavir/ritonavir and other HIV protease inhibitors in hospitalized or nonhospitalized patient • There are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Further clinical trials are required on the role of ivermectin in treatment of COVID-19 • There are insufficient data to recommend either for or against the use of vitamin C and D and zinc for the treatment of COVID-19	

(COVID-19: coronavirus disease-2019; CT: computed tomography; HIV: human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2)

FAVIPIRAVIR

During worst hit pandemic COVID-19, repurposed drugs, already in use against other viral infections, have been introduced into quick service agent against the SARS-CoV-2 as discovery of a new and specific antiviral would involve a long timeline. One such drug is favipiravir, initially marketed as an anti-influenza agent in Japan and used in Japan for the management of emerging pandemic influenza infections in 2014. Favipiravir is administered as a prodrug. It has an excellent bioavailability (~94%), 54% protein binding, and a low volume of distribution. Within the tissue, it converts to the active form of drug by phosphoribosylation to favipiravir-RTP.

Influenza

Favipiravir inhibits 53 types of influenza viruses including seasonal strains A (H1N1), A (H3N2), and influenza B; the A (H1N1) pandemic virus; highly pathogenic avian influenza virus A (H5N1) isolated from humans.

TABLE 5: Suggested treatment guidelines for moderate-to-severe cases of SARS-CoV-2.

1. Asymptomatic to mild infection (no oxygen dependency) with CT evidence of disease and/or at high risk for deterioration with epidemiological risk factors present or elevated inflammatory markers
2. Moderate-to-severe infection (increasing oxygen dependency)

General measures and oxygen therapy	• Target SpO_2: 92–96% (88–92% in patients with COPD) • The device for administering oxygen (nasal prongs, mask, or masks with breathing/nonrebreathing reservoir bag) depends upon the increasing requirement of oxygen therapy. If HFNC or simple nasal cannula is used, N95 mask should be applied over it • Awake proning may be used as a rescue therapy • All patients should have daily 12-lead ECG • Follow CRP, D-dimer, and ferritin every 48–72 hourly (if available); CBC with differential count, absolute lymphocyte count, KFT/LFT daily • Add antacid, zinc, vitamin C, and vitamin D • Antibiotic as per local guidelines
Strongly recommended therapy (steroid)	Tablet dexamethasone 6 mg/day orally for 10 days OR IV dexamethasone 20 mg per day intravenous × 5 days followed by 10 mg per day IV × 5 days; titrate dose and duration to culmination of oxygen dependency OR IV methylprednisolone 2 mg/kg intravenous total dose in three divided doses for 7 days followed by 1 mg/kg for 5 days and then 0.5 mg/kg for 5 days (preferably within 48 hours of admission or if oxygen requirement is increasing and if inflammatory markers are increased) OR IV hydrocortisone 50 mg intravenous 6 hourly × 7 days followed by 50 mg IV 12 hourly × 4 days followed by 50 mg IV 24 hourly × 3 days *The UK RECOVERY trial has demonstrated mortality benefit with low dose dexamethasone in COVID-19 patients requiring oxygen.*
Low-molecular-weight heparin (LMWH)	• Association between COVID-19 infection and thromboembolism associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers. In some studies, elevations in these markers have been associated with worse clinical outcomes • Prophylactic dose of UFH or LMWH (e.g., enoxaparin 40 mg per day SC)
Remdesivir (emergency use approval-experimental)	• Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg) • IV remdesivir 200 mg intravenous day 1 followed by 100 mg IV daily for 4 days • Remdesivir may be considered in patients with moderate disease (those on oxygen) with none of the following contraindications: ○ AST/ALT > 5 times upper limit of normal (ULN) ○ Severe renal impairment (i.e., eGFR < 30 mL/min/m^2 or need for hemodialysis) ○ Pregnancy or lactating females ○ Children (<12 years of age)
Baricitinib	Janus kinase inhibitors: Baricitinib plus remdesivir is superior to remdesivir alone in reducing recovery time
Favipiravir (emergency use approval-experimental)	• Favipiravir is a pyrazinecarboxamide derivative that acts as an inhibitor of viral RNA-dependent RNA polymerase, causing chain termination and preventing RNA elongation • Tablet favipiravir 1,800 mg BD (9 tablets of 200 mg each BD) on day 1 followed by 800 mg BD (4 tablets of 200 mg each BD) for a total duration of 7–14 days.
Experimental therapies	
Targeting cytokine storm (tocilizumab)	• Indications: Special considerations before its use include: Presence of raised inflammatory markers (e.g., CRP, ferritin, and IL-6). Patients should be carefully monitored post tocilizumab for secondary infections and neutropenia. Active infections and tuberculosis should be ruled out before use. CT suggestive of active disease with radiological worsening + IL-6 >70 + rising serum ferritin/rising CRP/rising D-dimer/rising LDH + >48 h of steroids (dexamethasone 20 mg/day or methylprednisolone 80–120 mg/day or hydrocortisone 200 mg/day) • Dose: 6–8 mg/kg (maximum 400 mg at one time) given slowly in 100 mL NS over 1 hour; dose can be repeated once after 12–24 h, if needed
Plasma therapy	• May be considered in patients with moderate/severe disease who are not improving (oxygen requirement is progressively increasing) despite use of steroids. • Special prerequisites while considering convalescent plasma include: ○ ABO compatibility and crossmatching of the donor plasma ○ Recipient should be closely monitored for several hours post-transfusion for any transfusion-related adverse events ○ Use should be avoided in patients with IgA deficiency or immunoglobulin allergy • Dose: Dose is variable ranging from 4 to 13 mL/kg (usually 200 mL single dose given slowly over not <2 h

(CBC: complete blood count; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease-2019; CRP: C-reactive protein; CT: computed tomography; eGFR: estimated glomerular filtration rate; HFNC: high-flow nasal cannula; IgA: immunoglobulin A; KFT: kidney function test; LDH: lactic dehydrogenase; LFT: liver function test; RNA: ribonucleic acid; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: oxygen saturation; UFH: unfractionated heparin)

TABLE 6: CO-RADS categories and suspicion of pulmonary involvement in COVID-19.

CO-RADS categories	*Level of suspicion*	*Interpretation*
0	Not interpretable	Scan not sufficient to interpret
1	Very low	Normal of noninfectious
2	Low	Typical for infection other than COVID-19
3	Equivocal	Feature symptom of COVID-19 but also other disease
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

Typical features for pulmonary involvement of COVID-19

Obligatory features: Ground glass opacities, with or without consolidations, in lung regions close to visceral pleural surfaces, including the fissures (subpleural sparing is allowed) and multifocal bilateral distribution

Confirmatory patterns:

- Ground glass regions
- Unsharp demarcation, (half) rounded shape
- Sharp demarcation, outlining the shape of multiple adjacent secondary pulmonary lobules
- Crazy paving
- Patterns compatible with organizing pneumonia
- Thickened vessels within parenchymal abnormalities found in all confirmatory pattern

(CO-RADS: coronavirus disease 2019 Reporting and Data System; COVID-19: coronavirus disease-2019; RT-PCR: reverse transcription-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2)

Ebola

Favipiravir was one of the drugs shortlisted by WHO for trials during the Ebola virus outbreak in 2014. Apart from efficacy against influenza and Ebola viruses, favipiravir has been found to have therapeutic efficacy against arenavirus, bunyavirus, filovirus, West Nile virus, yellow fever virus, foot-and-mouth-disease virus, and Lassa virus including agents causing viral hemorrhagic fevers and encephalitis.

Role in SARS-CoV-2

To assess the efficacy of favipiravir in the management of COVID-19 various clinical studies have been performed all over the world. In spite of inconclusive results over its usefulness in COVID-19 patient, most countries, including India, using it in clinical dose of 1,800 mg bid on day 1, followed by 800 mg bid on days 2–14. Oseltamivir and ribavirin are not effective in the treatment of SARS-CoV-2. Repurposed antiviral drugs have all been introduced into treatment after rapidly conducted clinical trials. Furthermore, larger RCTs are urgently needed before this drug can be unreservedly recommended.

TOCILIZUMAB

Pathogenesis of COVID-19 is incompletely understood but evidence suggests the severity is associated with increased

TABLE 7: Indication for tocilizumab (TCZ) (clinical criteria and inflammatory markers).

Clinical criteria	
Grade I—mild disease—pneumonia without oxygen requirement	TCZ not required
Grade II—moderate disease—fever, no hypotension, fluid requirements and oxygen requirement, FiO_2 <40%	TCZ not required (send IL-6)
Grade III—new organ dysfunction, fluid and vasopressors requirements, FiO_2 >40%—(HNFC and NIV)	Send IL-6 consider TCZ
Grade IV life-threatening mechanical ventilation, high dose vasopressors	Send IL-6 and consider TCZ
Inflammatory markers—criteria for diagnosing cytokine release syndrome (CRS)	
• Ferritin 300 µg/dL with doubling time within 24 hours or 600 µg/dL • LDH >250 U/L • Raised D-dimer >1 mg/mL • CRP >150 • IL-6 (normal values <7) >10 times of ULN	

(CRP: C-reactive protein; FiO_2: fraction of inspired oxygen; HNFC: high-flow nasal cannula; IL-6: interleukin 6; LDH: lactic dehydrogenase; NIV: noninvasive ventilation; ULN: upper limit of normal)

inflammatory markers such as cytokines interleukins (IL-6 and IL-10), tumor necrotic factors, and chemokines. Cytokines release syndrome (CRS) is key pathophysiologic process behind sudden deterioration of COVID-19 patient and progression of diseases to ARDS and multi-organ failure (**Table 7**). TCZ is a monoclonal antibody against IL-6 receptors has been used in various studies with variable effects. TCZ can improve outcome by decreasing the need for mechanical ventilation and reduces the mortality though large sample size studies are required to evaluate its role in COVID-19 treatment.

CONVALESCENT PLASMA THERAPY IN PATIENTS WITH COVID-19

Anti-SARS-CoV-2 antibody containing plasma obtained from recovered patients who had confirmed COVID-19 is collected by apheresis devices and stored in blood banks. It may be an adjunctive treatment option to the antiviral therapy. The protective effect of convalescent plasma (CP) may remain for weeks and months. After the assessment of the donor, 200–600 mL of plasma can be collected with apheresis devices.

Mechanism of Action

Based on previous studies in other viral infections such as Ebola and respiratory syncytial virus, the mechanism of action is mainly viral neutralization. Though the exact mechanism of CP in COVID-19 has not been clearly established. The other mechanisms are antibody-induced cellular cytotoxicity, complement activation, and phagocytosis. Neutralizing antibody can provide control of viral load. Non-neutralizing antibodies may also contribute to prophylaxis and/or enhance recovery. The Food and Drug Administration (FDA) does not allow the use of CP for prophylaxis. The WHO advised using

CP when vaccines and antiviral drugs are not available in the treatment of critically ill patients with COVID-19.

Collection of Convalescent Plasma

All the steps are important and should be organized carefully and performed by expert healthcare workers.

Eligibility of Donor

According to the FDA, individuals fulfilling following criteria can be a donor.

- Recovered from COVID-19, blood donor tests were done, and suitable for donation.
- Evidence of COVID-19 documented by a laboratory test either by a diagnostic test (e.g., nasopharyngeal swab) at the time of illness, or a positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.
- Complete resolution of symptoms at least 14 days prior to donation.
- Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for human leukocyte antigen (HLA) antibodies.
- When measurement of neutralizing antibody titers is available, neutralizing antibody titers of at least 1:160 is recommended. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

Evaluation of Donors before Donation

As RNA detectability is low in samples collected for RT-PCR before 7 days and during days 15–39, that is why coronavirus predonation screening should be supported by antibody detecting tests. Minimize the risk of transfusion-related acute lung injury (TRALI) by screening for HLA antibodies in pregnant females. The relationship between total anti-SARS-CoV-2 antibodies and neutralizing anti-SARS-CoV-2 antibodies is not clear. The antibody titer will differ according to the duration between the collection time and onset of infection. Seroconversion has been observed to occur between 8 days and 21 days after the onset of symptoms. Reports suggest that CP that is collected ≥14 days after resolution of symptoms contain high titer of antibodies. According to the FDA, neutralizing antibody titer should be at least 1:160 but a titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

Convalescent Plasma Collection

Approximately 200–600 mL plasma can be collected with apheresis devices depending on total blood volume of the donor. The collected plasma volume (excluding the anticoagulant solution) should not exceed 750 mL for each procedure. CP is stored by freezing or applied within 6 hours without freezing. Freezing should be started within the first 6 hours after the apheresis process is completed. Barcoded products should be stored at or below –18/25°C in a separate storage cabinet. ABO blood group should preferably compatible. It is recommended that CP should have undergone pathogen inactivation process such as amotosalen + ultraviolet light; riboflavin + ultraviolet light; methylene blue; or a solvent/detergent may be used. It should be irradiated if it will be given to the patient without being frozen within 6 hours after plasma collection. The frozen plasma does not need to be irradiated.

Convalescent Plasma Dosage

One unit may be used for prophylaxis and one to two units for the treatment. The duration of efficacy of the antibodies is not known, but it is estimated to last in weeks to a few months. According to linear proportionality, 3.125 mL/kg of plasma with a titer of >1:64 would provide an equivalent immunoglobulin level to one quarter of 5 mL/kg plasma with a titer of 1:160.

Coronavirus disease 2019 is rarely symptomatic in pediatric age group. In pediatric population dose by weight should be used. In previous use of CP therapy in SARS, 5 mL/kg of plasma at a titer of 1:160 was used.

Patient Selection

The FDA suggests the following criteria for the use of CP:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19
  - Severe disease is defined as one or more of the following:
    - Dyspnea
    - Tachypnea ≥ 30/min
    - Blood oxygen saturation ≤ 93%
    - Partial pressure of oxygen (PaO_2)/FiO_2 < 300
    - Lung infiltrates > 50% within 24–48 hours
  - The life-threatening disease is defined as one or more of the following:
    - Respiratory failure
    - Septic shock

Prophylaxis

The FDA does not allow the use of CP for prophylaxis. The new phase 2–3 trial is evaluating the use of postexposure prophylactic plasma in COVID-19 patients who have had close contact exposure but have not yet presented symptoms.

Risks associated with CP are following:

- Infection (bacterial or viral)
- Immunological reaction, e.g., serum sickness
- Nonhemolytic transfusion reactions (fever, tremors, and urticarial)
- Transfusion-associated circulatory overload and TRALI.

Transfusion-transmitted SARS-CoV-2 is theoretical specific risk of anti-SARS-CoV-2. Other theoretical risk of CP is an antibody-dependent enhancement (ADE). Antibodies that develop during a previous infectious disease caused by a different serotype may exacerbate clinical severity. One more theoretical risk of CP is attenuation of the development of a natural immune response, especially when administered for prophylaxis. Even though published studies are not prospective or randomized, until the development of vaccines or therapeutics, CP appears to be a safe and probably effective treatment for critically ill patients with COVID-19.

VACCINES FOR SARS-CoV-2

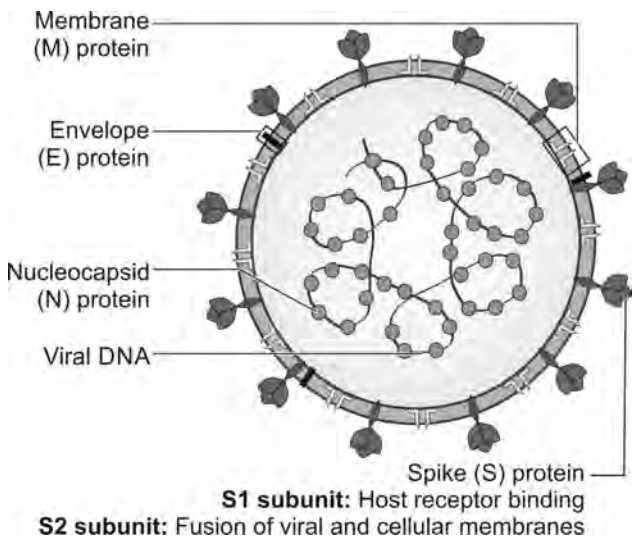
The COVID-19 SARS-CoV-2 is the disease caused by a novel beta coronavirus, first case reported in December 2019 in Wuhan (China) further spread globally and declared pandemic by March 11, 2020, at the time of writing, 23nd April 2021, there has been over 145 million people infected and more than 3

million deaths worldwide and 17 million cases and 187,000 death in India. COVID-19 (SARS-CoV-2) primarily a respiratory tract disease severity ranging from very mild fever, body ache, rhinorrhea to severe ARDS, and death. Nonrespiratory symptoms of SARS-CoV-2 are anosmia, diarrhea, rash, thromboembolic disorders, myocarditis, and vasculitis. The median incubation period is estimated to be 5 days with a majority developing symptoms by 11.5 days. The case fatality rate is highest in elderly (aged >70 years). Coronaviruses have a large (30 + kb) single-stranded positive sense RNA genome encased by a helical nucleocapsid (N) and an outer envelope comprised of matrix protein (M), envelope protein (E), and spike proteins (S) (**Fig. 2**). The S protein of SARS-CoV-2 is responsible for binding onto the ACE2 and entry into the cell which naturally occurs in a trimeric form, contains the receptor-binding domain (RBD). In SARS-CoV-2, S protein is a major target antigen for vaccine development and found to elicit neutralizing antibody.

During global pandemic setting, developing and scaling-up mass production of a vaccine rapidly is challenging because it requires coordination of many activities and in normal situation process is usually decade long, sequential process with preclinical testing, phased clinical trials, planned production, and distribution. In humans, live-attenuated viruses (e.g., measles, mumps, and rubella), inactivated viruses (e.g., inactivated polio vaccine), protein or polysaccharide conjugated subunit vaccines (protein: acellular pertussis and hepatitis B; polysaccharide conjugated: pneumococcus and meningococcus), and virus-like particles are used. With the advancement of new technology, vaccines composed of nucleic acid (DNA and RNA) and viral vectors and recombinant proteins are also developed over the last decade.

Recombinant Vaccines/Viral Vectors

One or more genes that encode a target antigen within an unrelated and engineered virus can be delivered by viral vector technology. The viral vector can be replication competent (live attenuated) or replication deficient. Viral vectors technology is used for developing vaccines for human immunodeficiency virus (HIV), Ebola, Zika, and Chikungunya, including adenovirus (Ad), measles virus (MV), vesicular stomatitis virus (VSV), alphaviruses, poxviruses, and herpesviruses allowing ability to stimulate cellular and humoral immunity.



(DNA: deoxyribonucleic acid; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2)

FIG. 2: Structure of SARS-CoV-2.

Nucleic Acid Vaccines

Antigen-encoding plasmid DNA or RNA, messenger RNA (mRNA), or viral replicons are used for developing nucleic acid vaccines. Once the nucleic acid enters in the cell, protein synthesis started and similar to natural infection humoral and cell-mediated immune response is expected to occur. The benefit of a nucleic acid platform-based vaccines is that it allows antigen manipulation easily and the speedy production. Nucleic acid, especially mRNA, are fragile and require an uninterrupted cold-chain process for transport and storage is one the disadvantages. Clinical trials are on various stages for SARS-CoV and MERS-CoV DNA vaccines.

SARS-CoV-2 VACCINES IN INDIA

Two vaccines (Covishield and Covaxin) approved by India's top drug regulator for emergency and restricted use against COVID-19 on 3 January 2021. *Covishield* vaccine is by the Oxford University-AstraZeneca with average efficacy of 70.4%. Covishield is developed by the world's largest vaccines manufacturer, the Serum Institute of India. Against COVID-19, *Covaxin* is India's first home produced vaccine developed by Bharat Biotech in collaboration with the Indian Council of Medical Research and the National Institute of Virology. The Lancet published Covaxin's phase I trial data on 21st January 2021, giving positive conclusion for safety and stating that it generates adequate immune response, with recommendation of further trials. Both vaccines work by priming the immune system with a SARS-CoV-2 spike protein and require two doses. Covishield uses a weakened version of adenovirus, while Covaxin uses an inactivated SARS-CoV-2 virus extracted from an asymptomatic patient. Characters of both vaccines are summarized in **Table 8**. From 16 January 2021 health ministry started India's huge immunization drive to vaccinate four priority groups: healthcare workers, people over 50, public workers, and those under 50 with comorbidities—with the former two groups to be inoculated first in an initial rollout to 30 million people. Till 23rd April 2021, 140 million people received vaccination in India. From 1st May 2021 Government of India (GOI) has started vaccination drive to all population over 18 years of age. Russia's Sputnik V vaccine is also given approval for emergency use and may prove crucial as the powdered version of the vaccine can be stored at refrigerator temperatures, making it more suitable for India's climate. India's biotech companies are also expected to produce 300 million doses of Russia's Sputnik V vaccine.

Indications

Active immunization for individuals ≥18 for COVID-19 prevention.

Precautions

If required, COVID-19 vaccine and other vaccines should be separated by an interval of at least 14 days. Interchangeability of vaccines is not permitted; second dose should be of the

TABLE 8: Characteristics of Covishield and Covaxin vaccine.

Indicators	*Covishield*	*Covaxin*
Type of vaccines	Recombinant vaccine based on viral vector technology	Whole virion inactivated coronavirus vaccine
No. of doses in each vial/ dose	• 10/0.5 mL each dose • Discard 4 hours of opening of vials	• 10/0.5 mL each dose • Discard 4 hours of opening of vials
Route	Intramuscular	Intramuscular
Shelf life	6 months	6 months
Course/schedule	Two doses/6–8 weeks apart	Two doses/6–8 weeks apart
Storage and transportation	+2°C to +8°C at all levels	+2°C to +8°C at all levels
Adverse events following immunization (AEFI)	• Injection site tenderness, headache, fatigue, myalgias, malaise, pyrexia, and chills • Paracetamol may be used for symptomatic relief	• Injection site tenderness, headache, fatigue, myalgias, malaise, pyrexia, chills, nausea, vomiting, dizziness, giddiness, and sweating • Paracetamol may be used for symptomatic relief

same COVID-19 vaccine which was administered as first dose. Vaccine should be administered with precaution in person with history of any bleeding or coagulation disorder.

Contraindications

A confirmed anaphylactic reaction to a previous dose of COVID-19 vaccine, immediate or delayed onset anaphylaxis or allergic reaction to vaccines or injectable therapies, pharmaceuticals products, food items, etc. COVID-19 vaccines are currently not recommended in pregnant or lactating women.

Temporary Contraindications (Differ for 4–8 Weeks)

- Active SARS-CoV-2 infection
- SARS-CoV-2 patients who have been given monoclonal antibodies or CP
- Acutely unwell or hospitalized patients due to any illness

OMICRON—NEW VARIANT OF SARS-COV-2

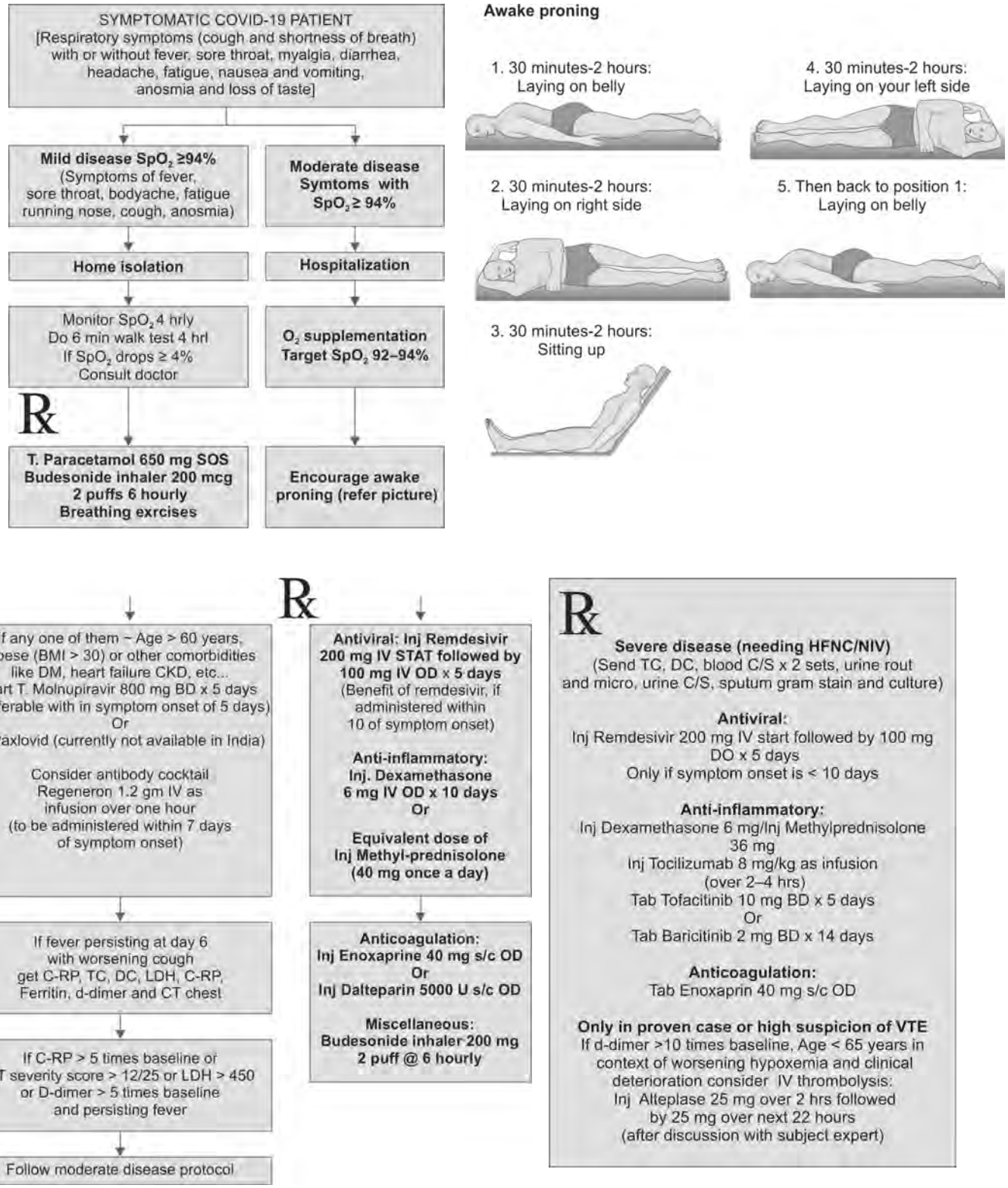
Mutation in spike protein region gives the variant the potential to develop an immune escape mechanism. The omicron variant has more than 30 mutations in spike protein region. This variant is a major cause of concern because most of the vaccines work by forming antibodies against spike proteins. Hence, vaccines have to be reviewed to check the possibilities of decreased efficacy of the existing COVID-19 vaccines. Structural changes have been observed in the omicron variant which is indicative of adherence to the same cellular receptors with an increase in affinity and transmission.

Oxygen and steroid still remain the promising drugs. Apart from Favipiravir which is described earlier in this chapter, two new promising drugs, Molnupiravir and Paxlovid, are investigational drugs for the treatment of SARS-CoV-2. Molnupiravir is an oral drug which inhibits the multiple RNA virus including SARS-CoV-2 and is most effective when used early. Paxlovid, a protease inhibitor, is an investigational drug which inhibits the viral replication at proteolysis (a stage that occurs before proteolysis).

The Drug Regulator of India approved two new covid vaccines, Covovax by the Serum Institute of India and Corbevax by Biological E, for restricted use in an emergency situation. The Drug Regulator of India also approved Molnupiravir, an oral drug, which has shown promising results in early use in the treatment of mild-to-moderate SARS-CoV-2 infection in an adult and reduces the risk of hospitalization and death.

SUMMARY

A large number of populations of world are affected by the COVID-19 pandemic. Various groups of drugs are proposed to treat the COVID-19, e.g., antivirals, antimalarials, and immunomodulators. Remdesivir (antiviral) shows promising results in the treatment of the COVID-19. Hydroxychloroquine (HCQ) also used extensively for the treatment of COVID-19. TCZ (immunomodulatory therapy) and plasma therapy can be used in moderate-to-severe disease to control the cytokine storm. Low-molecular-weight heparin is used in both prophylactic and therapeutic therapy. Adjunctive therapy, vitamin C, and vitamin D may be useful. Several vaccines are currently under trial and also given approval for emergency use in various countries. Current proposed management for COVID-19 is given in **Flowchart 1**.


SYMPTOMATIC COVID-19 PATIENT
[Respiratory symptoms (cough and shortness of breath) with or without fever, sore throat, myalgia, diarrhea, headache, fatigue, nausea and vomiting, anosmia and loss of taste]
Mild disease SpO2 ≥94%
(Symptoms of fever, sore throat, bodyache, fatigue running nose, cough, anosmia)
Moderate disease Symtoms with SpO2 ≥ 94%
Home isolation
Hospitalization
Monitor SpO2 4 hrly
Do 6 min walk test 4 hrl
If SpO2 drops ≥ 4%
Consult doctor
O2 supplementation
Target SpO2 92–94%
Rx
T. Paracetamol 650 mg SOS
Budesonide inhaler 200 mcg
2 puffs 6 hourly
Breathing exrcises
Encourage awake proning (refer picture)
Awake proning
1. 30 minutes-2 hours: Laying on belly
2. 30 minutes-2 hours: Laying on right side
3. 30 minutes-2 hours: Sitting up
4. 30 minutes-2 hours: Laying on your left side
5. Then back to position 1: Laying on belly
Rx
If any one of them ~ Age > 60 years, Obese (BMI > 30) or other comorbidities like DM, heart failure CKD, etc...
start T. Molnupiravir 800 mg BD x 5 days
(preferable with in symptom onset of 5 days)
Or
T. Paxlovid (currently not available in India)
Consider antibody cocktail
Regeneron 1.2 gm IV as infusion over one hour
(to be administered within 7 days of symptom onset)
Antiviral: Inj Remdesivir 200 mg IV STAT followed by 100 mg IV OD x 5 days
(Benefit of remdesivir, if administered within 10 of symptom onset)
Anti-inflammatory:
Inj. Dexamethasone 6 mg IV OD x 10 days
Or
Equivalent dose of Inj Methyl-prednisolone (40 mg once a day)
If fever persisting at day 6 with worsening cough
get C-RP, TC, DC, LDH, C-RP, Ferritin, d-dimer and CT chest
Anticoagulation:
Inj Enoxaprine 40 mg s/c OD
Or
Inj Dalteparin 5000 U s/c OD
Miscellaneous:
Budesonide inhaler 200 mg
2 puff @ 6 hourly
If C-RP > 5 times baseline or
CT severity score > 12/25 or LDH > 450
or D-dimer > 5 times baseline
and persisting fever
Follow moderate disease protocol
Rx
Severe disease (needing HFNC/NIV)
(Send TC, DC, blood C/S x 2 sets, urine rout and micro, urine C/S, sputum gram stain and culture)
Antiviral:
Inj Remdesivir 200 mg IV start followed by 100 mg DO x 5 days
Only if symptom onset is < 10 days
Anti-inflammatory:
Inj Dexamethasone 6 mg/Inj Methylprednisolone 36 mg
Inj Tocilizumab 8 mg/kg as infusion (over 2–4 hrs)
Tab Tofacitinib 10 mg BD x 5 days
Or
Tab Baricitinib 2 mg BD x 14 days
Anticoagulation:
Tab Enoxaprin 40 mg s/c OD
Only in proven case or high suspicion of VTE
If d-dimer >10 times baseline, Age < 65 years in context of worsening hypoxemia and clinical deterioration consider IV thrombolysis:
Inj Alteplase 25 mg over 2 hrs followed by 25 mg over next 22 hours
(after discussion with subject expert)

Criteria for discharge: Resolution of clinical symptoms, patient remaining asymptomatic for 3 days. No need for RT-PCR/CBNAAT/True-NAT before discharge. Post discharge ~ home quarantine × 10 days.

Ancillary measures: Normal feeding, no dietary restrictions. No role of maintenance IV fluids. Maintain blood glucose levels < 180 mg/dL. Patients on oxygen should always remain in propped up and prone position. Mandatory incentive spirometry every hour for 35–35 breaths. Maintain net-neutral fluid balance in patients on supplemental oxygen.

Disclaimer: There is no conclusive evidence of outcome benefit with the use of antiviral drugs and novel therapies. However, the suggestions made are derived from the prevailing trials published so far and collation of literature that has come out so far. These recommendations would change with the evolving evidence.

FLOWCHART 1: Proposed management algorithm for SARS CoV-2 (COVID-19) infection.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Abdominal Pain

Roberta Petrino, Aldo Tua

INTRODUCTION

Abdominal pain is a very common symptom of presentation for patients admitted to the emergency department and represents a strong challenge for physicians and nurses involved in diagnosis and treatment. Incidence and clinical manifestations are both influenced by many demographic variables (age, gender, geography, etc.). Although in most of the cases it is not related to a serious disease, in some cases it can be the only symptom of a potential rapidly evolved situation.

ETIOLOGY

Many intra-abdominal disorders cause abdominal pain and also several extra-abdominal diseases can present with abdominal pain. Some of these are immediately life-threatening, requiring rapid diagnosis and surgery. The knowledge of abdominal anatomy and its innervation helps for differential diagnosis; however, a systematic and logical approach, with a careful medical history and clinical evaluation, is fundamental. Focused clinical history and physical examination are able to place a right diagnostic hypothesis in 80% of patients with abdominal pain There are some alert signs and symptoms that must always be taken into careful consideration because they probably underlie a serious condition. Often a definitive diagnosis is impossible in the emergency department but the emergency physician has always to identify and rule out life-threatening clinical conditions. These include ruptured *abdominal* aorta aneurysm (AAA), perforated viscus, mesenteric ischemia, and ruptured ectopic pregnancy. Other diseases (e.g., acute appendicitis, acute diverticulitis, severe acute pancreatitis, intestinal obstruction) are also serious and nearly as urgent. The emergency physician must correlate between the anatomical site of abdominal pain and the differential diagnosis (**Fig. 1**).

PATHOPHYSIOLOGY

The abdominal viscera are innervated by nociceptive fibers on the mesenteric surface and inside the wall of the hollow organs. These fibers are sensitive to both mechanical, mainly stretching, and chemical stimuli. They can produce dull, continuous, crampy, or violent pain.

The abdominal pain is divided into the following:

- *Visceral*: Usually secondary to stretching of hollow organs, twist or spastic contraction. It can be deaf and continuous or colic, often located in the median site, as visceral innervation is bilateral, and it corresponds to the dermatome relative to the involved organ. Therefore, for the organs located above the Treitz ligament, it will be epigastric; for those between the Treitz and the hepatic flexure of the colon, it will be umbilical; and for the most distal organs, it will be hypogastric.
- *Parietal*: It is usually acute, due to direct irritation of the peritoneum located above the involved organ. The parietal innervation is unilateral, so the pain will be well localized. Only when there is widespread involvement of the peritoneum, as for leak of gastric contents, blood, pus, or other, the pain will be extended to all of the abdomen. The peritoneal irritation may cause a reflex contracture of abdominal muscles whereby the abdomen will become stiff and untreatable. The irritant reaction to organic or chemical substances is different so that the peritonitic pain will be much more striking during gastric perforation with spreading of gastric acid than during colic perforation, with the leaking of stool or blood.
- *Referred*: It appears when the afferent fibers from an injured abdominal organ enter the spinal cord at the same level of somatic fibers coming from distant regions (e.g., the gallbladder pain can be referred to the right shoulder).

CLINICAL PRESENTATION

Clinical features of concern *(red flags)*, which are important for the emergency physician to know are, as follows:

- Signs of shock (e.g., tachycardia, hypotension, diaphoresis, confusion)
- Severe pain
- Signs of peritonitis
- Abdominal distention
- Attention to nonabdominal diseases that present with abdominal pain

Major diseases that cause acute abdomen of immediate surgical interest are described further.

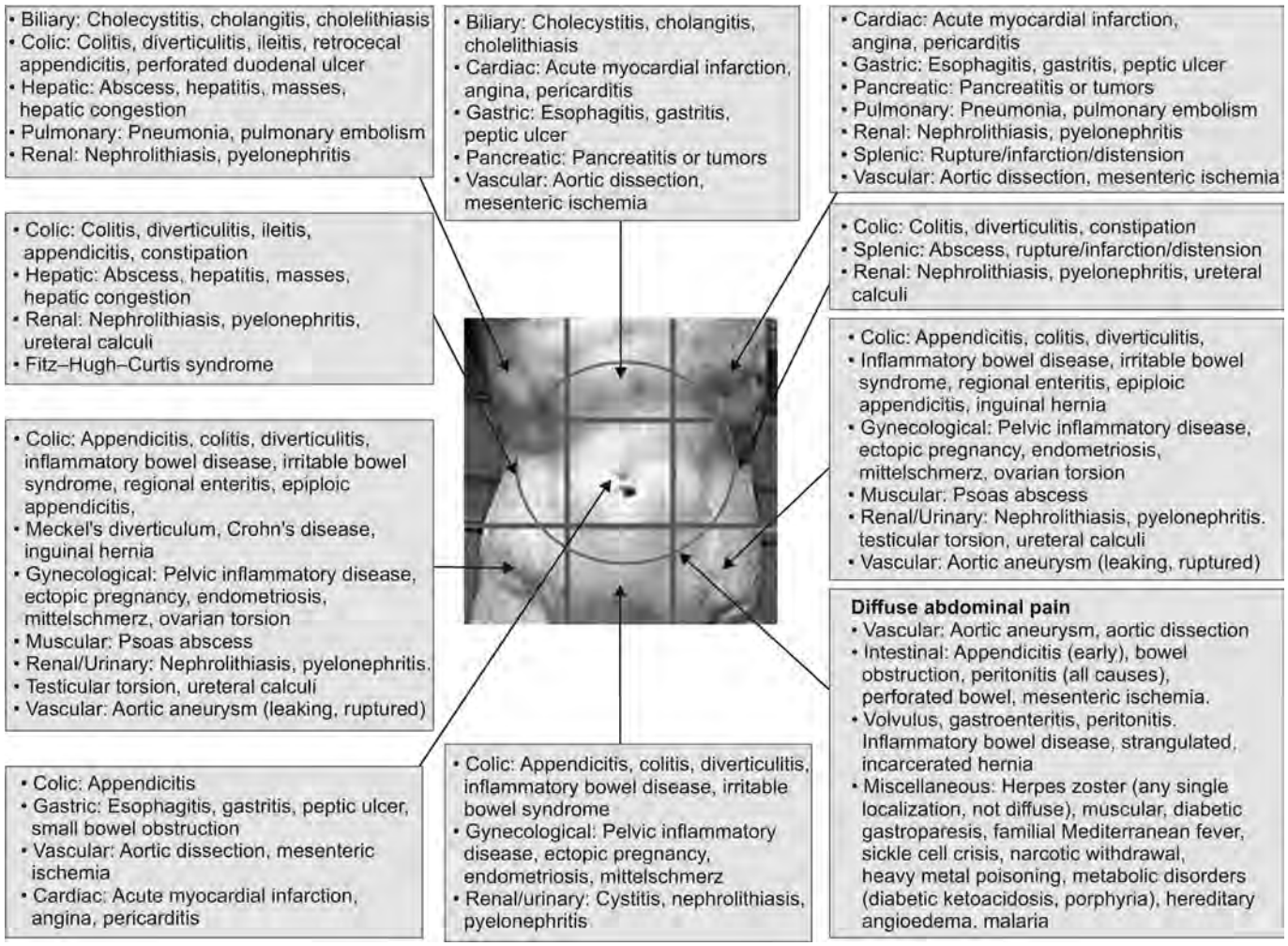

• Biliary: Cholecystitis, cholangitis, cholelithiasis
• Colic: Colitis, diverticulitis, ileitis, retrocecal appendicitis, perforated duodenal ulcer
• Hepatic: Abscess, hepatitis, masses, hepatic congestion
• Pulmonary: Pneumonia, pulmonary embolism
• Renal: Nephrolithiasis, pyelonephritis
• Biliary: Cholecystitis, cholangitis, cholelithiasis
• Cardiac: Acute myocardial infarction, angina, pericarditis
• Gastric: Esophagitis, gastritis, peptic ulcer
• Pancreatic: Pancreatitis or tumors
• Vascular: Aortic dissection, mesenteric ischemia
• Cardiac: Acute myocardial infarction, angina, pericarditis
• Gastric: Esophagitis, gastritis, peptic ulcer
• Pancreatic: Pancreatitis or tumors
• Pulmonary: Pneumonia, pulmonary embolism
• Renal: Nephrolithiasis, pyelonephritis
• Splenic: Rupture/infarction/distension
• Vascular: Aortic dissection, mesenteric ischemia
• Colic: Colitis, diverticulitis, ileitis, appendicitis, constipation
• Hepatic: Abscess, hepatitis, masses, hepatic congestion
• Renal: Nephrolithiasis, pyelonephritis, ureteral calculi
• Fitz–Hugh–Curtis syndrome
• Colic: Colitis, diverticulitis, constipation
• Splenic: Abscess, rupture/infarction/distension
• Renal: Nephrolithiasis, pyelonephritis, ureteral calculi
• Colic: Appendicitis, colitis, diverticulitis, inflammatory bowel disease, irritable bowel syndrome, regional enteritis, epiploic appendicitis,
• Meckel's diverticulum, Crohn's disease, inguinal hernia
• Gynecological: Pelvic inflammatory disease, ectopic pregnancy, endometriosis, mittelschmerz, ovarian torsion
• Muscular: Psoas abscess
• Renal/Urinary: Nephrolithiasis, pyelonephritis.
• Testicular torsion, ureteral calculi
• Vascular: Aortic aneurysm (leaking, ruptured)
• Colic: Appendicitis, colitis, diverticulitis, inflammatory bowel disease, irritable bowel syndrome, regional enteritis, epiploic appendicitis, inguinal hernia
• Gynecological: Pelvic inflammatory disease, ectopic pregnancy, endometriosis, mittelschmerz, ovarian torsion
• Muscular: Psoas abscess
• Renal/Urinary: Nephrolithiasis, pyelonephritis. testicular torsion, ureteral calculi
• Vascular: Aortic aneurysm (leaking, ruptured)
Diffuse abdominal pain
• Vascular: Aortic aneurysm, aortic dissection
• Intestinal: Appendicitis (early), bowel obstruction, peritonitis (all causes), perforated bowel, mesenteric ischemia.
• Volvulus, gastroenteritis, peritonitis. Inflammatory bowel disease, strangulated, incarcerated hernia
• Miscellaneous: Herpes zoster (any single localization, not diffuse), muscular, diabetic gastroparesis, familial Mediterranean fever, sickle cell crisis, narcotic withdrawal, heavy metal poisoning, metabolic disorders (diabetic ketoacidosis, porphyria), hereditary angioedema, malaria
• Colic: Appendicitis
• Gastric: Esophagitis, gastritis, peptic ulcer, small bowel obstruction
• Vascular: Aortic dissection, mesenteric ischemia
• Cardiac: Acute myocardial infarction, angina, pericarditis
• Colic: Appendicitis, colitis, diverticulitis, inflammatory bowel disease, irritable bowel syndrome
• Gynecological: Pelvic inflammatory disease, ectopic pregnancy, endometriosis, mittelschmerz
• Renal/urinary: Cystitis, nephrolithiasis, pyelonephritis

FIG. 1: Correlation between the anatomical site of abdominal pain and the differential diagnosis.

Acute Appendicitis

The inflammatory process is due to appendicular lumen obstruction, which can cause an increase in pressure within the lumen with consequent local circulatory dysfunction with ischemia of the wall (catarrhal or phlegmonous form) and necrosis. If perforation of the necrotic bowel wall occurs, appendicitis becomes complicated by perforative peritonitis, localized, or diffuse (gangrenous or perforated form), generally caused by aerobic (*Escherichia coli*, *Streptococcus*, and *Staphylococcus*) and anaerobic (*Bacteroides*) bacteria superinfection.

In case of acute inflammation, there will be spontaneous, dull pain, which arises in the epi-mesogastric or periumbilical area. Later, when serosa involvement and peritoneal irritation develop, the pain is localized in the right lower abdominal quadrant. In addition, the pain is exacerbated by the cough and is not modified by body position changes. Vomiting is sometimes present, and a low-grade fever (37–38°C) can be detected. Steadily, the patient loses appetite, so that the evaluation of this data is very important for diagnostic exclusion of appendicitis. At the physical examination, pain is evoked by palpating the right lower quadrant (RLQ) or, more commonly, Blumberg's sign can be present, but Markle's sign is more sensitive to define a peritoneal irritation. Markle's sign, or jar tenderness, consists in the evocation of pain in RLQ by dropping from standing on the toes to the heels with a jarring landing. In case of suspicion, a white blood cell count (WBC) and C-reactive protein (CRP) detection should be tested since the concomitance of neutrophilic leukocytosis and elevated CRP significantly increases the possible diagnosis of appendicitis.

In the presence of a striking clinical picture, no further tests are necessary, but surgical advice must be activated as soon as possible. In less obvious cases, it is necessary to study the diagnosis more in depth. With an expert operator, ultrasonography (US) has good specificity, but if this examination is not diagnostic or not reliable, a computed tomography (CT) scan of the abdomen and pelvis must be performed. Then, based on the evidence of direct examination, the radiologist will decide whether to complete CT using an intravenous or an oral contrast agent.

Intestinal Ischemia

Intestinal ischemia can present itself with three distinct syndromes, of which the first two generally have a favorable prognosis. The first syndrome is "*chronic mesenteric ischemia,*" determined by gradual reduction of blood supply to the affected intestinal tract, generally due to mesenteric vessels

atherosclerosis. This condition is present with postprandial intermittent abdominal pain (angina abdominis). The patient is ill when he/she eats and consequently tends to reduce food intake and may appear debilitated to medical examination, also considering that elderly subjects are the most affected by the disease.

"*Ischemic colitis*" is caused by inadequate vascularization of some colon fragments, not necessarily on atherosclerotic basis, and generally starts as per rectal bleeding rather than abdominal pain.

"Acute mesenteric ischemia" is due to acute thrombo-embolic occlusion of the celiac tripod, superior or inferior mesenteric artery, which leads to rapid necrosis of a no longer vascularized intestinal region, with subsequent development of a systemic toxic syndrome if not operated immediately.

The syndrome occurs more often in the presence of risk factors for ischemia. Most frequently, the symptom of onset is a severe periumbilical pain with an abdominal physical examination not proportional to the pain described by the patient. When the intestinal infarction has already been established, signs of peritoneal involvement are present. Rectal bleeding is rare.

Blood tests show signs of dehydration, metabolic acidosis, and multiorgan involvement when the situation is advanced, while in earlier stages it is possible to detect leukocytosis or increase in D-dimer, but with little specificity. It is important to consider the risk factors and the onset symptoms, as the mortality once the intestinal infarction has been established is approximately 90%.

Acute Diverticulitis

About 30% of people over 50 years and 60% of those over 80 years of age have a diverticular disease that mainly affects the sigmoid colon. Diverticulitis is caused by the inflammation and perforation of the diverticulum, which can be circumscribed and buffered by the mesentery or can be opened with abscess formation or frank peritonitis. The patient presents with cramping abdominal pain, more frequently located in the left lower quadrant (LLQ), but in the case of dolichocolon or diverticulosis of the ascending colon, the right lower quadrant (RLQ) can also be affected. Nausea, vomiting, and anorexia are frequently associated. The diagnostic workup, in case of clinical suspicion of diverticular disease, involves a CT scan with an intravenous or oral contrast medium (**Fig. 2**), while the colonoscopy is contraindicated when diverticular perforation is suspected. Uncomplicated diverticulitis can be managed at home with antibiotic therapy and liquid diet, while perforation with abscess or peritonitis requires immediate surgical evaluation.

Bowel Obstruction

Intestinal occlusion occurs when a mechanical block prevents the progression of intestinal contents. This causes bowel distension upstream from the obstruction due to the ingested air, the gases produced by the bacteria, and the endoluminal secretions. If the occlusion is not recognized and treated rapidly, ischemia and subsequent necrosis of the intestinal tract will develop. **Box 1** lists the main causes of intestinal obstruction. The abdominal pain is widespread and intermittent and the passage of feces and gases is absent; however, in the initial stage, diarrhea may be present, caused by the irritation of the mucosa. In advanced stages, vomiting will occur, which may be fecaloid due to bacterial activity.

At the physical examination, the abdomen is distended and painful and the bowel sounds could be increased with a metallic sound, reduced or absent. If peritonitis occurs, the abdomen will be rigid with rebound tenderness present. Laboratory tests show hemoconcentration, with possible electrolytic imbalances and renal insufficiency. The abdominal plain X-ray makes evident the presence of hydro-air levels, intestinal distention, and absence of air in the rectum (**Figs. 3** and **4**). The diagnostics can be completed with a CT scan if the clinical condition allows it, which can identify the cause of the occlusion with an approximate sensitivity of 100%. In the event of intestinal obstruction, the surgical evaluation must be timely; however, it is essential to correct fluids and electrolyte imbalances and to decompress the bowel with a nasogastric tube.

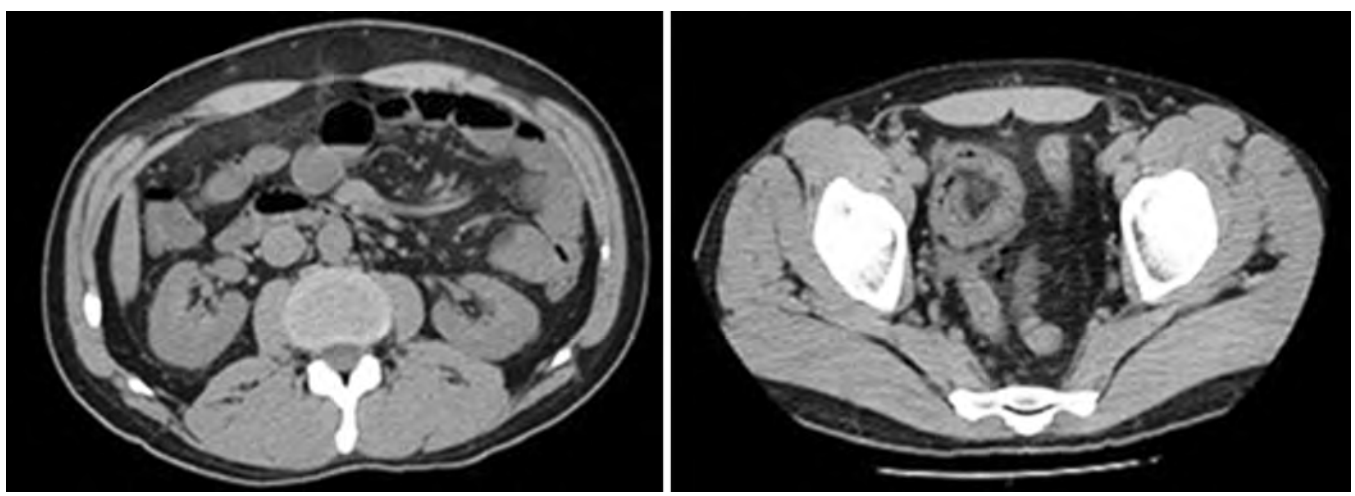


FIG. 2: Contrast enhancement CT scan that highlights the presence of loose ileal loops and with hydro-air levels, thickening of the wall of the sigma with air bubbles in its context, the surrounding liquid flap. The findings are compatible with perforated diverticulitis.

EVALUATION

Evaluation of mild and severe pain follows the same process, although with severe abdominal pain or important systemic impairment, therapy must precede the other steps and include early surgical consultation. Life-threatening conditions should always be ruled out before focusing on less serious diagnoses. In seriously ill patients with severe abdominal pain, early surgical exploration may be appropriate. In less critical patients, observation and diagnostic workup is generally the right choice. **Box 2** summarizes the steps for the evaluation of abdominal pain.

History

A thorough history usually suggests the diagnosis. It is necessary to promptly investigate the symptomatology in particular with regard to onset, quality, duration, intensity, irradiation, relationship with meals, and trigger or relieving factor. Of particular importance are characteristics and pain location, associated symptoms, and duration. Concomitant symptoms such as fever, melena, mucus or blood in the stools, hematuria, vomiting, hematemesis, heartburn, nausea, diarrhea, constipation, jaundice, and weight loss help direct subsequent evaluation. Past medical history and medications are essential, taking care that anticoagulants can increase the chances of bleeding and hematoma formation and alcohol predispose to pancreatitis. The use of nonsteroidal anti-inflammatory drugs is also associated with epigastric pain. Recent antibiotic use should be asked if the patient experiences diarrhea. Collect information on the known allergies, on the date and time of the last meal, on any travel and activity employment, and on the use of drugs of abuse.

It is necessary to consider that while in most of the cases an acute abdominal inflammatory process, so as an acute bleeding, causes tachycardia, if the process affects the diaphragm wall and therefore leads to the terminations of the vagus nerve, the patient may have a normal or bradycardic heart rate.

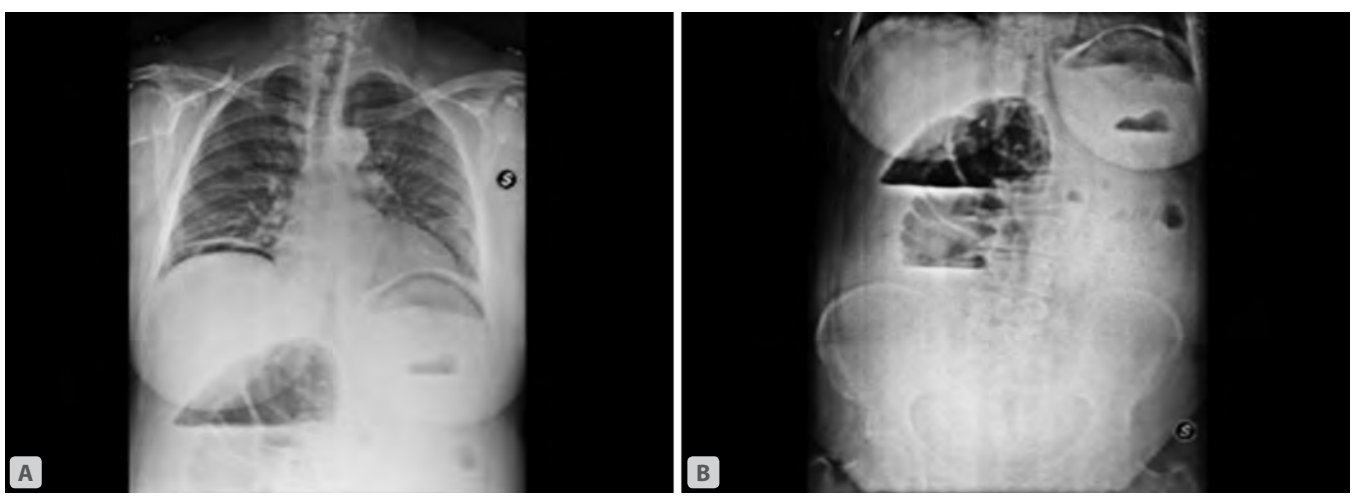
BOX 1: Main causes of intestinal occlusion.

- Postlaparotomy adhesions
- Incarcerated or strangulated hernia
- Tumors
- Crohn's disease
- Volvulus
- Intussusception
- Calculations
- Ischemia

Note: The most common cause of obstruction is constipation with fecalith.

Physical Examination

Vitals signs must be evaluated in all patients as well as the level of consciousness. The general appearance is important: A sick patient is anxious, pale, diaphoretic, or in obvious pain. The abdomen must be evaluated starting with the inspection to evaluate skin color, palpation to check distention of obvious masses, and auscultation of bowel sounds. Decreased bowel sounds suggest functional ileus or mesenteric infarction while hyperactive bowel sounds are present in small bowel obstruction. Palpation starts gently, away from the area of referred pain, detecting areas of particular tenderness, as well as the presence of guarding, rigidity, and rebound (all suggesting peritoneal irritation) and any masses. Voluntary guarding can be diminished by asking patients to flex their knees. Distracting the patient with conversation may divert attention from the examination. The inguinal area and all surgical scars should be palpated for hernias. It is important to look for typical signs such as Murphy sign or stopping the breathing because of the intense pain evoked by palpation of the gallbladder; rebound, or Blumberg sign, indicative of peritoneal irritation, which consists in evoking release pain after deep palpation; and the characteristics of the bowel signs. There are controversial opinions on the indication in literature to perform rectal exploration routinely in a patient with abdominal pain. In fact, the sensitivity and the specificity of this maneuver are rather low, but the presence of blood in the ampoule can suggest diagnosis such as diverticulitis,



FIGS. 3A AND B: (A) Plain X-ray of the chest; (B) X-ray of the abdomen with evidence of perforation, with typical free gas between the hemidiaphragm and the bowel wall, and hydro-air levels.

FIG. 4: Plain X-ray of the abdomen with evidence of the classic signs of intestinal obstruction: Distension of ileal loops, presence of hydro-air levels, absence of air in the rectum.

BOX 2: Evaluation of abdominal pain.

- *History:*
  - Extreme ages
  - Impossibility to feed
  - Vomiting in jet
  - Hematemesis
  - Syncope
  - Pregnancy
  - Recent surgical or endoscopic treatment
  - Fever
  - Severe pain of rapid onset
  - Caustic ingestion of foreign bodies
- *Physical examination:*
  - Abnormal vital signs
  - Bleeding per rectum and melena
  - Incarcerated or strangulated hernia
  - Mental deterioration
- *Laboratory testing:*
  - Renal insufficiency
  - Metabolic acidosis, BGA lactates
  - Hyper-hypoglycemia
  - Anemia, leukocytosis
  - High levels of lipases and amylases
  - High levels of bilirubin, alkaline phosphatase, and transaminases
- *Imaging:*
  - Free air in the abdomen
  - Thickening of the walls of the gallbladder and pericholecystic fluid
  - Dilatation of the biliary tract
  - Hydro-air levels
  - Intra-abdominal abscess
  - Air in the portal venous system

(BGA: blood gas analyzer)

BOX 3: Extra-abdominal diseases that can present with abdominal pain.

- *Cardiac:*
  - Acute myocardial infarction
  - Aortic aneurysm
  - Aortic dissection
- *Dermatological:*
  - Herpes zoster
- *Endocrinological and metabolic:*
  - Diabetic ketoacidosis
- *Other acidosis:*
  - Addison crisis
  - Porphyria
- *Gynecological and obstetric:*
  - Ectopic pregnancy
  - PID
  - Ovarian cyst rupture
  - Ovarian torsion
- *Hematologic:*
  - Familial Mediterranean fever
  - Sickle cell crisis
- *Musculoskeletal causes*

(PID: pelvic inflammatory disease)

tumor, or intestinal ischemia, while rectal tenderness poses in differential diagnosis anal fissures, perirectal abscess, and prostatitis. It is important to consider all the extra-abdominal conditions that can present with abdominal pain (**Box 3**).

Interpretation of Finding

Abdominal distention, vomiting, dullness at percussion, and high-pitched peristalsis strongly suggest bowel obstruction. Severe pain in a patient with a silent abdomen who is lying as still as possible suggests peritonitis whereas a patient who cannot sit or stand still suggests renal colic. Back pain and migrant pain with shock suggest ruptured abdominal aortic aneurysm, particularly if there is a tender, pulsatile mass. Previous abdominal surgery makes obstruction caused by adhesions more likely. Advanced age, generalized atherosclerosis, and hypertension increase the possibility of myocardial infarction, aortic abdominal aneurysm, and mesenteric ischemia. Shock and vaginal bleeding in a pregnant woman suggest ruptured ectopic pregnancy.

INVESTIGATIONS

Laboratory Tests

Blood tests in abdominal pain should be focused according to clinical evaluation, keeping in mind that specificity and diagnostic accuracy are low. For example, a positive likelihood ratio (LR+) of acute appendicitis with WBC > 10,000/mm^3 is only 1:59, while that with WBC > 15,000/mm^3 is 4:5.

Among laboratory tests, it is important to include glucose, electrolytes, creatinine, and liver function tests. A dangerous

approach is to rely on "normal" blood test rather than on clinical evidence and avoid observation and re-evaluation. In the case of women of childbearing age, pregnancy must be considered, both as a cause of the pain (ectopic pregnancy) and for the treatment to use. Finally, urinalysis, tested by dipstick or laboratory, is a routine test. It provides data in suspicion of renal colic, urinary tract infections, or porphyria, to test ketonuria and glycosuria and to define urine-specific gravity.

Arterial blood gas analysis is essential for critically ill patients with abdominal pain: Metabolic acidosis and hyperlactatemia, if combined with high levels of creatine phosphokinase and creatinine, must create the suspicion of a systemic involvement, a widespread and advanced pathologic process.

Role of Abdominal X-ray

A standing chest radiograph remains the primary investigation of choice for the detection of free intraperitoneal gas and may detect lower lobar pneumonia. Plain abdominal radiography should be used selectively in the event of suspected intestinal obstruction or perforation (**Figs. 3A** and **B**). In several studies, the use of abdominal X-ray as the first diagnostic step for abdominal pain has shown a very low diagnostic power, being significant only for intestinal obstruction (**Figs. 3** and **4**). In this situation, the sensitivity of abdominal X-ray is 65–90% while specificity is 50–80%. Therefore, even if the CT scan sensitivity and specificity are higher, in the suspicion of intestinal obstruction the abdomen X-ray is a first-level test. Ingestion of foreign body is another indication for abdominal X-ray, which allows to evaluate the shape, the size, and the position in order to establish the subsequent procedures. Several studies have shown a higher sensitivity of US in the suspicion of hollow organ perforation (US 90% vs. abdominal X-ray 70%). The only limit is the operator skill.

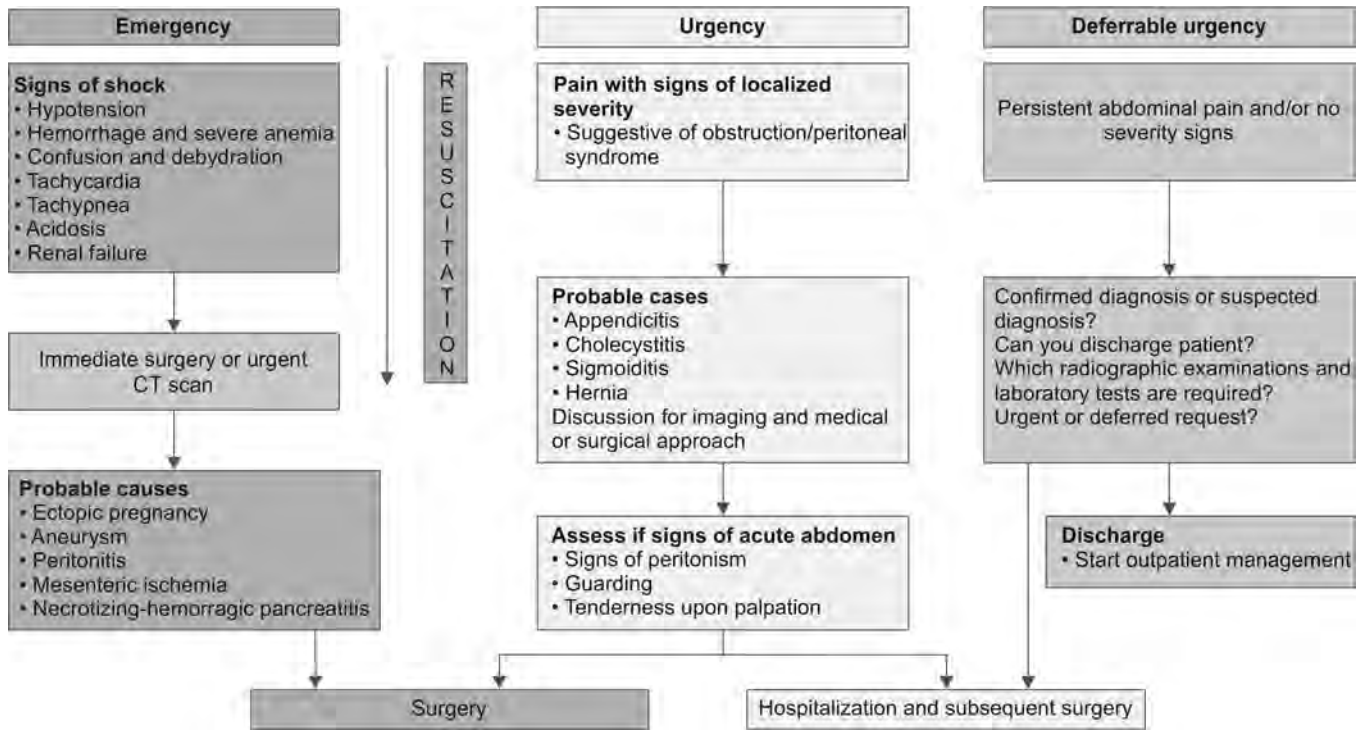
Role of Ultrasonography and Computed Tomography

Abdominal, contrast enhancement CT scan is the exam with the highest specificity and sensitivity, but bedside ultrasound is now considered the first diagnostic approach in the emergency department. In most cases, the ultrasound abdominal examination is sufficient to diagnose diseases of the upper right abdominal quadrant (cholecystitis, cholangitis) and in the diagnosis of renal colic, urinary tract infections, and ectopic pregnancy. It is also fundamental in the diagnosis of the aortic syndrome, also in diagnosing perforation in intestinal obstruction.

If the ultrasound examination is negative or nondiagnostic but the clinical presentation is persistently altered, it is necessary to perform an abdominal CT scan, generally with the contrast medium, except that there are absolute contraindications (history of anaphylactic shock or severe renal impairment). In the literature, it has been shown that by using this method of approach (CT execution to patients with nonconclusive ultrasound), it is possible to reduce the number of CT scans to <50%.

TREATMENT

It is still not uncommon to think that treating abdominal pain with an analgesic can mask the clinical evidence. On the contrary, it has been widely demonstrated that correct analgesia facilitates clinical evaluation because it makes the patient better and more collaborative to examination, thus reducing possible complications, increasing the sensitivity of instrumental investigations, without altering the objective framework. **Flowchart 1** summarizes the management of abdominal pain.



FLOWCHART 1: Summary of management of abdominal pain.

The class of drugs most indicated in the treatment of acute abdominal pain is that are effective, almost without side effects, and have an antidote if necessary. Nonsteroidal anti-inflammatory drugs, used extensively in the past because considered "safer," are actually burdened from important cardiovascular, gastrointestinal, and renal side effects, particularly in elderly patients. In mild-to-moderate abdominal pain, paracetamol can be used as a first-choice drug. Antibiotics are indicated in diseases such as peritonitis and abdominal sepsis, urinary tract infections, and pelvic inflammatory disease (PID). Particular attention must be reserved for spontaneous bacterial peritonitis due to gram-positive aerobes.

Remember two nonpharmacologic treatments: (1) Nasogastric tube to decompress a bowel obstruction or to confirm a gastrointestinal bleeding; and (2) Urinary catheter in presence of bladder obstruction or to monitor urinary output in the critically ill patient.

SUMMARY

Although patients with abdominal pain in most cases do not have severe pathology, the symptom may accompany very serious and potentially deadly clinical conditions, if not recognized promptly. The knowledge of abdominal anatomy and the careful evaluation of clinical signs and symptoms, together with a precise focused medical history, allows to correctly orient the diagnosis in 80% of cases. There are no specific laboratory tests for the various morbid conditions, but the laboratory investigation serves mainly to quantify the degree of systemic involvement of the disease. The most cost-effective diagnostic-instrumental approach in terms of cost/benefit is represented by the execution of abdominal-focused ultrasound in all patients; an abdominal CT scan must be performed only in case of nonconclusive ultrasound. Abdominal pain must be treated even before diagnosis, and the use of opioids is safe and recommended. Also, fluids and electrolytes imbalance must be treated promptly while making the diagnostic workup. When the diagnosis is uncertain but the patient is still symptomatic, it is often advisable and safe to keep patients under observation to evaluate the possible evolution. It is important to keep in mind that normal exams do not exclude an abdominal serious process. A plain X-ray of the abdomen is significant only in the suspicion of intestinal obstruction or perforation.

MULTIPLE CHOICE QUESTIONS

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92 CHAPTER

Nausea, Vomiting, Hiccups, Constipation

Devendra Richhariya

NAUSEA AND VOMITING

Vomiting refers to expulsions of gastric contents due to strong abdominothoracic muscle and gut contractions. It may occur as a protective response to certain ingested toxins or may be an indicator of serious organ system dysfunction. Vomiting is usually associated with nausea (subjective feeling to vomit) and retching (abdominal contraction without oral expulsion). Vomiting should be differentiated from regurgitation and rumination which are effortless expulsion of food.

Etiology

Nausea and vomiting are associated with a variety of gastrointestinal (GI) and non-GI disorders (**Table 1**). In tropical countries, acute onset vomiting most commonly is due to gastroenteritis or systemic infections and is usually associated with diarrhea. Food-borne infections can be due to contaminated water or food material. *Staphylococcus aureus* and *Bacillus cereus* produce toxins which cause emesis. Viral infection by rotavirus, adenovirus, etc., can also cause gastroenteritis. Systemic infections such as meningitis, hepatitis, and upper respiratory infections can also cause nausea and vomiting.

TABLE 1: Etiology of vomiting.

Gastrointestinal causes	*Other organ systems*	*Miscellaneous*
• Gastric • Gastritis GERD peptic ulcer • Gastric outlet obstruction • Gastroparesis malignancy • Bowel obstruction • Ischemic bowel, food poisoning • Hepatobiliary • Hepatitis cholecystitis • Biliary colic pancreatitis	• Endocrine metabolic • Uremia • Diabetic ketoacidosis • Pregnancy • Addison's disease • Hypercalcemia • Cerebral lesions • SOL brain hemorrhage • Cardiac—acute MI • Psychiatric • Bulimia anorexia nervosa	• Drug-induced • NSAIDs • Antimalarials • Chemotherapeutic agents • Oral contraceptive • Alternative medicine • Toxins • Alcohol foodborne poisoning • Radiation • Motion sickness • Cyclic vomiting syndrome

(GERD: gastroesophageal reflux disease; MI: myocardial infarction; NSAIDs: nonsteroidal anti-inflammatory drugs; SOL: space-occupying lesion)

Another most frequent cause is medication. Drugs act on the vomiting center as well as on the GI tract to cause nausea and vomiting. Nonsteroidal anti-inflammatory drugs (NSAIDs) commonly cause gastritis and peptic ulcers, sometimes resulting in stricture and resultant obstruction. They also can cause acute kidney injury. Non-NSAID analgesics, such as tramadol, frequently cause nausea and emesis. Aspirin and cardiac antiarrhythmic and antihypertensive can induce emesis. Other common agents are anticancer treatment, metronidazole, antidiabetic (metformin, exenatide), antidepressants [selective serotonin reuptake inhibitors (SSRIs), *tricyclic antidepressants* (TCAs)], oral contraceptives, diuretics, and nicotine. Consumption of bottle gourd (known as *lauki* or *dudhi* in India) juice is a treatment advocated by alternative medicine practitioners. Bitter juice contains the toxin cucurbitacin and can lead to nausea, vomiting, GI bleeding, and death.

Mechanical gut obstruction due to various causes is associated with abdominal distension, pain, and nausea which may get partial relief on vomiting. The obstruction could be due to strictures, volvulus, or adhesions or due to extrinsic compression by the superior mesenteric artery. Gastroparesis due to diabetes and neurological conditions, such as Parkinsonism and malignancy, can cause nausea and vomiting in 70–80% of patients. Other abdominal conditions such as acute cholecystitis, appendicitis, and pancreatitis may also induce nausea and vomiting.

Cyclic vomiting syndrome is an idiopathic disorder characterized by intermittent episodes of nausea vomiting with intervening normal periods. Each episode lasts for 4–6 days with exacerbation due to emotional stress, food allergy, menses, or pregnancy. Patients with diabetic gastroparesis and marijuana addicts can also have cyclic patterns of vomiting.

Pathophysiology

Vomiting primarily appears to be a protective reflex; it may occur in response to various types of stimuli. Unpleasant, strong thoughts, pain, smell, or sight can produce vomiting. Area postrema, also known as the chemoreceptor trigger zone (**Fig. 1**), is located outside blood–brain barrier and is sensitive to various toxins including foodborne as well as endogenous such as in uremia and ketoacidosis and drugs. The labyrinth in the inner ear is sensitive to movements. Muscarinic M1 and histaminic H1 receptors get stimulated in motion sickness, morning sickness, and ear infection. Cannabinoid CB1 receptors located in dorsal vagal nuclei in the brain stem inhibit the vomiting reflex. Neurokinin NK-1 receptors in area postrema are activated by substance P and are responsible for chemotherapeutic agents-induced vomiting. Serotonergic 5-HT3 receptors on vagal afferents are stimulated by serotonin release by enteroendocrine cells in response to toxins and drugs. Coordination of vomiting is done at the vomiting center in the medulla. Stimulation of brain 5-HT3 receptors release dopamine which acts on D2 receptors in the vomiting center. This starts emesis by induction of nausea, gastric contraction, and inhibition of gut peristaltic slow waves. Thoracic muscles contract with closed glottis which leads to retching. Reverse peristalsis in the small intestine in a combination of thoracoabdominal muscle contraction leads to the expulsion of food contents through the mouth.

Clinical Presentation

Vomiting must be differentiated from regurgitation which is the effortless expulsion of gastric contents. Acute onset vomiting usually is a result of strong painful stimuli in the abdomen, gut obstruction, toxins, metabolic causes (uremia, diabetic ketoacidosis), or foodborne infections. Early morning vomiting is seen in pregnancy, alcohol, and metabolic disorders. Vomiting after meals occurs in gastroparesis, gastric outlet obstruction, and achalasia cardia. Achalasia patients may also report regurgitation of food at night and nasal regurgitation. Bilious vomiting with obstipation and abdominal distension suggest intestinal obstruction. Sudden onset vomiting without nausea or retching (projectile vomiting) may indicate raised intracranial pressure usually due to intracerebral space-occupying lesions. It may be associated with headache and visual symptoms. Symptoms of concern (red flags) are abdominal pain, jaundice, weight loss, hematemesis, presence of lump, severe headache, and postural symptoms.

Evaluation

History: Evaluation of the patient with acute onset vomiting (<1-week duration) requires a detailed history of recent travel, food habits, associated abdominal pain, or diarrhea. Vomiting and diarrhea of acute onset suggest acute gastroenteritis. History of amenorrhea is important in women of

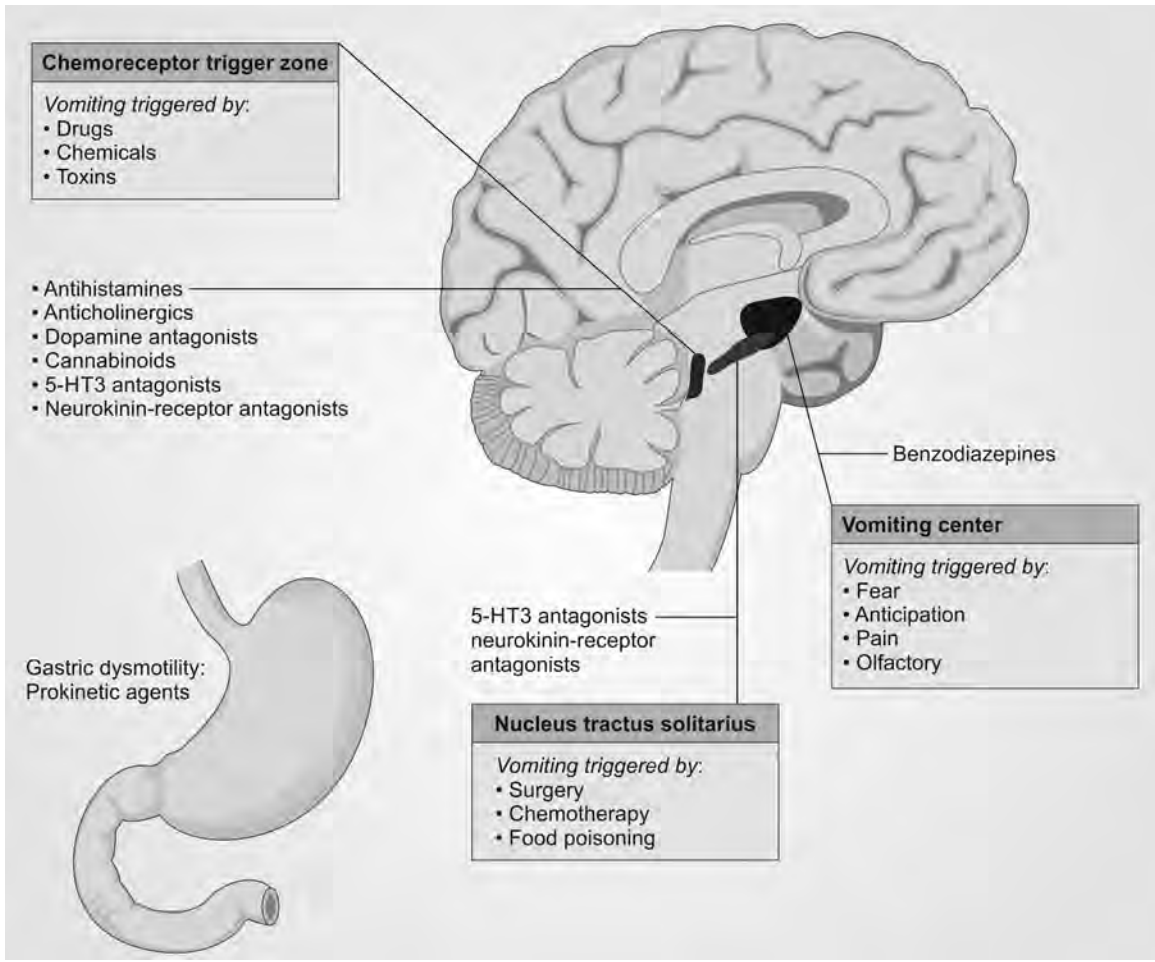


FIG. 1: Areas of the brain and triggers involved in the vomiting reflex, with sites of action of antiemetic and prokinetic agents.

childbearing age. Careful interrogation about any poisoning or drug overdose is required. History of associated abdominal pain, distension, and obstipation may suggest peritonitis due to perforation, pancreatitis, or obstruction. Vomiting relieves abdominal pain due to obstruction but not in other conditions such as pancreatitis and cholecystitis. The presence of anorexia, nausea, and vomiting before the onset of jaundice suggests acute hepatitis. History of postural giddiness, excessive thirst, and oliguria suggest significant volume depletion. History of fever and headache with or without altered sensorium points toward meningeal irritation or raised intracranial pressure. Vomiting due to gastric outlet obstruction or gastroparesis occurs within an hour after meals and may contain food ingested hours before. It may be associated with postprandial fullness. Cough and fever may be indicative of aspiration. Dyspnea and chest pain after vomiting should alert for possible esophageal perforation.

Physical examination: Assessment should be made for hydration and nutritional insufficiency. Tachycardia, orthostatic hypotension, and dehydration suggest significant volume loss. Lymphadenopathy may be due to tuberculosis or disseminated malignancy. Jaundice and epigastric lump with excoriation marks on skin may suggest obstructive jaundice due to malignancy. Distended abdomen with high-pitch bowel sounds suggests intestinal obstruction while absent bowel sound and tender abdomen with guarding suggest peritonitis. Per rectal examination may reveal impacted fecal matter, growth, rectal shelf (pelvic metastatic deposits), or empty rectum (intestinal obstruction). The presence of blood on the examining finger could be due to rectal growth, ulceration, or ischemic bowel. Epigastric lump with visible peristalsis and presence of succussion splash suggest gastric outlet obstruction.

Investigations

Complete blood counts, creatinine, electrolytes arterial blood gas (ABG), serum calcium, serum glutamic pyruvic transaminase (SGPT), random blood sugar, and ketones should be sent for examination and chest and abdominal radiographs should be ordered to look for obstruction, bowel perforation, and esophageal perforation (Boerhaave's syndrome). Further evaluation with cross-sectional imaging (CT/MRI) may be required. ABGs are to be sent for acid–base imbalance.

Treatment

Management of acute vomiting requires assessment for etiology, dehydration, electrolyte imbalance, and possible complications. Patients with mild symptoms can be managed with oral prokinetics and antiemetics. Poisoning and drug overdose are to be treated by nasogastric aspiration and lavage, activated charcoal, and a specific antidote. Antiemetics should be started. Fluid resuscitation should be started according to the degree of dehydration. Endoscopy can be done, if required, after initial resuscitation. Patients with gastric outlet obstruction may require nasogastric aspiration and lavage to empty stomach before endoscopy. Patients with chronic vomiting should be assessed for malnutrition. Replacement of fluid, electrolytes, and vitamins is done wherever indicated. Chronic vomiting should be treated with prokinetics and antiemetic agents. The most commonly used antiemetics (**Table 2**) are substituted benzamides, which act as D2 receptor antagonist. D2 receptor antagonism at area postrema reduces nausea and vomiting while the effect on gastric D2 receptors improves gastric emptying.

Metoclopramide and levosulpiride are available in oral and intravenous (IV) preparation (**Table 3**). Rapid IV metoclopramide injection may produce restlessness. Metoclopramide crosses blood–brain barrier and causes dystonia, extrapyramidal symptoms, tardive dyskinesia, QT prolongation, and hyperprolactinemia. It also acts on peripheral 5-HT4 receptor causing acetylcholine release leading to increased antroduodenal motility. *Domperidone* is much safer as it does not cross the blood–brain barrier although it can cause hyperprolactinemia and galactorrhea. It can be used in levodopa to induce vomiting in Parkinson's diseases. *Itopride* acts as an antagonist of the D2 receptor and acetylcholine esterase inhibitor. Motilin agonist erythromycin enhances gastric emptying.

TABLE 2: Commonly used agents for the treatment of nausea and vomiting.

Class	*Drug*	*Comments*	*Adverse effect*
Antihistamine	• Dimenhydrinate • Diphenhydramine • Meclizine	Useful in motion sickness, migraines, and vertigo	Drowsiness
Benzodiazepine	• Alprazolam • Diazepam • Lorazepam	Add-on therapy in chemotherapy-induced nausea and vomiting	Sedation
Butyrophenone	Haloperidol	Chemotherapy-induced nausea and vomiting	Sedation, restlessness
Corticosteroids	Dexamethasone	Chemotherapy-induced nausea and vomiting	Insomnia
Serotonin antagonist	• Ondansetron • Granisetron • Dolasetron	Prolongs QT_c	Constipation, dizziness
Phenothiazine	• Prochlorperazine • Promethazine	Also useful in the treatment of migraine, vertigo, motion sickness	Extrapyramidal symptoms
Benzamide	• Metoclopramide • Trimethobenzamide	Useful in gastroparesis and reflux in children	Extrapyramidal symptoms

TABLE 3: Dopamine antagonists most commonly used in nausea and vomiting and their properties.

Drug name	*Usual oral dose and frequency*	*Oral bio-availability*	*Pharmaco-kinetics*	*Half-life*	*Drug interactions*	*Side-effects*	*Comments*
Prochlorperazine	5–10 mg, 2–3 times daily	<10%	Extensive first-pass metabolism	7 hours	Other drugs causing hypotension, lithium	Sedation, extrapyramidal reactions, hypotension	Available in several formulations including buccal tablets, oral liquid and injection
Metoclopramide	10 mg, 3 times daily	>90%	Undergoes first-pass metabolism; clearance is by hepatic metabolism; only 20% is excreted in the urine unchanged	4 hours	Antipsychotics	Extrapyramidal reactions, restlessness, stimulation of prolactin release	Also available as an injection; can be used as a prokinetic agent; contraindicated in gastrointestinal patients with an obstruction, perforation or hemorrhage. **Caution:** Can cause severe dystonic reactions (see main text for details)
Domperidone	10–20 mg, 3–4 times daily	13–17%	Undergoes extensive presystemic metabolism	12–16 hours	None significant	Stimulates prolactin release, reduced libido	Less likely to cause extrapyramidal side effects and sedation; also available as suppositories and oral liquid but not as an injection; also has prokinetic properties. **Caution:** Can lead to increased cardiac side effects (see main text for details)

The 5-HT3 antagonists ondansetron and granisetron are useful in postsurgical and chemotherapeutic agents-induced vomiting. They block 5-HT3 receptors in the stomach and vomiting center. Side effects are raised liver enzymes, QT prolongation, and headache. Ondansetron can be used safely in pregnancy. Palonosetron is very effective in chemotherapeutic drugs-induced nausea and vomiting. Ginger and doxylamine–pyridoxine combination is also used in pregnancy.

Phenothiazines such as prochlorperazine block D2 receptors and muscarinic M1 receptors. They are potent antiemetic but with extrapyramidal side effects. Olanzapine does not have extrapyramidal side effects and is a good alternative. *Antihistaminic agents*: Cyclizine and dimenhydrinate block central H1 receptors and are useful for motion sickness. A combination of glucocorticoids, NK1 receptor antagonist (aprepitant), and cannabinoids (tetrahydrocannabinol) is used for chemotherapeutic-induced vomiting. Nausea and vomiting is the expulsion of GI food contents due to abdominothoracic muscle contractions and occurs in a wide variety of conditions. It can be treated by various antiemetics and prokinetics. The presence of significant adverse effects poses difficulty in prolonging treatment with these agents.

HICCUPS

Hiccups as a symptom are very commonly seen in clinical practice and are usually a transient condition affecting almost all people in their lifetime. Intractable hiccups and complications from hiccups are rarely seen. The precise epidemiology of hiccups, including severe intractable hiccups, is uncertain in the general population as well as in the palliative care population. Most people have experienced hiccups at some point in their life, and these hiccups are generally self-limited. Hiccups can, however, become chronic and persistent in rare cases.

What are Hiccups?

Hiccups are sudden, inspiratory activities generated due to contraction of intercostal muscle and diaphragm; contraction is intermittent, involuntary, and spasmodic in nature with the frequency of 5–50/min. On the basis of duration, hiccups can be divided into three groups:

1. A "hiccup bout" is an episode of hiccups lasting up to 48 hours.
2. "Persistent hiccups" are hiccups that continue longer than 48 hours and up to 1 month.
3. "Intractable hiccups" are hiccups that continue longer than 1 month.

Hiccups may be associated with comorbid conditions: Vascular, *chronic kidney disease* (CKD), postoperative, *central nervous system* (CNS) disease, duodenal ulcer, reflux esophagitis, advanced cancer.

Hiccups can cause significant adverse effects which include, dehydration, malnutrition, fatigue, weight loss, insomnia, nervous stress, and poor quality of life.

Pathophysiology

The exact mechanism which provokes the hiccups including severe intractable hiccups remains unclear. In majority of the patients, hiccups involve unilateral contraction of the left

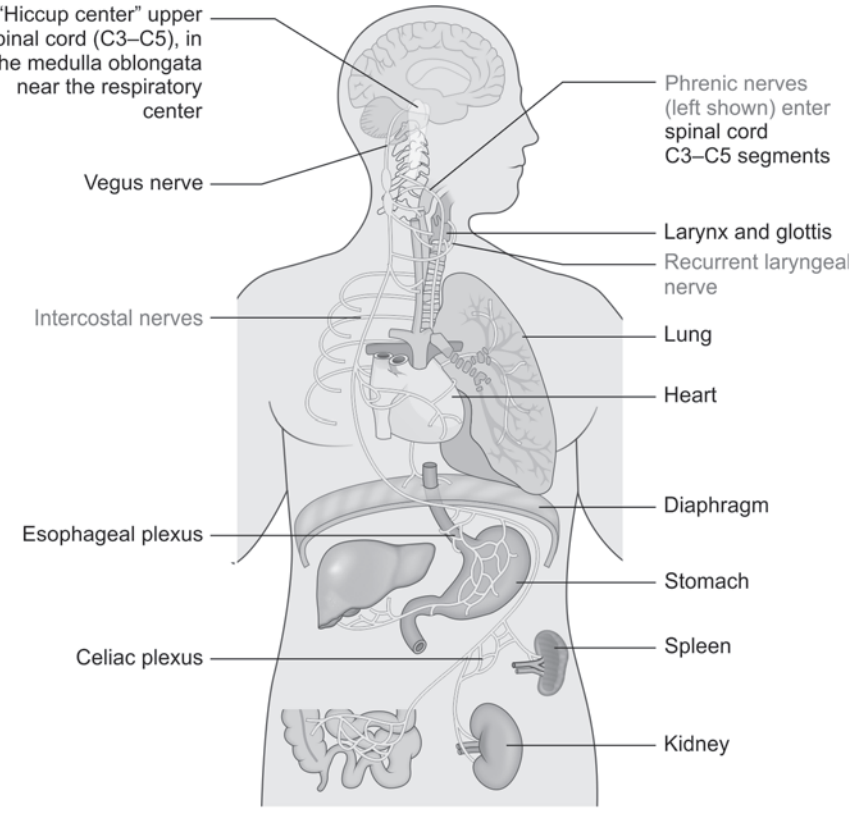


FIG. 2: Hiccups reflux arc. Pathology affecting the brain, diaphragm, thoracic, or abdominal viscera can stimulate vagal or phrenic afferents that activate the diffuse "hiccup center" in the midbrain, brainstem, and proximal cervical cord. This triggers repetitive myoclonic contractions of the diaphragm and other respiratory muscles via the phrenic and the intercostal nerves (motor efferent colored dark gray). Immediately afterward, activation of the recurrent laryngeal nerve closes the glottis, producing the characteristic "hic" in hiccups.

hemidiaphragm. Several neural pathways make up the hiccup reflex arc (**Fig. 2**): Gamma-aminobutyric acid (GABA) appears to be the most important mediator for neural connections in the hiccup reflex arc. Other mediators may include dopaminergic, muscarinic, and serotonergic pathways (i.e., 5-HT1A receptors).

Etiology

Common and benign causes of hiccups are overeating carbonated drinks, stress, emotional changes, and spicy and alcohol ingestion. Intractable hiccups may reflect serious underlying diseases, such as an infection (e.g., meningitis, encephalitis) or a structural lesion (e.g., intracranial neoplasm, hydrocephalus). Potential causes of persistent and intractable hiccups are given in **Box 1**.

Evaluation

Hiccup bouts are common, and most of the individuals do not need thorough evaluation or medical attention. However, intractable hiccups required thorough evaluation to ascertain the underlying causes.

The history should include the severity and duration of hiccups, any associated medical conditions and previous surgery, drug abuse or alcohol intake, and a complete list of medications. The persistence of hiccups during sleep suggests an organic rather than psychogenic etiology.

Physical examination of external auditory canals is done to rule out infection or foreign body which may be a potential irritant of tympanic membranes. A detailed head and neck examination is important to exclude an enlarged thyroid and lymphadenopathy. Neurological examination (including cranial nerve assessment), auscultation of the chest, and per abdominal examination should be done to palpate for any mass lesions.

Investigations

Patients with persistent or intractable hiccups following investigation should be considered:

Complete blood count, renal function test (RFT), liver function test (LFT), serum electrolytes, serum calcium, serum amylase/lipase electrocardiogram (ECG), radiological investigations, X-ray of chest, and contrast-enhanced computed tomography (CECT). A chest radiograph or CT scan is helpful to detect pulmonary and mediastinal abnormalities irritating the vagal or phrenic nerves or the diaphragm in patients presenting with dyspnea. Patients with esophageal symptoms and dysphagia should undergo upper GI endoscopy for evaluation to find out esophagitis stricture or malignancy. In patients with advanced malignancy, the cause of intractable hiccups is often multifactorial, and an exhaustive evaluation is required.

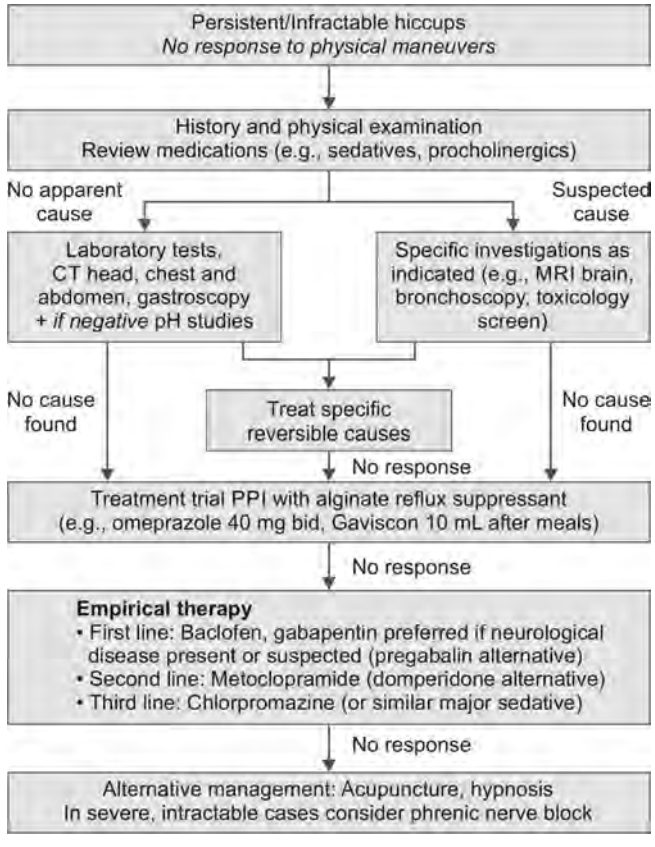
Treatment

Most of the patient hiccups are self-limiting and do not require any treatment. Treatment of an underlying illness is required if it is due to any medical illness. Treatment of intractable hiccups requires pharmacological or nonpharmacological management for persistent or intractable hiccups (**Flowchart 1**).

BOX 1: Causes of persistent and intractable hiccups.

Vascular
Ischemic/hemorrhagic stroke, AV malformations, temporal arteritis
Infections
Encephalitis, meningitis, brain abscess, neurosyphilis, subphrenic abscess
Structural
Head trauma, intracranial neoplasms, brainstem neoplasms, multiple sclerosis, syringomyelia, hydrocephalus
Vagus and phrenic nerve irritation
Goiter, pharyngitis, laryngitis, hair or foreign body irritation of tympanic membrane, neck cyst, or another tumor
GI disorders
Gastric distention, gastritis, peptic ulcer disease, pancreatitis, pancreatic cancer, gastric carcinoma, abdominal abscesses, gallbladder disease, inflammatory bowel disease, hepatitis, aerophagia, esophageal distention, esophagitis, bowel obstruction
CV disorders
Myocardial infarction, pericarditis
Thoracic disorders
Enlarged lymph nodes secondary to infection or neoplasm, pneumonia, empyema, bronchitis, asthma, pleuritis, aortic aneurysm, mediastinitis, mediastinal tumors, chest trauma, pulmonary embolism
Toxic and metabolic
DM, alcohol, hypocalcemia, hyponatremia, herpes zoster, hypocapnia, tuberculosis, malaria, uremia
Postoperative
Drugs
Alpha methyldopa, short-acting barbiturates, diazepam, dexamethasone
Psychogenic
Anorexia nervosa, schizophrenia, stress, malingering, conversion reaction

(AV: arteriovenous; CV: cardiovascular; DM: diabetes mellitus; GI: gastrointestinal)


Persistent/Infractable hiccups
No response to physical maneuvers
History and physical examination
Review medications (e.g., sedatives, procholinergics)
No apparent cause
Suspected cause
Laboratory tests, CT head, chest and abdomen, gastroscopy + if negative pH studies
Specific investigations as indicated (e.g., MRI brain, bronchoscopy, toxicology screen)
No cause found
Treat specific reversible causes
No cause found
No response
Treatment trial PPI with alginate reflux suppressant (e.g., omeprazole 40 mg bid, Gaviscon 10 mL after meals)
No response
Empirical therapy
• First line: Baclofen, gabapentin preferred if neurological disease present or suspected (pregabalin alternative)
• Second line: Metoclopramide (domperidone alternative)
• Third line: Chlorpromazine (or similar major sedative)
No response
Alternative management: Acupuncture, hypnosis
In severe, intractable cases consider phrenic nerve block

(PPI: proton pump inhibitors)

FLOWCHART 1: Treatment algorithm of persistent and intractable hiccups.

- If a specific pathology is found to be potentially causing the hiccups, the choice of treatment should be directed toward treating the illness. As an example, treatment with a proton-pump inhibitor or an H2 blocker should be given if *gastroesophageal reflux disease* (GERD) is a likely cause.
- If the cause is idiopathic, empiric therapy with physical maneuvers is the first-line treatment. These maneuvers are easy to perform and have a low risk of complications.
- Physical therapy (**Table 4**): Common maneuvers suggested are breath-holding, Valsalva maneuver, sipping cold water, gargling with water, swallowing a teaspoon of dry sugar, compression over the eyeballs, pulling knees to chest, and leaning forward to compress the chest.

Pharmacologic therapy: Drug therapy should be reserved for the treatment of hiccups when physical maneuvers have failed. If hiccups subside following treatment, drug treatment can usually be stopped the day after cessation of hiccups. Most drug treatments can be used for 7–10 days. If hiccups persist, it is reasonable to consider another pharmacologic or nonpharmacologic treatment option.

Chlorpromazine: It is centrally acting dopamine, acts by antagonism in the hypothalamus, remained the drug of choice for many years, and is the only medication approved for hiccups by the US Food and Drug Administration. IV administration may be more effective, although the drug must be infused in 500–1,000-mL saline with the patient in the supine position to avoid hypotension; the lower dosing for hiccups is generally well tolerated. It is generally not recommended as the first drug of choice due to serious side effects and is also contraindicated in older people.

TABLE 4: Physical therapy for hiccups.	
Nasopharyngeal stimulation	• Intranasal application of vinegar • Inhalation of "smelling salts" or similar stimulant/irritant (e.g., ammonia, ether) • Oropharyngeal stimulation (e.g., ice water)
Vagal stimulation	• Cold compress to the face • Carotid massage • Induced fright • Induced vomiting
Respiratory maneuver	• Breath-holding (inspiration, expiration) • Valsalva maneuvers • CPAP respiration
Note: These maneuvers are, in general, effective only to shorten an attack of acute hiccups and are not the treatment of persistent or intractable hiccups. None has been subjected to clinical trials.	

(CPAP: continuous positive airway pressure)

Metoclopramide: It also has central dopamine antagonism but slightly weaker than chlorpromazine. The usual oral dose is 10 mg three or four times daily for up to 7–10 days. Metoclopramide is also associated with tardive dyskinesia, especially at high doses and with chronic use.

Other drugs effective in hiccups are: Baclofen, haloperidol, anticonvulsants, nifedipine, methylphenidate, midazolam, lidocaine, antidepressants (e.g., amitriptyline), antiarrhythmic drugs (e.g., quinidine), olanzapine, amantadine, oral viscous lidocaine (2%) solution.

Surgery: A surgical approach including phrenic nerve crushing or blocking with a local anesthetic may be successful in refractory cases.

CONSTIPATION

Less than three bowel movements per week and dry and hard stool are generally considered as constipation. The stool is painful to pass. Very common complaints in outpatient are chronic constipation and few people also experience occasional constipation. Causes of constipation can be divided into primary and secondary causes:

Primary: Primary causes are most common, nonlife-threatening, usually >6 months, and not due to any medication or medical problem. Inadequate intake of dietary fiber, fluid intake, and decreased physical activities are the common cause.

Secondary: Causes are medication such as opiates, endocrine (hypothyroidism) and metabolic disorders, and obstruction such as colorectal cancer.

Fiber in diet: Fiber promotes bowel movements and prevents constipation. It is important to include good quality of fiber in the diet such as fruits, vegetables, and whole grains.

Physical activity: Constipation is common in a less physically active person, especially in the elderly group. The risk of constipation is more in a bedridden patient.

Medications: Opiates, antidepressants, anticonvulsants, iron supplements, calcium channel blockers, aluminum-containing antacids, and diuretics are the drugs which frequently cause constipation.

Irritable bowel syndrome: Patient with irritable bowel syndrome (IBS) is more frequently constipated than other population.

Pregnancy: Hormonal changes in pregnancy make women more susceptible to constipation.

Problem with colon and rectum: Patients with tumor, scar tissue, diverticulosis, and colorectal stricture are prone to constipation.

Disease and conditions: Diseases of the colon, rectum, or anus can cause constipation. Neurological disorders such as Parkinson's disease, multiple sclerosis, stroke, and spinal cord injuries can lead to constipation. Uremia, diabetes, hypocalcemia, hypothyroidism, and other systemic diseases such as lupus, scleroderma, amyloidosis, and carcinoma also cause constipation.

Others: Aging, changes in routine, overuse of laxatives, not going to the toilet when needed, and not drinking enough water are other causes of constipation.

Symptoms

Common symptoms include abdominal pain, bloating, hard and dry consistency stools, difficult to pass. Red flag symptoms (features of concern) are new onset without any cause, weight loss, blood in stool, anemia and family history of malignancy. Complications of constipation clinically present as hemorrhoids, rectal prolapse, anal fissure, urinary incontinence, urinary retention, and fecal impaction.

Diagnosis

Examination

Abdominal examination and rectal examination guide the physician to evaluate constipation further. Rectal examination will provide information about sphincter tone, presence of hemorrhoids, fecal impaction, and any other perianal irregularities. In addition to general physical examination and rectal examination, the following tests and procedures are required to find out the cause.

Investigations

Blood tests, X-ray of abdomen, sigmoidoscopy (examination of rectum lower or sigmoid colon), colonoscopy (examination of rectum and entire colon), anorectal manometry (evaluation of anal rectal muscle function), and defecography (X-ray while defecation) should be conducted.

Management

Stepwise Approach

In most of the cases, constipation resolves without any treatment. Stepwise management of constipation is implemented (**Fig. 3**). Recurrent constipation can be dealt with lifestyle changes such as increase in activities, eating more fiber-rich

diet, and drinking more water; laxative can be used but carefully and only when necessary.

Medications

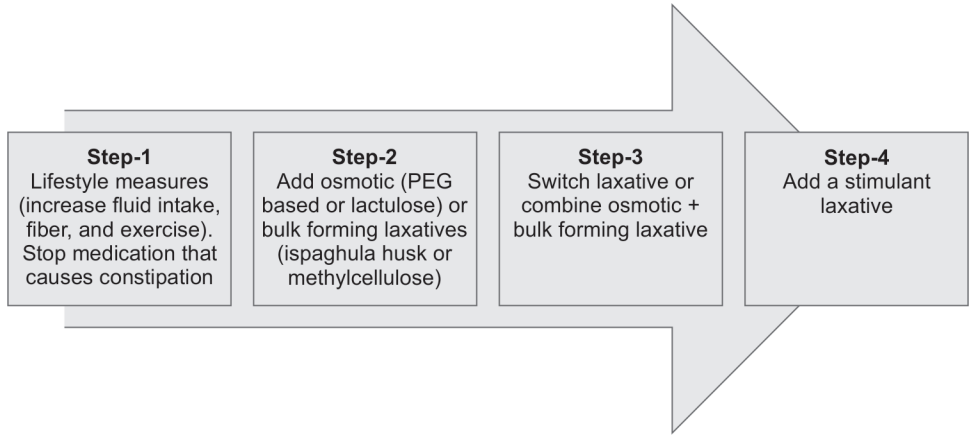
A variety of laxatives are available such as stimulants, lubricants, stool softeners, fiber supplements, osmotic laxatives, saline laxatives, chloride channel activators, and 5-HT4 agonists (**Table 5**). Constipation is a common symptom in general practice. For appropriate management of the constipation, it is important to know the type of constipation, whether it is primary or secondary. General physical examination and rectal examination are important for further evaluation. Lifestyle changes, fiber intake, and medications are helpful in relieving constipation.

Chronic Constipation

Constipation should be evaluated further if lifestyle modification and stepwise medication therapy do not work (chronic constipation) as summarized in **Flowchart 2**.

SUMMARY

Nausea and vomiting are common, usually short-lived and self-limiting symptoms encountered in both inpatient and outpatient settings. Thorough clinical history and physical examination are vital in establishing a cause for symptoms. Simple investigational tests can also lead to a quick but essential diagnosis. It is important to treat not only the symptoms but also the consequences of nausea and vomiting, as


Step-1
Lifestyle measures (increase fluid intake, fiber, and exercise). Stop medication that causes constipation
Step-2
Add osmotic (PEG based or lactulose) or bulk forming laxatives (ispaghula husk or methylcellulose)
Step-3
Switch laxative or combine osmotic + bulk forming laxative
Step-4
Add a stimulant laxative

(PEG: polyethylene glycol)

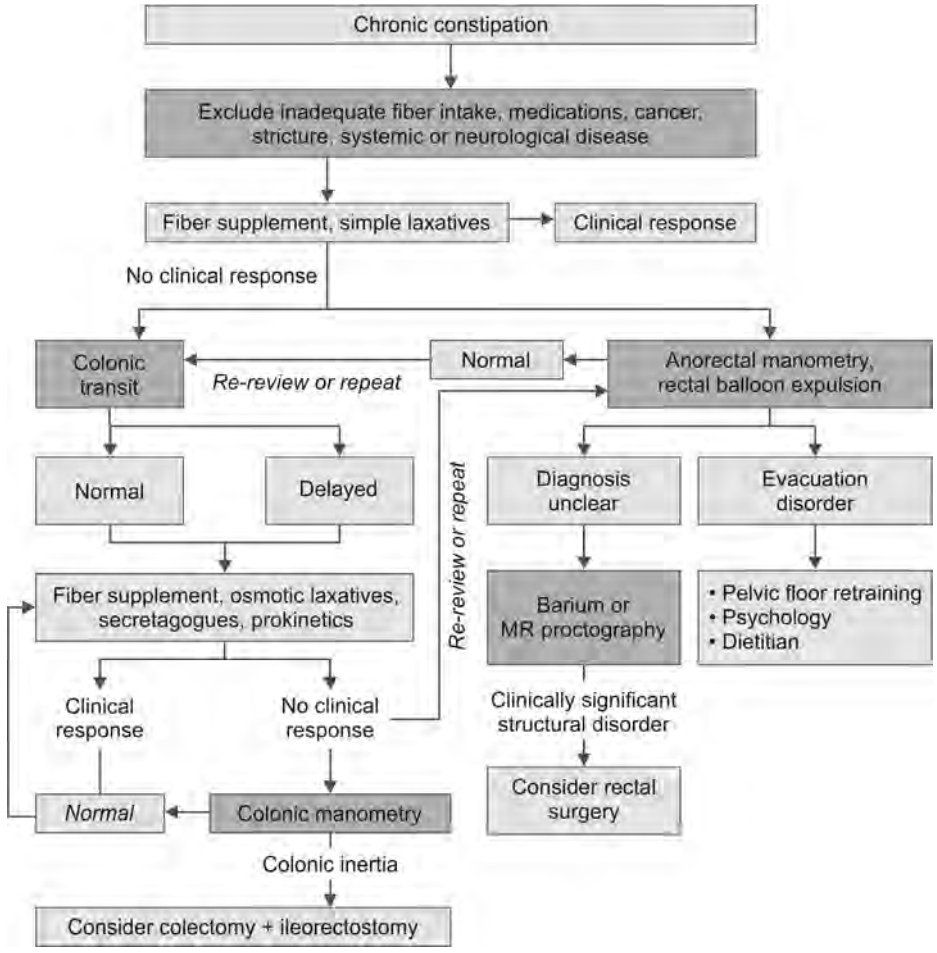
FIG. 3: Stepwise management of constipation in adult.

TABLE 5: Available medications for constipation.

Fiber	Psyllium	One teaspoon three times a day	Stool bulking agents
Emollient	Docusate sodium	100 mg once/twice a day	
Stimulants	Bisacodyl	10 mg per rectal	Increases intestinal motility by stimulation of myenteric plexus
	Anthraquinones	1–2 tablets orally/twice daily	
	Senna	Two tablets orally twice daily	
Saline laxatives	Milk of magnesium	15–30 mL twice daily	Osmotic laxative
Suppository	Glycerin suppository	One per rectal/day	Locally stimulant
Hyperosmolar agents	Lactulose/sorbitol	15–30 mL twice daily	Pulls fluid into the gut
Enemas	Mineral oil/soap water	100–250 mL per-rectally	Colonic distension
Serotonergic agents	Prucalopride	2 mg daily	Stimulate GI motility
Prosecretory agents	Lubiprostone	24 µg/day	Moves water into the lumen
***Initial options*:** Fiber, magnesium hydroxide, PEG			
***Severe infrequent or acute constipation*:** PEG-3350, saline laxative (magnesium hydroxide), bisacodyl, senna			
***Severe idiopathic constipation*:** Larger doses of osmotic laxatives (saline or PEG), lactulose, neuromuscular drugs combination therapy			
***Outlet obstruction*:** Liquify stool with osmotic laxatives, enemas			
***Pregnancy*:** Fiber and bulk laxatives, PEG, lactulose, bisacodyl			

(GI: gastrointestinal; PEG: polyethylene glycol)

intractable cases or severely affected patients will often present dehydrated and with electrolyte imbalances. Hiccups are familiar to all and remain a medical quiz. Acute hiccups are very common, remain for few minutes, and are self-limiting. Persistent and chronic hiccups are rare, remain for weeks or month, are very distressing, and difficult to treat. Chronic constipation has a large negative impact on the quality of life and causes significant psychological distress. It is a common condition where over-the-counter (OTC) laxatives and visits to physicians are taken. Constipation can be divided into slow-transit constipation, dysfunctional constipation that is treated with biofeedback and medications, and constipation-predominant IBS. Available therapeutic options are lifestyle modifications and medications.



FLOWCHART 2: Evaluation and management of chronic constipation.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Diarrhea-associated Diseases

Sanjay Kumar

INTRODUCTION

Diarrhea is best defined as increased fluidity of stool though increased frequency and volume are also sometimes a consideration. It is one of the most common gastrointestinal (GI) symptoms. It is the second most common cause of mortality in children and is one of the most common reasons for absenteeism from job in adults globally. Most cases are self-limiting and do not require treatment, but some of them could be serious due to dehydration, acute kidney injury (AKI), electrolyte imbalance, and rarely sepsis. Diarrheal illness accounts for 2.5 million deaths per year worldwide. In the United States alone, an estimated 48 million foodborne diarrheal illnesses occur annually. In the developing world, infectious causes of acute diarrhea are largely related to contaminated food and water supplies.

PATHOPHYSIOLOGY

Increased stool volume/increased fluidity or increased frequency results whenever there is excess unabsorbed fluid/stool traveling through the left colon. So, this would happen either if there is excessive secretion in the small bowel or defective absorption or if there is poor absorption of fluids in the colon. Sometimes, there is no problem with absorption/secretion, but still, there may be diarrhea such as in case of increased motility, seen in functional bowel disease or hyperthyroidism. The most common cause of acute diarrhea in adults is infection. Amongst infections, viral infections are the most common. The causes of diarrhea are listed in **Table 1**.

TABLE 1: Causes of diarrhea.

Causes of acute diarrhea	***Infections (bacteria, viruses, parasites, protozoa), food allergies, food poisoning, medications, initial presentation of chronic diarrhea***
Infection that causes diarrhea	*Bacteria*: • *Aeromonas* species • *Campylobacter* species • *Clostridium difficile* • *Escherichia coli* (enterotoxigenic, enteroinvasive, enterohemorrhagic) • *Salmonella* species • *Shigella* species *Viruses*: • Adenovirus • Norovirus • Rotavirus *Parasites or protozoa*: • *Cryptosporidium* • *Cyclospora* • *Entamoeba* • *Giardia lamblia* • *Microsporidia*

APPROACH TO ACUTE DIARRHEA

Diarrhea is classified as acute or chronic, inflammatory or noninflammatory, osmotic or secretory. But while evaluating a patient at the bedside, it is more useful to ascertain whether it is small bowel diarrhea or large bowel diarrhea because that guides you to further evaluation and proper management. Frequency and volume are the most important points in history. Voluminous stools three to six times a day are suggestive of small bowel origin while more frequent but scanty stools are suggestive of large bowel origin. Next is contents. The presence of blood/mucous suggests a large bowel, i.e., colitis, while profuse watery diarrhea suggests a small bowel, i.e., enteritis. Crampy abdominal pain can be present in both, but the tenesmus points to a large bowel/rectal origin. A detailed history will go a long way in providing a clue to the cause of diarrhea and one can manage accordingly (**Table 2**).

Physical Examination

The goal of the physical examination is to assess the patient's degree of dehydration. Generally, ill appearance, dry mucous membranes, delayed capillary refill time, increased heart rate, and abnormal orthostatic vital signs can be helpful in identifying more severe dehydration. Fever is more suggestive of inflammatory diarrhea. The abdominal examination is important to assess for pain and acute abdominal processes. A rectal examination may be helpful in assessing for blood, rectal tenderness, and stool consistency.

TABLE 2: Clues to diagnosis—based on history and clinical findings.

History	*Potential pathogenic etiology*
Afebrile, abdominal pain with bloody diarrhea	Shiga toxin-producing *Escherichia coli*
Bloody stools with fever	*Salmonella, Shigella, Campylobacter,* Shiga toxin-producing *E. coli, Clostridium difficile, Entamoeba histolytica, Yersinia*
Camping, consumption of untreated water	*Giardia*
Fried rice	*Bacillus cereus*
Raw ground beef or seed sprouts	Shiga toxin-producing *E. coli* (e.g., *E. coli* O157:H7)
Raw milk	*Salmonella, Campylobacter*, Shiga toxin-producing *E. coli*, *Listeria*
Seafood, especially raw or undercooked shellfish	*Vibrio cholera*, *Vibrio parahaemolyticus*
Undercooked beef, pork, or poultry	*Staphylococcus aureus*, *Clostridium perfringens*, *Salmonella, Listeria* (beef, pork, poultry), Shiga toxin-producing *E. coli* (beef and pork), *B. cereus* (beef and pork), *Yersinia* (beef and pork), *Campylobacter* (poultry)
Exposure to daycare centers	Rotavirus, *Cryptosporidium, Giardia, Shigella*
Fecal-oral sexual contact	*Shigella, Salmonella, Campylobacter*, protozoal disease
Hospital admission	*C. difficile*, various drug-induced
Human immunodeficiency virus infection, immunosuppression	*Cryptosporidium, Microsporidia, Isospora, Cytomegalovirus, Mycobacterium avium* intracellular complex, *Listeria*
Medications or other therapies associated with diarrhea	• Antibiotics (especially broad-spectrum), laxatives, antacids (magnesium- or calcium-based), chemotherapy, colchicine, pelvic radiation therapy • Less common: Proton pump inhibitors, mannitol, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, cholesterol-lowering medications, lithium
Pregnancy	*Listeria*
Recent antibiotic use	*C. difficile*
Receptive anal intercourse, with or without rectal pain or proctitis	Herpes simplex virus infection, chlamydia, gonorrhea, syphilis
Rectal pain or proctitis	*Campylobacter, Salmonella, Shigella, E. histolytica, C. difficile, Giardia*
Rice-water stools	*V. cholera*
Several persons with common food exposure have an acute onset of symptoms	• Food poisoning with preformed toxins • Onset of symptoms within 6 hours: *Staphylococcus, B. cereus* (typically causes vomiting) • Onset of symptoms within 8–16 hours: *C. perfringens* type A (typically causes diarrhea)
Travel to a developing country	• Enterotoxigenic *E. coli* is most common • Many other pathogens (e.g., *Shigella, Salmonella, E. histolytica, Giardia, Cryptosporidium, Cyclospora*, enteric viruses) are possible because of poorly cleaned or cooked food, or fecal contamination of food or water

Investigations

Hardly any investigations are required in routine cases. Stool routine and culture may be advised if there is a suspicion of invasive diarrhea based on the presence of fever and blood in stools. Hemogram and renal function tests must be done if the patient is dehydrated. A film for malarial parasite may be handy if there is a high fever with chills as sometimes malaria can present as diarrhea (algid malaria).

Treatment

The mainstay of treatment of acute diarrhea is restoring/maintaining fluid and electrolyte balance.

Rehydration Therapy

The accumulated fluid deficit (calculated roughly as the difference between the patient's normal weight and his or her weight at presentation with diarrheal illness) must first be addressed. Once you know the deficit, you can supplement fluids orally. Various oral rehydration formulae are available. In 2002, the World Health Organization (WHO) endorsed oral rehydration solution (ORS) with reduced osmolarity (250 mOsm/L or less compared with the prior standard of 311 mOsm/L). Reduced osmolarity ORS decreases stool output, episodes of emesis, and the need for intravenous (IV) rehydration without increasing hyponatremia, duplicate by mixing 1/2 teaspoon of salt, 6 teaspoons of sugar, and 1

L of water. If the patient is having vomiting or heightened gastrocolic reflex, oral rehydration is not possible and we have to give IV fluids. While giving IV fluids, the best way to monitor adequacy is urine output but if the patient is too sick or has comorbidities, especially *chronic kidney disease* (CKD)/congestive *heart failure* (CHF)/chronic liver disease (CLD), fluid balance should be ensured by ultrasonographic inferior vena cava (IVC) monitoring or *central venous pressure* (CVP) monitoring by putting in a central venous catheter.

Antibiotic Therapy

Because acute diarrhea is most often self-limited and caused by viruses, routine antibiotic use is not recommended for most adults with nonsevere, watery diarrhea. Antibiotics may be considered in patients who are older than 65 years, immunocompromised, severely ill, or septic.

Zinc Supplementation

Zinc supplementation (20 mg/day for 10 days in children older than 2 months) may play a crucial role in treating and preventing acute diarrhea, particularly in developing countries. Most cases of acute diarrhea are self-limiting and can be managed with ORS. Those who have red flags (features of concern) can be managed with hospitalization IV fluids and antibiotics. Very rare cases will develop complications such as AKI or sepsis and these will require prolonged hospitalization, intensive care, and can be fatal too.

Indications for Hospitalization

Concerning features (red flags), clinical signs of dehydration, blood in stool, high fever, very high frequency, and liquidity leading to incontinence.

TRAVELER'S DIARRHEA

Traveler's diarrhea means loose stools and abdominal cramps during a visit to a place where the climate or sanitary practices are different from yours at home. It is caused by eating contaminated food or drinking contaminated water. It usually begins abruptly during your trip or shortly after you return home. Most cases improve within 1–2 days without treatment and clear up completely within a week. The most common signs and symptoms of traveler's diarrhea are:

- Abrupt onset of the passage of three or more loose stools a day
- An urgent need to defecate
- Abdominal cramps
- Nausea
- Vomiting
- Fever—occasionally

Traveler's diarrhea usually goes away on its own within a few days. But if there is:

- Persistent vomiting
- Bloody stools or severe diarrhea
- A fever of 102°F (39°C) or more or signs of dehydration
- Decreased volume of urine

Then one needs immediate attention and hospitalization. The most common cause of traveler's diarrhea is enterotoxigenic *Escherichia coli* (ETEC). High-risk destinations for traveler's diarrhea include many areas of Central and South America, Mexico, Africa, the Middle East, and most of Asia including India. It is generally low in Northern and Western Europe, Japan, Canada, Australia, New Zealand, and the United States. Certain groups of people have a greater risk of developing this condition.

These include young adults; people with weakened immune systems; people with diabetes, inflammatory bowel disease (IBD), or cirrhosis of the liver; and people who take acid blockers or antacids.

Prevention

Watch what you eat—the rule of thumb is to boil it, cook it, peel it, or forget it. Do not consume food from street vendors, avoid unpasteurized milk and dairy products, and avoid raw or undercooked food.

Drink boiled water when visiting high-risk countries, avoid unsterilized water, and avoid locally made ice cubes and sliced fruit. Keep your mouth closed while showering. Use bottled water to brush your teeth. Experts generally do not recommend taking antibiotics to prevent traveler's diarrhea; some suggest taking bismuth subsalicylate (Pepto-Bismol), which has been shown to decrease the likelihood of diarrhea. However, do not take this medication for >3 weeks.

Treatment

Avoiding dehydration: Dehydration is the most likely complication of traveler's diarrhea, so it is important to try to stay well hydrated. An ORS solution is the best way to replace lost fluids. Bottled oral rehydration products are available in drug stores; you can find packets of powdered ORS, labeled WHO-ORS, at stores, pharmacies, and health agencies. If these products are unavailable, you can prepare your own rehydrating solution.

Drugs

Antimotility agents include loperamide and diphenoxylate and bismuth subsalicylate (Pepto-Bismol). Antibiotics should be taken if you have more than four loose stools a day or severe symptoms.

PERSISTENT AND CHRONIC DIARRHEA

Diarrhea occurring for >14 days is considered as persistent diarrhea and diarrhea >30 days is considered as chronic. The emergency department (ED) may be the first point of contact for patients with chronic diarrhea and their initial management should take consideration of subsequent follow-up testing and initiate appropriate tests or therapies. In addition, patients with chronic diarrhea with systemic involvement require rapid diagnosis and aggressive resuscitation in the ED. Chronic diarrheas for consideration in ED patients are presented in **Table 3** with selected topics discussed in additional detail.

CLOSTRIDIUM DIFFICILE-INDUCED DIARRHEA

Clostridioides (formerly *Clostridium*) *difficile* infection (CDI) is one of the most common hospital-acquired (nosocomial) infections *C. difficile* colonizes the human intestinal tract after the normal gut flora has been disrupted

TABLE 3: Causes of persistent and chronic diarrhea.	
Surgical	Bowel ischemia, partial obstruction, fecal impaction, malabsorption due to resection or gastric bypass, malignancy
Endocrine	Chronic secretory diarrhea due to Addison disease, carcinoid tumors, Verner–Morrison syndrome, gastrinoma (Zollinger–Ellison syndrome), mastocytosis, hyperthyroidism
Bacterial	• *Tropheryma whipplei* (need treatment with systemic antimicrobials) • Tropical sprue (caused enteric bacteria; the combination of antibiotics and folic acid supplementation for 3–6 months) • Small intestine bacterial overgrowth (due to postoperative motility disorders or immune deficiency or reduced gastric acid secretion requires prolonged management)
Other	Irritable bowel syndrome, inflammatory bowel disease, food sensitivities, carbohydrate malabsorption, celiac disease, hepatobiliary or pancreatic disorder, diverticulitis, radiation colitis
Medications	Laxative use and abuse, antibiotics, antineoplastics, colchicine, nonsteroidal anti-inflammatory drugs, acarbose, and others

TABLE 4: Antimicrobial agents associated with *Clostridioides* (formerly Clostridium) *difficile* diarrhea and colitis.	
Frequently associated	• Fluoroquinolones • Clindamycin • Penicillin (broad-spectrum) • Cephalosporin
Occasionally associated	• Macrolides • Trimethoprim-sulfamethoxazole
Rarely associated	• Aminoglycosides • Tetracycline • Chloramphenicol • Metronidazole • Vancomycin

(frequently in association with antibiotic therapy) and is the causative organism of antibiotic-associated diarrhea and pseudomembranous colitis. Almost all antibiotics have the potential to cause diarrhea, but it is more often seen with clindamycin and cephalosporins (**Table 4**). Additional risk factors for CDI include age > 65 years, recent hospitalization, and use of proton-pump inhibitors. Watery diarrhea (≥3 loose stools in 24 hours) is the cardinal symptom of CDI. Other manifestations include lower abdominal pain and cramping, low-grade fever, nausea, and anorexia.

Diagnosis is by stool examination for toxins A and B and glutamate dehydrogenase (GDH) antigen. GDH is an essential enzyme produced constitutively by all *C. difficile* isolates; however, its detection cannot distinguish between toxigenic and nontoxigenic strains. Therefore, testing for GDH antigen is useful as an initial screening step in a multistep approach, which also consists of subsequent testing with more specific assays such as toxin A and B enzyme immunosorbent assay (EIA) or nucleic acid amplification test (NAAT) on specimens that are GDH antigen positive. GDH antigen testing has good sensitivity and results are available in <1 hour.

Most *C. difficile* strains produce both toxins A and B, although some strains produce toxin B only. No CDI due to strains producing toxin A alone has been reported. The sensitivity of EIA for toxins A and B is about 75%; the specificity is high (up to 99%). Lower GI endoscopy may show characteristic pseudomembranes but is not warranted in patients with classic clinical manifestations of *C. difficile* infection, a positive laboratory test, and/or clinical response to empiric treatment. In general, endoscopy may be pursued for circumstances in which an alternative diagnosis is suspected that requires direct visualization and/or biopsy of the bowel mucosa. It may also be helpful for patients with ileus or fulminant colitis in the absence of diarrhea since it may allow visualization of pseudomembranes (severe inflammation of the inner lining of the bowel) and collection of samples. However, an abdominal X-ray is a must before proceeding to colonoscopy to rule out toxic megacolon/perforation. The biopsy is not needed for the diagnosis of *C. difficile* but is sometimes done to rule out the alternative diagnosis.

Treatment

An important initial step in the treatment of CDI is the discontinuation of the inciting antibiotic agent(s) as soon as possible. Treatment with concomitant antibiotics (i.e., antibiotics other than those given to treat *C. difficile* infection) is associated with prolongation of diarrhea, increased likelihood of treatment failure, and increased risk of recurrent CDI. If ongoing antibiotics are essential for the treatment of the primary infection, if possible, it may be prudent to select antibiotic agents that are less frequently implicated in antibiotic-associated CDI (**Table 4**). Further treatment depends upon stratifying the patient as per the severity and follow the antibiotic protocol (**Table 5**).

TABLE 5: Antibiotic regimens for treatment of *Clostridioides difficile* infections in the adult.	
Nonsevere disease (white blood cells ≤15,000 cells/mL and creatinine <1.5 mg/dL)	• Vancomycin 125 mg orally four times daily for 10 days or fidaxomicin 200 mg orally twice daily for 10 days or if both drugs are not available • Metronidazole 500 mg orally thrice daily for 10 days
Severe disease (white blood cells ≥15,000 cells/mL and creatinine >1.5 mg/dL)	Vancomycin 125 mg orally four times daily for 10 days or fidaxomicin 200 mg orally twice daily for 10 days
Fulminant disease (hypotension or shock, ileus megacolon)	• Enteric vancomycin plus parenteral metronidazole • Vancomycin 500 mg orally via a nasogastric tube four times daily • Metronidazole 500 mg intravenously thrice daily for 10 days • If ileus presents, rectal vancomycin as retention enema every 6 hours (500 mg in 100-mL normal saline per rectally, retain as long as possible)

Nonsevere CDI: White blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL

Severe CDI: White blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL

Fulminant colitis (previously referred to as severe, complicated CDI): Hypotension or shock, ileus, or megacolon

For those who do not respond to standard medical management, options are FMT (fecal microbiota transplantation) or surgery. Factors that have been associated with poor prognosis in patients with CDI are:

- Hypotension
- Fever ≥38.5°C
- Ileus or significant abdominal distention
- Peritonitis or significant abdominal tenderness
- Altered mental status
- White blood cell count ≥20,000 cells/mL
- Serum lactate levels >2.2 mmol/L
- Admission to the intensive care unit
- End-organ failure (e.g., requiring mechanical ventilation, renal failure)
- Failure to improve after 3–5 days of maximal medical therapy

In all these situations, the surgeon should also be involved in management. In spite of good recovery, recurrences are common in CDI and require a methodical approach. For the first recurrence, tapered and pulsed vancomycin or fidaxomicin should be considered if the initial episode was treated with standard vancomycin. Alternatively, fidaxomicin or a standard 10-day course of vancomycin can be used for those previously treated with metronidazole. For the second recurrence, tigecycline or vancomycin followed by rifaximin, a standard course of fidaxomicin or FMT can be considered. To conclude, physicians should be aware of CDI; a high index of suspicion and a methodical approach are rewarding in most cases.

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease is an immune-mediated chronic intestinal condition where there is inflammation and ulceration of bowel and can have extraintestinal manifestations too. IBD majorly has two diseases: (1) Ulcerative colitis (UC) and (2) Crohn's disease (CD). They generally present with abdominal pain, diarrhea, or bleeding per rectum.

Ulcerative colitis should be suspected in any patient who presents with diarrhea with or without blood which has persisted for >2 weeks or even earlier if it has not subsided after adequate antibiotic use and stool examination shows increased fecal leukocytes. The presence of tenesmus and crampy lower abdominal pain followed by small-volume frequent stools are characteristic features. Stool examination shows pus cells and *red blood cells (*RBCs) and the same can be quantified by doing stool calprotectin or lactoferrin. Lower GI endoscopy with rectal biopsy is usually diagnostic. Though the disease process may involve variable extent of colon, the rectum is almost always involved; hence, in a sick patient, we may avoid doing a full-length colonoscopy and only sigmoidoscopy may be sufficient.

On the contrary, the diagnosis of CD is more complex and challenging. Symptoms will depend on the site of involvement which could be ileocolonic, jejunoileal, colonic, gastroduodenal, or perianal. The colonic disease presents such as UC while jejunal disease presents as malabsorption, gastroduodenal as vomiting, and postprandial pain. Hence, one has to keep a high index of suspicion, especially in patients with chronic symptoms. Fistula is common in CD as inflammation extends transmurally while it is rare in UC as it is a mucosal disease only.

The most important differential diagnoses of IBD are infective diarrheas, intestinal tuberculosis, malabsorption syndrome, eosinophilic enteritis, radiation enterocolitis, colonic malignancies, and irritable bowel syndrome (IBS).

Once a diagnosis of IBD is suspected, the clinically next step is to do an endoscopy to visualize a mucosal lesion. It could be colonoscopy/gastroduodenoscopy/enteroscopy or capsule endoscopy depending upon the suspected part of the bowel involved. Endoscopic biopsies must be taken as they show characteristic features though they may not be diagnostic. Serum markers such as anti-*Saccharomyces cerevisiae* antibodies (ASCA) and antineutrophil cytoplasmic antibodies (ANCA) are often done but rarely help to make a diagnosis. Stool tests are useful as fecal leukocytes confirm the inflammatory nature of colitis. Stool for calprotectin is useful in differentiating from noninflammatory causes of diarrhea, such as IBS, and also helps in the follow-up of a patient to avoid repeated sigmoidoscopies.

Treatment of IBD is complex. One can take a step-up approach starting with salicylates and adding steroids, immunosuppressants, and biologicals in that order or a step-down approach where you start with biological agents such as infliximab or adalimumab or steroids to achieve quick remission and then keep the patient on maintenance regimens. In UC, there is a good role of local preparations in the form of enemas or suppositories, especially for a limited-extent disease such as proctitis or proctosigmoiditis (**Table 6**).

Similarly, in CD, a stepwise approach is important and the need for surgical intervention is more than that in UC as CD is a structuring and fistulizing disease (**Flowcharts 1** and **2**).

The most important aspect of IBD is patient education and follow-up as this is a lifelong disease, and exacerbations and remissions are common. These patients also need surveillance for malignancy after a certain duration; hence, treating physicians and patients should be aware of it.

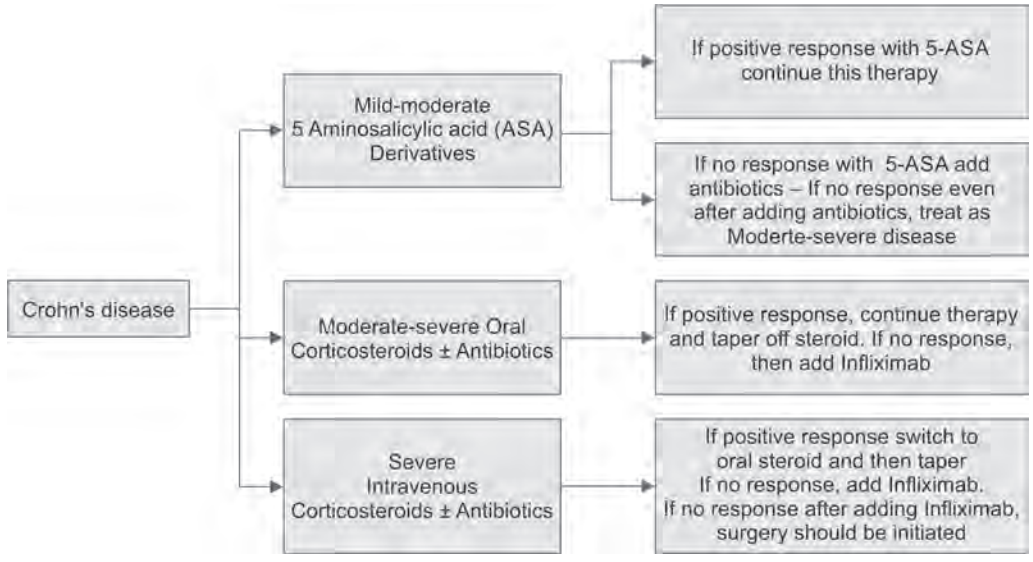
CELIAC DISEASE

Celiac disease may present as chronic diarrhea with weight loss, vitamin deficiency (iron, folic acid, B12, and fat-soluble vitamins) and steatorrhea, and the most common inflammatory disorder of the small intestine in the Western world. The inflammation results from an immune reaction against gluten that is present in wheat, barley, and rye and can be detected initially by tissue transglutaminase or endomysial antibodies and will ultimately require gastroenterologist referral for biopsy (the gold standard for diagnosis). Management focuses on a lifelong gluten-free diet.

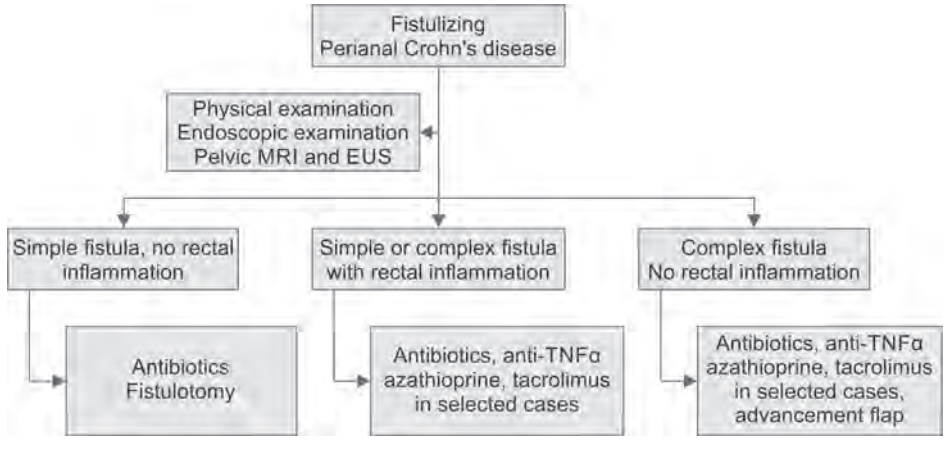
TABLE 6: Therapy for ulcerative colitis.

	Mild	*Moderate*	*Severe*	*Fulminant*
Active ulcerative colitis				
Distal disease	5-ASA oral and/or enema	5-ASA oral and/or enema, glucocorticoid enema, oral glucocorticoids	5-ASA oral and/or enema, glucocorticoid enema, oral/ IV glucocorticoids	Intravenous glucocorticoids and intravenous cyclosporine
Extensive disease	5-ASA oral and/or enema	5-ASA oral and/or enema, glucocorticoid enema, oral glucocorticoids	5-ASA oral and/or enema, glucocorticoid enema, oral/ IV glucocorticoids	Intravenous glucocorticoids and intravenous cyclosporine
Maintenance therapy ulcerative colitis				
Distal disease	5-ASA oral and/or enema 6-MP or azathioprine			
Extensive disease	5-ASA oral and/or enema 6-MP or azathioprine			

(ASA: aminosalicylic acid; IV: intravenous; MP: mercaptopurine)



FLOWCHART 1: Algorithm for Crohn's disease management.



(EUS: endoscopic ultrasound; MRI: magnetic resonance imaging; TNF: tumor necrosis factor)

FLOWCHART 2: Algorithm for managing fistulizing perianal Crohn's disease.

SUMMARY

Initial management of a diarrheal illness starts with a thorough history and examination, evaluation of dehydration, or risk for treatment failure. Valuable education and counseling should be provided for patients and caregivers regarding symptomatic care and the expected course of their illness. Antibiotics should be avoided in patients presenting with bloody diarrhea and no fever as they are associated with the hemolytic uremic syndrome. Public health authorities should be informed if the diarrheal illness is suspected from cholera, enterohemorrhagic *E. coli*, *listeria*, *Salmonella*, *Shigella*, or Norovirus. The emergency physician should focus on the evaluation of chronic diarrhea, its stabilization with further advanced testing, and coordination for ongoing care.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Gastrointestinal Bleeding

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INTRODUCTION

Acute gastrointestinal (GI) bleed is a serious life-threatening emergency which is a common cause of hospital admission, responsible for more than a million hospitalizations annually in the United States. The GI bleed can originate from the upper gastrointestinal (UGI) tract (50%), i.e., from the esophagus, stomach, and duodenum, or from the lower gastrointestinal (LGI) tract [from the colon and anorectum (40%) or small bowel (10%)].

Severe GI bleeding is defined as bleed associated with shock or syncope or decrease in hemoglobin level of at least 2 g/dL or requiring a minimum of two units packed red blood cells (PRBCs) transfusion.

Blood in vomiting is known as hematemesis, which signifies the source in the UGI tract proximal to the ligament of Treitz. Melena is defined as black tarry foul-smelling, sticky stools occurring due to degradation of blood in the intestinal lumen by bacteria; melena can occur due to bleeding originating from the esophagus, stomach, small intestine, or proximal colon. Hematochezia refers to fresh red bleed per rectally and it signifies active UGI bleed, distal large bowel, or anorectal bleed.

EPIDEMIOLOGY

There are approximately 300,000 patients admitted to hospitals across the United States due to GI bleed annually. The annual incidence of UGI bleed is about 40–150 cases per 100,000 with a mortality rate of 4–10% whereas the annual incidence of LGI bleed ranges from 20 to 25 cases per 100,000 population with a mortality rate of 4–10%. Men have more chances of having GI bleed as compared to women and advancing age is a risk factor.

CAUSES

The GI bleed is defined as bleeding in the GI tract from mouth to anus. It is further divided into UGI bleed (bleed that occurs from source in the esophagus to ligament of Treitz in the duodenum) and LGI bleed (bleed that occurs from source distal to the ligament of Treitz). The most common causes of UGI bleed are peptic ulcer, varices (esophageal or gastric), Mallory–Weiss tear, and neoplasms. Other common causes of UGI bleed include esophagitis, erosive gastritis, vascular malformations, and Dieulafoy's lesions. LGI bleed signifies bleed from the colon, rectum, or anus; common causes of LGI bleed are diverticular hemorrhage, neoplasm, colitis, ischemia, inflammatory bowel disease, infections, rectal ulcers, hemorrhoids, and vascular malformations. Diverticulosis is the most common cause accounting for almost 30% cases of LGI bleed followed by colonic polyps/cancer (18%) and colitis (17%). The causes of GI bleed are enumerated in **Table 1**.

TABLE 1: Causes of GI bleed.

Upper GI bleed	• Peptic ulcer disease • Variceal hemorrhage (esophageal or gastric) • Mallory–Weiss tear • Esophagitis • Cameron ulcer • Erosive gastritis/duodenitis • Neoplasms (esophageal/gastritis/duodenal) • Portal hypertensive gastropathy • Vascular malformations • Gastric antral vascular ectasia (GAVE) • Dieulafoy's lesion • Crohn's disease
Lower GI bleed	• Diverticular disease • Malignancy (colon and rectum) • Inflammatory bowel disease • Colitis (infective, radiation, ischemia) • Vascular malformation • Hemorrhoids • Anal fissure • Rectal varices

(GI: gastrointestinal)

INITIAL ASSESSMENT AND PROGNOSTICATION

Rapid evaluation and resuscitation should be done before the diagnostic evaluation in unstable patients with acute severe bleeding. The patient should be evaluated for the immediate risk of rebleeding, complications, and the cause of bleed after he/she is hemodynamically stabilized. Patients who are hemodynamically stable at the time of presentation with minor GI bleed can be evaluated in an outpatient setting. The Rockall score (**Table 2**) and Glasgow–Blatchford score (GBS; **Table 3**) have been developed and validated for stratification of the patients at the time of presentation as UGI bleed. While the Rockall score uses endoscopic findings, the GBS is based upon the patient's clinical presentation such as systolic blood pressure, pulse, presence of melena, syncope, hepatic disease, cardiac failure, and laboratory parameters such as blood urea nitrogen (BUN) and hemoglobin. A meta-analysis found that a GBS of 0 decreases the likelihood of requiring urgent intervention [likelihood ratio 0.02, 95% confidence interval (CI): 0–0.05]. Therefore, the GBS may be best suited for initial risk evaluation of suspected acute UGI bleeding such as in the emergency department setting.

Approximately 80% of GI bleed stop spontaneously and 15% of the patients continue to bleed requiring urgent intervention like endoscopy. Patients who present with continued bleed, history of syncope, hypotension, tachycardia, low urine output, hemoglobin level <8 g, and advanced age can be categorized as high-risk patients who require urgent intervention whereas patients of younger age, without any feature of hypovolemic shock, are low-risk patients. So, early categorization of patients in the emergency department is important for management planning.

The mortality associated with GI bleed is correlated with advanced age and presence of comorbidities. The cause of death is not mostly blood loss but rather an end-organ injury, blood transfusion-related complications, worsening of the underlying comorbidities, and nosocomial infections. According to a study of LGI bleed, advanced age, intestinal ischemia, and associated comorbidities were the strongest predictors of mortality. The severe GI bleed, defined as a presentation with features of shock and fall in the hematocrit level by 6%, is associated with a mortality rate of 20–39%.

HISTORY AND PHYSICAL EXAMINATION

The clinical history, physical examination, and initial laboratory findings are crucial in ascertaining the likely cause of bleeding, therefore helping us in deciding the appropriate definitive investigation and intervention. A history of consumption of any drug, especially nonsteroidal anti-inflammatory drugs

TABLE 3: Glasgow–Blatchford scoring system.

Admission risk marker	*Score value*
Blood urea (mmol/L)	
6.5–8.0	2
8.0–10.0	3
10.0–25	4
>25	6
Hemoglobin (g/dL) for men	
12–12.9	1
10–11.9	3
<10.0	6
Hemoglobin (g/dL) for women	
10.0–11.9	1
<10	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Other markers	
Pulse ≥ 100/min	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac disease	2
Patients with a score of >6 are at >50% risk of requiring some intervention to stop the bleed	

TABLE 2: Rockall score.

Variable	*Score 0*	*Score 1*	*Score 2*	*Score 3*
Age (years)	<60	60–79	>80	
Shock	No shock	Pulse >100/min Systolic BP >100 mm Hg	Systolic BP <100 mm Hg	
Comorbidities	Nil major		CHF/IHD, major comorbidity	Kidney/liver failure, metastatic cancer
Diagnosis	Mallory–Weiss tear	All other diagnoses	GI malignancy	
Evidence of bleeding	None		Blood, adherent clot, spurting vessel	
A Rockall score <3 carries a good prognosis whereas a total of >8 indicates a high risk of mortality				

(CHF: congestive heart failure; GI: gastrointestinal; IHD: ischemic heart disease)

(NSAIDs) or aspirin or anticoagulants, is very important, as these drugs are a very common cause of UGI bleed, particularly in elderly patients.

The degree of blood loss should be determined with functional assessment rather than the patient's reporting as mostly it is inaccurate. Patients presenting with features of hypovolemia, such as lightheadedness, dizziness, syncope, and marked weakness, have had a massive GI bleed. The bright red color of the bleed indicates recent massive or active GI bleed whereas patients having coffee-colored or black-colored blood indicate that bleed has stopped.

On physical examination, the presence of pallor, tachycardia, and hypotension (systolic BP <90 mm Hg) is suggestive of massive GI bleed. We must look for the stigma of chronic liver disease, such as jaundice, alopecia, gynecomastia, spider nevi, and ascites, during the physical examination as the presence of these features favors varices (esophageal or gastric) as the cause of bleed. A history of chronic alcohol abuse also favors variceal bleed.

LABORATORY INVESTIGATIONS

Laboratory reports are helpful in the stratification of the risk and also may be useful in determining the probable cause. Hemoglobin levels <10 g% at the time of admission are correlated with higher mortality. Coagulation profile, liver function tests, and platelet counts are helpful in the determination of cause and assessment of coagulopathy. Electrocardiogram and cardiac enzymes should be evaluated particularly in elderly patients as these patients may develop silent cardiac ischemia due to GI bleed. Initial serum lactate levels can be a predictor of the amount of blood loss or GI ischemia and the final outcome of the patient. In one of the studies by Shah et al., the mortality rate was 6.4 times higher in those patients who had lactate levels >4 mmol/L in the emergency department. There is a mild increase in BUN in patients with GI bleed due to renal hypoperfusion and absorption of digested blood from the GI tract. Derangement of kidney function tests is more common in patients with a massive GI bleed and in the elderly with a history of hypertension, diabetes, and coronary artery disease and is associated with poor outcomes.

TREATMENT

The emergent treatment of the patient presenting with GI bleed is very important. Initial rapid resuscitative measures should be promptly started in the emergency which includes putting two large-bore intravenous (IV) cannulas and fluid resuscitation. Blood samples should be collected for complete blood counts, liver and renal function tests, coagulation profile, and blood grouping/cross-matching. Patients with massive UGI bleed may need endotracheal intubation for airway protection.

Antibiotics

Every patient should be started with antibiotics to prevent sepsis caused by bacterial translocation from the gut, particularly in cirrhotic. The risk of rebleed is more in a patient who develops bacterial infections. Patients with liver cirrhosis presenting with acute UGI bleed have shown to have improve survival with short-term prophylactic antibiotics. A dose of 1-g IV ceftriaxone has been recommended for the prevention of serious bacterial infections in patients with GI bleed.

Packed Red Blood Cell Transfusion

Patients presenting with massive GI bleed should be given PRBC in the emergency department only as rapid blood loss can result in vital organ hypoperfusion leading to multiorgan dysfunction. In euvolemic patients with UGI hemorrhage, the PRBC transfusion should be planned to target a hemoglobin level of 7 g%. An overzealous PRBC transfusion should be avoided as it may increase the risk of rebleed and transfusion-related complications.

In patient with LGI bleed, the decision of PRBC transfusion should be individualized as no specific target hemoglobin level has been identified. Clinicians should assess the hemodynamic status and transfusion-related untoward reactions before planning for PRBC transfusion.

Nasogastric Tube Placement

There is a controversial role of nasogastric tube placement in all GI bleeds, which can be useful in UGI bleed. Bloody nasogastric aspirate confirms the source in the UGI tract. Nasogastric tube placement should be done in patients with suspected UGI bleed and gastric lavage should be done as it facilitates in clear view during the endoscopic procedure. The role of nasogastric tube placement in LGI bleed is not indicated. The sensitivity of nasogastric aspirate for UGI bleed ranges from 42 to 84% in a recent systemic review. However, the nonbloody nasogastric aspirate does not rule out the UGI source of the bleed.

Anticoagulation Reversal

For patients with acute GI bleed who are on anticoagulants, efforts should be made by emergency physicians to reverse the effect of anticoagulants. Patients on warfarin or dicoumarin (vitamin K antagonists) should be given IV vitamin K. Patients with elevated prothrombin time and international normalized ratio (INR) with acute GI bleed should be transfused with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP). For patients on newer direct oral anticoagulants such as dabigatran or rivaroxaban, the ideal strategy remains unclear due to the unavailability of the antagonist of these agents. Fluid resuscitation can increase the renal clearance of these drugs.

Proton-pump Inhibitor

An intravenous proton-pump inhibitor (PPI) is recommended in all patients presenting with acute UGI bleed. The emergency physician should consider IV PPI in all patients with UGI hemorrhage before the endoscopic therapy. In patients with ulcer-related UGI bleed, 80 mg IV pantoprazole/omeprazole in the emergency department followed by continuous infusion of 8 mg/h for at least 72 hours (preferably up to 5 days) reduces the risk of rebleed and need for surgery.

Somatostatin and its Analogs

Somatostatin and its long-acting analog, octreotide, cause selective splanchnic vasoconstriction, thus causing a reduction in portal pressure. These drugs reduce the chances of ongoing UGI bleed in both variceal and nonvariceal bleed. Somatostatin and its analog reduce the blood flow to the portal system by causing vasoconstriction, thus decreasing the variceal bleed.

The dose of somatostatin is 250 μg IV bolus followed by 250 μg/h continuous infusion for 3–5 days whereas the dose of octreotide is 50 μg IV bolus followed by 50 μg/h continuous infusion for 3–5 days.

Vasopressin Analog (Terlipressin)

Terlipressin causes vasoconstriction and therefore reduces portal blood flow and also increases the resistance to variceal blood. This drug is widely used and recommended for variceal bleed. Terlipressin also has the advantage of preserving renal function so it is particularly useful in patients with variceal bleed with renal dysfunction. The dose of terlipressin in variceal bleed is 1 mg IV every 6 hours for 5 days. Cardiac and bowel ischemia are potential side effects which can limit the use of this agent.

ENDOSCOPY THERAPY

Upper Gastrointestinal Endoscopy

In patients with UGI bleed, the endoscopy is both diagnostic and therapeutic as it helps in confirming the cause of the bleed and also enables us to take measures to stop the bleed. High-risk patients, such as those with hypotension, tachycardia, and fresh red nasogastric aspirate, have been shown to have mortality benefit with early endoscopy, i.e., within 12 hours of the presentation. In low-risk patients, the endoscopy can be done in a planned manner after stabilization. For varices-related bleed, endoscopic band ligation of varices, glue injection (for gastric varices), and endoscopic sclerotherapy can be performed to stop the bleed. For nonvariceal bleed (such as ulcer related, Mallory–Weiss tear, Cameron ulcer, esophagitis), injection therapy/hemoclip/argon plasma coagulation/hemospray, or combination therapy can be used to achieve hemostasis. It is recommended to use combination therapy over a single intervention to stop the bleed. Hematochezia may be an indicator of massive UGI bleed so it is reasonable to do upper endoscopy before colonoscopy. Every patient who presents with UGI bleed should undergo endoscopy unless the patient is very hemodynamically labile or we are able to get an informed consent for the procedure.

Colonoscopy

Urgent colonoscopy after rapid colonic purge has been shown to be safe and localizes the cause of bleed and also helps to perform therapeutic intervention to achieve hemostasis. As most of the bleeds stop spontaneously, the colonoscopy can be performed on a semielective basis after initial stabilization. Injection therapy can be done, in case of bleed ulcer, to stop the bleed. Glue injection is a recommended method in bleeding rectal varices. Polypectomy can be done if bleeding polyp has been identified. Diverticular hemorrhages are mostly self-limiting with conservative treatment.

Conventional Angiography

Angiography is particularly useful if endoscopy and colonoscopy fail to localize the site of the bleed. It can detect the site of bleed if the bleed rate is 0.5–1 mL/min and allows us to perform transcatheter embolization of the bleeding vessel, particularly in LGI bleed. The potential risks of angiography include acute kidney injury, contrast reaction, and bowel ischemia. Therefore, angiography is particularly useful in patients with massive ongoing GI bleed where endoscopy is not possible or colonoscopy failed to localize the site of bleed.

Nuclear Scan

Technetium (Tc) 99m-labeled RBC scan is noninvasive and sensitive but a less specific modality to detect GI bleeds as low as 0.1 mL/min. This scan itself is not therapeutic but an extremely useful guide to decide further course of action such as endotherapy, surgery, or angiography.

Obscure Gastrointestinal Bleed

Obscure GI bleed is defined as bleeding from the GI tract where no source is identified even after performing upper endoscopy and colonoscopy. Obscure GI bleed can be occult and overt. Occult GI bleed means where blood is not visible but suggested by persistent hemoglobin drop and positive fecal occult blood testing. Overt obscure GI bleed means bleed is visible in the form of melena or hematochezia, but the source is not identified. Obscure GI bleed constitutes almost 5% of all GI bleeds. The common causes of obscure GI bleed include angioectasia of the small bowel, NSAID-induced enteropathy, and inflammatory bowel disease, especially Crohn's disease. Other uncommon causes include tumors (leiomyoma, carcinoids, lymphoma, and adenocarcinoma), Meckel's diverticulum, Dieulafoy's lesion, or small bowel varices. It is recommended to repeat the upper endoscopy and colonoscopy before small bowel evaluation. The methods of small bowel evaluation include double-balloon enteroscopy, *computed tomography* (CT) enterography/angiography, video capsule endoscopy, and nuclear scan which have different success rates in identifying the source of the bleed.

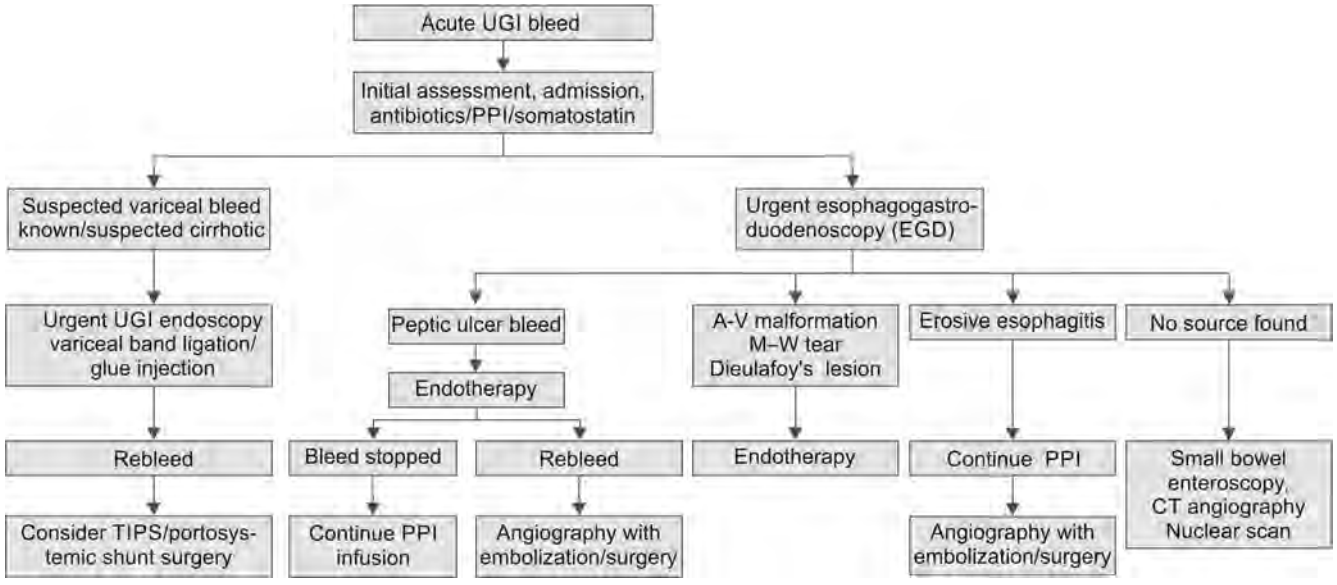
Surgery for Gastrointestinal Bleed

Indications for surgical intervention include intractable GI bleed where endoscopic and other resuscitative measures failed to stop the bleed. In portal hypertension-related UGI bleed, portosystemic shunt surgery can be lifesaving if medical, endoscopic and radiological interventions and transjugular intrahepatic portosystemic shunt (TIPS) have failed to control the bleed. Surgical interventions are more commonly needed in the case of LGI bleeds as compared to UGI bleeds. Causes of GI bleed requiring surgery include diverticular hemorrhage, neoplasia, mesenteric ischemia, anorectal disease (hemorrhoids), and angiodysplasia. Surgical interventions are seldom required to control the GI bleed due to advancements in endoscopy and intervention radiology.

SUMMARY

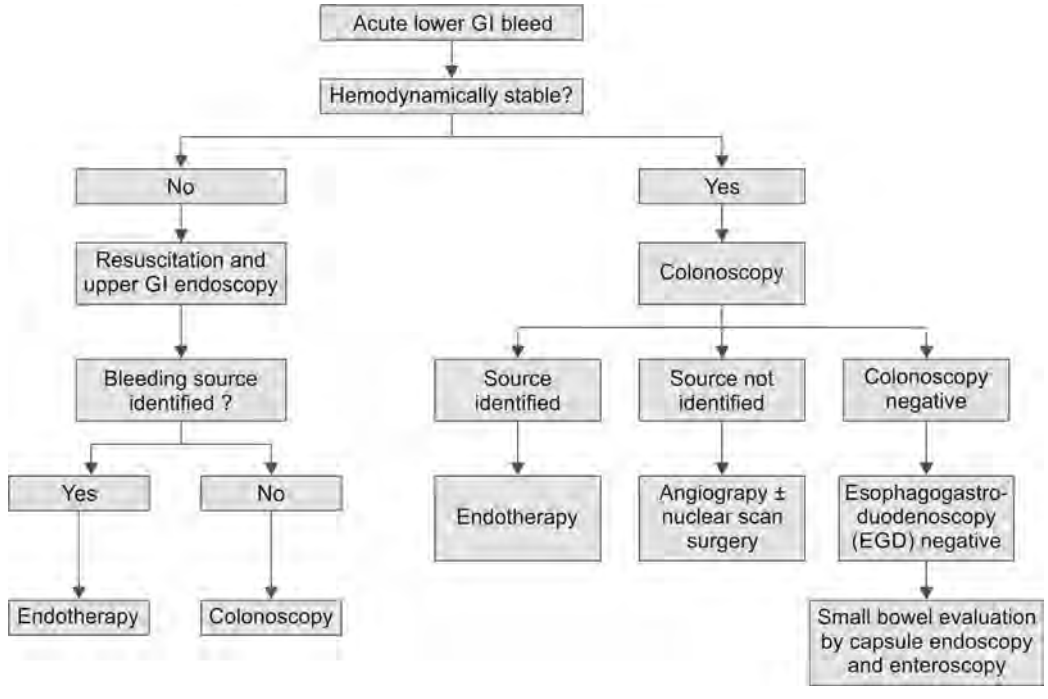
The acute GI hemorrhage is a serious emergency accounting for approximately 300,000 admissions in the United States and mortality ranging from 4 to 10%. UGI bleed is relatively common as compared to LGI bleed. The most common causes of UGI bleed include peptic ulcer, varices, esophagitis, and Mallory–Weiss tear whereas diverticulosis, neoplasm, anorectal diseases, and colitis account for the majority of cases

of LGI bleed. With the advancements of radiology, nuclear medicine, and endoscopic procedures, most GI bleeds can be localized and managed conservatively. In approximately 5% of the patients with GI bleed, the source is not identified on routine UGI and LGI endoscopies; these are called obscure GI bleed. Patients with obscure GI bleed require meticulous evaluation with CT enterography/angiography, double-balloon enteroscopy, and nuclear scan to localize the source of the bleed. The approaches to the treatment of UGI and LGI bleed are summarized in **Flowcharts 1** and **2**, respectively.



(A-W: arteriovenous; CT: computed tomography; M–W: Mallory–Weiss; PPI: proton-pump inhibitor; TIPS: transjugular intrahepatic portosystemic shunt; UGI: upper gastrointestinal)

FLOWCHART 1: Summary of management of upper GI bleed.



(GI: gastrointestinal)

FLOWCHART 2: Algorithm for management of acute lower GI bleeding.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Esophageal Emergencies

Purushottam Vashistha

INTRODUCTION

The esophagus is a hollow tube-like structure which acts as a conduit for the passage of food from mouth to stomach. This is about 18–26 cm in length and usually collapsed but stretches to 3 cm laterally and 2 cm anteroposterior during swallowing. The esophageal wall consists of four layers and is devoid of serosa, the outermost layer. There are four physiological constriction areas where a large food bolus or foreign body can be held up and gives rise to clinical dysphagia. There are few situations which can force a patient to seek medical help in emergency hours. These situations are as follows:

- Atypical chest pain
- Acute dysphagia
- Esophageal foreign bodies
- Caustic injury
- Esophageal perforation

ATYPICAL CHEST PAIN

Chest pain is the usual presentation to the emergency room at odd hours. Atypical chest pain means when a person presents with complaints of chest pain and does not fit into the pain of cardiac origin. A classic angina needs the following three criteria: (1) Substernal pain or discomfort which aggravates by exertion or emotional stress and is relieved by rest or nitroglycerine (NTG), (2) Atypical chest pain means the person is having only two criteria and here we need to examine and look for chest pain of esophageal origin, (3) It may be difficult to differentiate a cardiac pain from an esophageal one because the heart and esophagus are in the same vicinity and also share innervation. Also, esophageal pain is the second most common cause of chest pain. In one of the studies, it was found that 30% of coronary angiography have a normal study; of these, esophageal pain contributes to about 18–56%.

Evaluation and Management of Atypical Chest Pain

Esophageal pain is usually substernal discomfort which can be burning or squeezing sensation which radiates to the back, neck, and jaw or arms. Sometimes, patients can have perspiration and mimic classic angina too. It can be aggravated by food or stress and may awaken the patient from sleep. It can last for minutes to hours and may come intermittently. It usually disappears on its own or to a proton-pump inhibitor (PPI) or other antacids, but sometimes it may be severe and need the help of NTG or narcotics. Most of these patients also have some history of other dyspeptic symptoms.

Is history reliable enough to differentiate classic angina from esophageal chest pain and the answer is no. Exercise also aggravates reflux which can cause chest pain. Moreover, >50% of patients suffering from cardiac pain also have esophageal symptoms. Furthermore, sublingual NTG relieves both kinds of pain. Another factor is that both diseases may coexist in a patient and interact with each other.

Any patient who comes to the emergency room with chest pain must be evaluated for the cardiac cause. Appropriate tests to rule out cardiac disease in the emergency room are noninvasive cardiac tests and cardiac markers such as troponin T, troponin I, and creatine phosphokinase-myocardial band (CPK-MB) along with ECG and 2D echo. One entity that is difficult to diagnose in the emergency room is microvascular angina (insufficiency of coronary blood flow with normal-appearing coronary arteries).

Once we rule out cardiac disease, the institution of PPI and relief of pain usually indicate pain of esophageal origin. Esophageal pain usually originates due to gastroesophageal reflux disease (GERD), motility disorders, and enhanced visceral sensitivity of esophageal mucosa. Antidepressants or anxiolytics are needed in some patients who have increased sensitivity to esophageal mucosa.

Later on, these patients can be evaluated as outpatient by upper endoscopy, 24-hour pH metry, impedance pH metry, and manometry to establish the diagnosis of GERD, refractory GERD, alkali reflux, or motility disorders of esophagus such as hypercontractile (jackhammer) esophagus, nutcracker esophagus, distal esophageal spasm, and hypertensive lower esophageal sphincter (LES).

ACUTE DYSPHAGIA OR ODYNOPHAGIA

Dysphagia means difficulty in swallowing food. Patients usually complain of sticking sensation or holding food in

chest or throat or say that food is not going down and may complain of even swallowing their saliva along with pain while swallowing. Dysphagia is a common symptom that is present in 12% of patients admitted to an acute care hospital and in >50% of those in a chronic care facility. Dysphagia is usually of two kinds: (1) Oropharyngeal; and (2) Esophageal.

Oropharyngeal dysphagia means inability to propel a food bolus successfully from the hypopharynx to the upper esophagus across the upper esophageal sphincter. This happens usually immediately or within 1 second of swallowing. Patients normally describe choking or aspiration or nasal regurgitation upon eating food. They might have dysarthria, nasal speech, and hoarseness of speech. Most patients with esophageal dysphagia localize their symptoms to the lower esophagus but may sometimes locate to a suprasternal notch despite having a lower esophageal lesion. Esophageal dysphagia is usually relieved by repeated swallowing attempts, raising the arms overhead or Valsalva maneuvers.

The most common reasons for a patient to come to the emergency room with acute dysphagia or odynophagia are foreign body ingestion, caustic ingestion, pill injury, peptic stricture, esophageal candidiasis, esophagitis due to cytomegalovirus (CMV), Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), herpes or Koch's (tubercular) etiology, especially in immunocompromised patients, esophageal rings or web, eosinophilic esophagitis (poorly distensible lumen) or radiation esophagitis (poorly distensible lumen) and extrinsic compression of the esophageal lumen by vascular structures, osteophytes or cervical implant, and mediastinal mass.

To identify esophageal dysphagia, we need to get some information. Which kind of solid food or liquid is causing dysphagia? Whether it is progressive or intermittent? Is there any history of recurrent heartburn? Difficulty in swallowing solid food indicates mechanical obstruction. Benign peptic or malignant strictures, achalasia, and scleroderma have progressive dysphagia unlike Schatzki ring or other motility disorders. How to approach a dysphagia patient usually depends on proper history, site, severity of symptoms, and etiology of disease. We can use an X-ray of neck or chest, barium or contrast study, computed tomography (CT) scan of neck or chest, endoscopic evaluation, and manometry according to their clinical diagnosis.

PILL INJURY

Medication-induced injuries are common but underdiagnosed conditions which can present to the emergency department as severe chest pain which aggravates on inspiration, associated with acute dysphagia, or odynophagia, or heartburn. Some of the medicines which can produce mediastinitis or esophageal perforation or bronchopleural fistula are potassium chloride (KCl), quinine, nonsteroidal anti-inflammatory drug (NSAID), and bisphosphonates.

Pill injury is usually caused by direct injury to the esophageal mucosa by the production of acidic or alkali solution or may produce a hypertonic environment and direct toxicity to the esophageal mucosa. Most of the time, patients have underlying motility or anatomic disorders along with a history of medications taken just before sleep with a small amount of water. The severity of injury depends on the duration of exposure of medication to the esophageal mucosa and the type of pill.

The most common medications which give rise to pill injury are: Tetracycline, doxycycline, clindamycin, antiretroviral drugs, bisphosphonates, NSAID, iron tablets, quinidine, KCl, and even a PPI like lansoprazole, along with certain chemotherapeutic agents.

Endoscopy is the best test to diagnose pill injury. We can find variable findings from discrete ulcers to diffuse esophagitis or pseudomembrane mimicking candidiasis by Kayexalate or bisphosphonates or tumor-like mass.

ESOPHAGEAL FOREIGN BODY

Gastrointestinal (GI) foreign bodies are composed of food boluses or ingested foreign objects. Children from the age of 6 months to 3 years are most commonly affected by it and make almost 80% of true foreign body ingestions. Coins, marbles, pins, crayons, and disc batteries are some objects commonly ingested by children. In adults, the commonly ingested objects are dentures, coins, nails, pins, food boluses, and iatrogenic bodies. Food bolus impaction (fishbone) is the most common foreign body which needs urgent attention. Most of these patients have some underlying predisposing factors such as esophageal rings, web, strictures, eosinophilic esophagitis, prior operation on esophagus such as fundoplication or esophagectomy, or bariatric surgery. Most of these patients are in their fourth to fifth decade of life.

Normally, 80% of GI foreign body passes through the GI tract without any issue but 20% need endoscopic intervention and about 1% need surgical operation. Most of the GI foreign body is trapped in the hypopharynx but once it passes into the esophagus it can lodge at four areas of physiological constrictions: (1) Upper esophageal sphincters, (2) aortic arch, (3) mainstem bronchus, and (4) LES. One important thing to notice here is that the longer the foreign body stays in the esophagus, the chances of having complications are more; these complications are perforation, abscess, mediastinitis, pneumothorax, fistula, or cardiac tamponade.

Evaluation and Management

We need proper history, wherever we can get, from the patients although 20–30% of patients are asymptomatic. The presence of acute dysphagia, dysphonia, odynophagia, drooling of saliva, retrosternal pain, and chest pain suggests that a foreign body is present in the esophagus or hypopharynx. The localization of foreign body is not appropriate according to symptoms and it correlates only with 30–40% if the esophagus is the site of impaction. Various tests that can be done to detect a foreign body are X-ray of neck and chest and anteroposterior and lateral views, especially if a foreign body is known and radiopaque. For nonradiopaque objects, an X-ray does not help and a CT scan or magnetic resonance imaging (MRI) can help in such cases. Moreover, a CT scan can detect complications such as perforation, abscess, or pneumomediastinum. Contrast studies, such as barium and other contrast studies, are avoided due to the risk of aspiration and later on due to interference in endoscopic interventions.

Endoscopy is the most important tool to diagnose the object irrespective of its radio-opaqueness. It helps in diagnosis along with inspection of the esophagus for any predisposing factors or damage of the esophagus by objects and simultaneously offering treatment to such cases.

Endoscopic extraction success rates range from 90 to 100% with most series reporting success rates of >95%. Treatment offered should be dependent on the location, size, type, and duration of the object in the esophagus. Medical treatment in terms of muscle relaxants [most commonly intravenous (IV) glucagon 0.5–2-mg bolus] is used to relax the LES by 60% and succeed in almost 15–55% of cases. Carbonated beverages, nifedipine, and NTG are not recommended due to the risk of aspiration and hypotension. Generally, all esophageal foreign bodies need urgent attention and intervention. As a rule, no object should be lodged in the esophagus for >24 hours.

Flexible upper endoscopy is the preferred treatment of choice for esophageal foreign bodies. All foreign bodies should be removed within 6–12 hours except button battery or any sharp or long or large blunt objects in the esophagus which need immediate attention due to fear of pressure necrosis followed by perforation and fistula formation. There are different equipment for removal of foreign bodies in the esophagus, such as overtube, retrieval net, grasping forceps, Dormia basket, snare, vacuumed cap, or latex protector hood. Sedation in the endoscopic procedure is usually chosen by seeing the type and number of objects. Conscious sedation is usually adequate, but intubation is also needed in the case of children.

CAUSTIC INJURY TO ESOPHAGUS

Caustic ingestion causes progressive and devastating injury to the esophagus where the patient can survive an acute injury, but the reparative process might result in esophageal stenosis and increased chances of esophageal cancer. Most of the caustic injuries happen as accidental ingestion in children who are <6 years old and in adults as suicidal attempts in a person having a known or unknown mental health issue. The seriousness of injury is more in adults due to ingestion of a large amount of caustic agents.

Caustic agents are of two types: (1) Acidic or (2) alkali. Both kinds of agents are being used as household cleaning agents and for other uses. The main difference between acidic and alkali agents is that alkaline agents cause liquefaction necrosis which produces transmural necrosis contrary to coagulative necrosis by acidic agents. Moreover, they affect the esophagus more than the stomach due to neutralization by gastric acid in the stomach.

Evaluation and Management of Caustic Injury

The patient usually presents with different symptoms which might be dysphagia, odynophagia, oropharyngeal pain, chest pain, epigastric pain, drooling of saliva, hoarseness of voice, and dyspnea. One thing to remember is that the symptoms and signs of patients often do not correlate with the amount of ingestion. Plain X-ray of chest does not give much information but can guide about the presence of pneumomediastinum and pneumothorax. Usually, a CT scan of chest is done to rule out any perforation but can be avoided if there is no strong suspicion. Upper endoscopy is the modality of choice to diagnose, grade, guide the treatment, and prognosticate the injury. It should be done within 48–72 hours of ingestion. Almost 50% of a patient's symptoms do not correlate with endoscopic findings. Endoscopic injury is classified as given in **Table 1**.

TABLE 1: Endoscopic grading of injuries.

Grade	*Injuries*
Grade I	Edema and erythema
Grade IIA	Hemorrhages, erosions, blisters, ulcers with exudates
Grade IIB	Circumferential ulcerations
Grade III	Multiple deep ulcers with brown, black, or gray discoloration
Grade IV	Perforation

Treatment

Resuscitation: Airway, breathing, circulation. No gastric lavage should be done to such patients; no nasogastric tube or induced emesis should be tried in such circumstances. Neutralization is recommended by so many manufacturers and it should not be done with any other agents in the absence of controlled studies. Steroid and antibiotics should not be used until perforation is present where antibiotics should be given to prevent mediastinitis. Grade I or IIA patients are usually stable patients and can be managed in wards after endoscopic evaluation. Patients are given oral feed and can be discharged also within 24–48 hours. Grade IIB and more severe injury should be admitted in an intensive care unit to monitor for any early complications such as perforation and resultant mediastinitis. Documented perforation or having a strong suspicion of perforation in a patient is a contraindication for upper endoscopy. Emergency surgery is the best modality for documented perforation depending on the availability of highly skilled services in the hospital despite evidence of having high mortality prediction in emergency surgery. The patients who have deep necrosis and extensive damage are usually managed conservatively, although opinion differs in approaching such patients about the timing of surgery. Usually, 30% of patients develop fibrosis and strictures within 2–12 weeks of injury. The more severe the injury, the more the chances of developing strictures in such patients. Esophageal strictures are managed with repeated endoscopic dilatation. Endoscopic dilatations are done with the rule of 3 which means incremental gradual dilatation from the start point to avoid a perforation (0.5% perforation rate). Some institutions believe in early stent placement or early dilatation to avoid having strictures in the future, but results are inconsistent. Surgical interventions have very good results in dealing with refractory esophageal strictures. Colonic interposition is required in some patients with extensive injury. Intralesional injection of steroid is also effective in some patients with refractory strictures.

ESOPHAGEAL INJURY AND PERFORATIONS

Traumatic injury to the esophagus is common during motor accidents and other accidents. Besides motor accidents, gunshots, knife injury and fall are other common reasons. Cervical esophagus is involved more than the thoracic or distal esophagus. Cervical esophageal perforation can be diagnosed by the presence of extramural air on a plain X-ray of the neck and can be confirmed with a CT scan of neck and chest and

contrast (gastrografin) studies. Cervical esophageal injuries are associated with injuries of nearby organs too and hence there are different opinions for the management of such injuries. Some studies favor managing them conservatively and some favor aggressive management due to fear of developing sepsis and tissue dehiscence and later on the need of two-step closure if timed surgery is not done.

Upper endoscopy is the choice of investigation to identify the lesion and plan further course of action if a distal esophageal injury is being suspected since these cases are difficult to manage because these injuries may extend to the mediastinum and change the spectrum of management. These injuries are not suitable for primary simple closure due to aberrant esophageal blood supply and the development of ischemia and leakage later on. Therefore, esophagectomy and anastomosis are the choices of surgery. It is difficult to decide to operate or not in most of the cases, but surgery is the better choice and should be done within 12 hours of injury.

MALLORY–WEISS SYNDROME

In this condition, there are lacerations which usually extend from the gastroesophageal junction to the proximal stomach up to 2 cm from the gastroesophageal junction, although 20% can occur in the esophageal mucosa. This occurs due to forceful vomiting or any bodily action which increases the intra-abdominal pressure and resultant shearing force on this region as it herniates through the diaphragm. Most of the patients also have hiatus hernia. Patients usually have a history of forceful coughing, retching, binge alcohol and aspirin use, or recently done procedures such as endoscopy or transesophageal echocardiography. Mostly, these patients have a history of forceful vomiting (70%) followed by hematemesis. Bleeding is usually self-limiting but can be massive in 10% of cases. Endoscopy not only establishes the diagnosis but also finds some associated lesions in 30% of cases and simultaneously gives options of endotherapy such as injection of diluted adrenalin or clip application or band ligation. For endoscopic therapy failure patients, angioembolization is the choice of therapy. Surgical treatment is very rarely needed for such patients.

BOERHAAVE'S SYNDROME

It is the most extreme form of esophageal tear that occurs due to an increase in intragastric pressure. There is a tear along with perforation at the margin of contact between the clasp and oblique fibers of the esophageal muscle layer. This syndrome differs from the Mallory–Weiss syndrome in that this can present with severe pain in the chest or upper abdomen along with severe sepsis or shock and can mimic pulmonary embolism, acute myocardial infarction, pancreatitis, and aortic aneurysm rupture. The history of such patients is forceful vomiting. All predisposing factors and conditions similar to the Mallory–Weiss tear are important factors and aggravate the severity of tear in this syndrome. On clinical examination, patients usually have subcutaneous emphysema and pneumomediastinum and pleural effusion on imaging. Treatment is mainly primary surgery, but conservative treatment with esophageal stent (self-expanding) and simultaneous chest drain is also an option in some patients where surgery is not feasible.

SUMMARY

Esophageal disease is frequent presentation in the ED and often presents with mild form with a variety of symptoms that can mimic cardiovascular and respiratory disorders. Thus, diagnosis of esophageal disorders is frequently delayed. Laboratory testing and imaging are often helpful only in critically ill patients, and emergency physicians should focus on the history to differentiate esophageal disorders from cardiorespiratory disease and to guide management. Whereas unstable patients require aggressive measures and a multidisciplinary approach, ED treatment of stable patients is often limited to alleviation of symptoms. All patients should be referred for definitive evaluation and treatment.

MULTIPLE CHOICE QUESTIONS

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96 CHAPTER

Dyspepsia and Peptic Ulcer Disease

Ravindra Kale

INTRODUCTION

Dyspepsia is a feeling of upper abdominal pain or vague discomfort which encompasses postprandial fullness, early satiety, burning, nausea, and bloating in the upper abdomen, i.e., symptoms that presumably arise from stomach and duodenum. Heartburn is usually associated with these symptoms, but it is considered to be a symptom of gastroesophageal reflux disease (GERD) and not of dyspepsia.

ETIOLOGY

Dyspepsia most commonly results from peptic ulcer disease, gastritis, and reflux disease, but there are myriads of other causes which may lead to dyspeptic symptoms. Cardiac and pancreatobiliary conditions are particularly important to be differentiated for emergency management.

Peptic ulcer is responsible for 5–10% cases of dyspepsia. These ulcers occur due to acid and pepsin-related mucosal damage in gastroduodenal mucosa. The usual risk factors are *Helicobacter pylori* infection and frequent use of analgesics [nonsteroidal anti-inflammatory drug (NSAID)], particularly in elderly. Alcohol use and smoking are other risk factors. Most of the ulcers are asymptomatic and may directly present with complications. Complications can occur, especially in the elderly, with concomitant aspirin use in cardiac patients or NSAID use in patients with arthritis as they may bleed or perforate. Chronic ulcers may cause stricture and gastric outlet obstruction. Rarely gastroduodenal ulcers occur due to tuberculosis, ischemia, Crohn's disease, and cytomegalovirus (CMV) infection.

Reflux esophagitis is another important cause of dyspepsia in 20% of patients and an equal number of patients with reflux symptoms may not have endoscopic signs of reflux disease (nonerosive reflux disease). Gastric malignancy also causes dyspeptic symptoms. Risk increased with long-standing *H. pylori* infection. Gastroparesis usually due to diabetes is associated with postprandial fullness, nausea, and vomiting.

Medications are another important cause of dyspepsia. NSAID, theophylline, oral iron, potassium chloride, and antimalarials (chloroquine and quinine) frequently cause dyspepsia through direct mucosal injury, reflux, or idiosyncratic mechanisms.

Chronic pancreatitis and pancreatic malignancy may mimic symptoms of dyspepsia but usually have more severe pain, characteristic radiation, and weight loss. Presence of gall stones alone does not cause dyspepsia and other causes should be evaluated. Patients with hyperthyroidism, acute coronary syndrome, renal failure, and chronic obstructive pulmonary disease (COPD) can also have dyspepsia-like symptoms.

Functional dyspepsia is absence of any obvious cause for dyspepsia. The Rome criteria for functional gastrointestinal (GI) disorders (Rome IV) define functional dyspepsia as one or more of the following symptoms in the last 3 months: Bothersome symptoms of (1) postprandial fullness, (2) epigastric pain, (3) early satiety, and (4) epigastric burning, with onset at least 6 months prior to diagnosis. These symptoms should be present in the absence of a significant structural disease (including normal endoscopy) that can explain symptoms. Functional dyspepsia can be further classified as postprandial distress syndrome (PDS) which includes fullness and early satiety and epigastric pain syndrome (EPS) which includes epigastric pain and burning.

PATHOPHYSIOLOGY

There are several proposed mechanisms for dyspepsia. Abnormally enhanced perception of visceral stimuli (visceral hypersensitivity), impaired gastric relaxation to meals, and delayed gastric emptying can be responsible. *H. pylori* infection can be a cause of functional dyspepsia and eradication may improve symptoms. First-degree relatives of patients have increased frequency of dyspepsia suggestive of genetic predisposition.

CLINICAL PRESENTATION

The usual presentation is of chronic upper abdominal discomfort with epigastric pain or burning and fullness after meals, nausea, and vomiting. Food may worsen pain in peptic ulcer disease. Patients with duodenal ulcers usually have pain 2–3 hours after meals or nocturnal pain. Pain due to perforation is acute onset and soon becomes generalized. Most of the patients are well nourished and may be obese.

Some patients are on prolonged NSAID therapy. Presence of anemia and/or weight loss indicates serious disorders such as gastroesophageal or pancreatic malignancy or complicated peptic ulcer with bleeding or stricture. A patient with gastric outlet obstruction presents with vomiting of stale food and a moving lump in the upper abdomen. Patients with acute-onset epigastric pain and dyspnea, especially on exertion and improvement after rest, should be evaluated for cardiac disease. *Red flags*: Old age, significant weight loss, long-term aspirin and NSAID use, GI bleeding, anemia, persistent vomiting, and dysphagia.

EVALUATION

History

All patients should be evaluated with a detailed history of dietary habits and medications including complementary and alternative medicines. History of dyspnea on exertion and fatigue may suggest cardiac disease or anemia due to blood loss. History of melena and hematemesis points toward peptic ulcer disease. Dysphagia may be due to peptic stricture or malignancy. History of psychiatric disorders and past physical or sexual abuse may be relevant in those with refractory symptoms. History of diabetes and other endocrine disorders in the patient/family should be enquired for. Diabetic patients can have gastroparesis and drug- (metformin, acarbose) induced dyspepsia. Improper use of abdominal exercise techniques such as "*kapalbhati*" (a yogic breathing exercise) may be responsible for the aggravation of dyspepsia in some (personal experience).

Physical Examination

A detailed physical examination is to be done. Presence of anemia, lymphadenopathy, abdominal lump, or ascites requires further evaluation. Succussion splash in epigastrium in a fasting patient suggests gastric outlet obstruction or gastroparesis. Per rectal examination may show presence of blood in stools and rectal shelf deposits.

Investigations

A young, otherwise normal patient on examination need not undergo any further evaluation. Age >50 years old, family history of malignancy, history of NSAID use, and presence of alarm features such as GI bleed, anemia, dysphagia, and weight loss warrant further workup.

Initial workup consists of complete blood counts, creatinine, thyroid-stimulating hormone (TSH), blood sugar, electrolytes, calcium, liver function tests, and ultrasound of the abdomen. Upper GI endoscopy is very useful and needs to be done to look for mucosal lesions. Gastric biopsy from antral region and rapid urease test for *H. pylori* can be done. At the same time, bleeding lesions can be endoscopically treated and stricture dilatation can be done. Barium examination and serology for *H. pylori* can be done wherever access to endoscopy is not available. Endoscopy is superior to barium studies in detecting mucosal lesions. Also, biopsy from gastric ulcer (to rule out malignancy), antral biopsy (for a rapid urease test for *H. pylori*), and therapy of bleeding lesions can be performed during endoscopy. Duodenal ulcers rarely need biopsy as they are nonmalignant.

Stool test for ova, parasites, and occult blood is to be done. Contrast-enhanced computed tomography (CECT) of abdomen and manometry (esophageal and antroduodenal) are required in specific circumstances.

Differential Diagnosis

Conditions such as gastritis, pancreatitis, GERD, cholecystitis, stomach cancer, biliary colic, myocardial infarction (inferior), and referred pain should be differentiated from peptic ulcer disease.

TREATMENT

The clinical decision to initial treatment depends on age and presence of risk factors. Young patients without any alarm features can be directly given empirical therapy with acid antisecretory medication: Histamine 2-receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs). PPIs are the mainstay of treatment for ulcers. They act on H^+K^+ATPase on parietal cells and thus reduce acid secretion. It takes 5 days to get maximal effect while H2RA has more rapid onset of action. Both are efficient in relieving symptoms in 33–50% of patients with dyspepsia, particularly in those with predominant reflux-like symptoms. The usual doses are ranitidine 150 mg BD, omeprazole 10–20 mg/day, rabeprazole 20–40 mg/day, and lansoprazole 15–30 mg/day. Lafutidine is a second-generation H2RA with additional gastroprotective ability independent of antisecretory action. It activates capsaicin-sensitive afferent neurons and stimulates calcitonin gene-related peptide (CGRP) which inhibits acid secretion and stimulates mucosal blood flow. The therapeutic benefits of H2RA and PPI in familial dysautonomia (FD) seem independent of antisecretory action.

Dietary modification and lifestyle changes should be advised in every patient. These include eating small meals and avoiding high-fat diet. The patient should be told to avoid tea, coffee, NSAID, alcohol, and tobacco use.

Helicobacter pylori eradication can improve dyspepsia in few patients. Test and treat infection can be a strategy in those not responding to PPI. Those responding will have long-term sustained remission. Usually, a triple-drug regimen with one PPI and two antimicrobials—amoxicillin (1 g BD) and clarithromycin (500 mg BD) or metronidazole (500 mg BD)—for 14 days is given. Quadruple therapy with PPI, tetracycline, metronidazole, and bismuth is now recommended due to widespread antibiotic resistance.

Prokinetic agents stimulate GI motility and hence may be helpful in functional dyspepsia. Metoclopramide, levosulpiride, and domperidone are dopamine receptor antagonists. Domperidone does not cross the blood–brain barrier and is devoid of serious side effects. Levosulpiride additionally acts as a 5-HT_4 receptor agonist and is superior to the other two in improving gastric emptying and alleviating dyspepsia. However, these drugs have a lot of adverse effects including extrapyramidal symptoms and galactorrhea. Mosapride is a 5-HT_4 agonist and 5-HT_3 receptor antagonist and itopride is a dopamine D_2 antagonist and acetylcholinesterase inhibitor. Acotiamide is a new prokinetic and fundus-relaxing drug with muscarinic antagonist and cholinesterase inhibitor action and improves gastric emptying. In doses of 100 mg thrice daily, it improves postprandial fullness, bloating, and early satiety. It

is now approved for managing functional dyspepsia. It is not effective in EPS. Drugs such as erythromycin which have a pure prokinetic effect without an antiemetic effect are not found useful.

Antidepressants, especially tricyclic antidepressants, have some beneficial effects in functional dyspepsia (EPS) even in the absence of depression and can be added to PPI in nonresponders. Anxiolytic agent buspirone, a 5-HT_{1A} agonist, was superior to placebo in improving dyspeptic symptoms. It enhances gastric accommodation by fundic relaxation.

Psychological interventions such as cognitive therapy, hypnotherapy, and relaxation techniques may be useful in refractory patients. Meditation and yoga can also help. Referral to a psychiatrist can be considered in those with associated severe psychiatric symptoms.

Rikkunshito, a Japanese herbal medicine, has shown better response than placebo for treatment of FD. Another herbal preparation Iberogast (STW5), extract from the *Iberis amara* plant, has fundus-relaxing properties and has shown efficacy in FD in double-blind placebo-controlled studies.

Surgical treatment is indicated if the patient is unresponsive to medical treatment, noncompliant, or at a high risk of complications. Surgical options include vagotomy or partial gastrectomy.

Management of Complications of Peptic Ulcers

Bleeding, gastric outlet obstruction, perforation penetration, and stomach cancer are the complications of peptic ulcer disease.

Bleeding ulcer—patient usually presents with melena and coffee ground vomitus. Rarely, a patient may present with sudden onset hypotension or vasovagal reaction without overt signs of bleed. Patients with hemodynamic instability should be admitted to the intensive care unit (ICU). After securing airway and venous access, a large-bore nasogastric tube should be placed for gastric lavage. PPI bolus 80 mg followed by infusion at the rate of 8 mg/h should be started. Blood samples should be sent for hemogram, prothrombin time (PT), activated partial thromboplastin time (APTT), and blood grouping and matching. Volume should be replaced by crystalloids while awaiting packed cells. Endoscopy can be done after hemodynamic stabilization. Adrenaline injection at the base of actively bleeding ulcers and visible vessels followed by either coagulation with thermal probe or hemoclip application stops bleeding in majority. Surgical intervention is needed if there are two failed endoscopic attempts. Angiography with embolization is useful in refractory bleed. Peptic stricture may be managed either surgically or by endoscopic dilatation. Perforation requires laparotomy.

PROGNOSIS

Once the underlying cause is successfully treated, the prognosis of PUD is excellent. Recurrence of the ulcer may be prevented by maintaining good hygiene and avoiding alcohol, smoking, and NSAIDs.

SUMMARY

Dyspepsia is a very common condition defined as epigastric pain or discomfort. Rarely, it may be a manifestation of a serious condition like malignancy. Identification of red flag signs can help in planning further management. Those with no red flags can be treated with empirical PPI initially and investigate further if no response. Management of refractory dyspepsia requires a multidisciplinary approach.

MULTIPLE CHOICE QUESTIONS

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Acute Pancreatitis and Cholecystitis

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CHAPTER

Sanjay Kumar

ACUTE PANCREATITIS

Introduction

Acute pancreatitis is one of the most common diagnoses in patients presenting with abdominal pain in gastrointestinal (GI) clinics. In fact, it is now the most common GI diagnosis requiring hospitalization. The annual incidence ranges from 13 to 45/100,000 population and has increased by 30–62% in the last two decades. It has significant burden on healthcare costs and resource utilization.

Definition

In clinical practice, acute pancreatitis is defined as abdominal pain, centered in the epigastrium, which often radiates to the back along with raised serum amylase and lipase to >3 times the upper limit and evidence of pancreatic inflammation on imaging. Any two of the above three is sufficient to make a diagnosis. The level of amylase and lipase is diagnostic but does not correlate with severity. In the emergency room or outpatient department, it is very important to make an early diagnosis as damage is done very rapidly and early interventions (hydration) can change the outcome.

Etiology

Gallstone disease and alcohol are the most common causes of acute pancreatitis across the world (**Table 1**). Differential diagnosis includes perforation, myocardial infarction, acute cholecystitis, choledocholithiasis, intestinal obstruction, bowel ischemia, etc.

Pathophysiology

The pathophysiology of pancreatitis is not well known under normal physiology of trypsinogen produced in the pancreas and secreted in the duodenum while in acute pancreatitis trypsin is activated within the acinar cell and maybe because of obstruction, activated trypsin is not eliminated from the pancreas thus resulting in a high level of activated trypsin. This activated trypsin initiates injury, inflammation, and autodigestion of the pancreas by activating digestive enzyme compliments and kinins. Majority of the cases are limited to the local inflammation of the pancreas while the minority of cases progress to necrotizing pancreatitis and further involve the surrounding tissues and distant organ leading to multiorgan failure and death.

Clinical Features

Diagnosis should be considered in any patient who comes with severe abdominal pain in the upper abdomen/back/chest; is apparently in distress; has vomiting, tachycardia, and epigastric tenderness; and his/her pain is not easily controlled with analgesics. He/she may be an alcoholic or there may be a past history of pancreatitis/biliary colic.

Diagnosis

Investigations in the emergency department that would help to differentiate all these are electrocardiogram (ECG), complete blood count (CBC), liver function test (LFT), amylase, creatinine, abdominal X-ray (both erect and supine), and ultrasonography (USG). No laboratory test is the gold standard for acute pancreatitis. Amylase or lipase values should be at least three times the upper limit of the normal values according to the current recommendations. *Amylase* should not be considered as a good choice for diagnosis because it can be raised in nonpancreatic diseases such as renal failure, acute appendicitis, cholecystitis, intestinal obstruction, and ischemia of salivary glands (amylase starts rising few hours after the symptoms, peaks in 48 hours, and takes 3–5 hours to normalize). *Lipase* is more specific for pancreatic injury, remains elevated for a longer period of time, and is less associated with nonpancreatic disease. *Urine trypsinogen-2 dipstick test* is a noninvasive rapid test with high sensitivity and specificity, but it is less in use because of limited availability.

TABLE 1: Causes of acute pancreatitis.	
Common causes	• Gallstones • Alcohol • Hypertriglyceridemia • Endoscopic retrograde cholangiopancreatography (ERCP) • Drugs [azathioprine, 6-mercaptopurine, sulfonamides, estrogen, tetracycline, valproic acid, anti-HIV medications, 5-aminosalicylic acid (5-ASA)] • Trauma (especially blunt abdominal trauma) • Postoperative (abdominal and nonabdominal operations)
Uncommon causes	• Vascular causes and vasculitis (ischemic-hypoperfusion states after cardiac surgery) • Connective tissue disorders and thrombotic thrombocytopenic purpura (TTP) • Cancer of the pancreas • Hypercalcemia (hyperparathyroidism) • Periampullary diverticulum • Pancreas divisum • Hereditary pancreatitis • Viral and parasitic (mumps, coxsackievirus, cytomegalovirus, echovirus, *Ascaris*) • Autoimmune
Recurrent of acute pancreatitis without an obvious cause	• Microlithiasis, biliary sludge • Drugs • Alcohol abuse (hidden) • Hypertriglyceridemia, hypercalcemia • Pancreas divisum with minor papilla stenosis • Pancreatic cancer • Intraductal papillary mucinous neoplasm (IPMN) • Cystic fibrosis • Idiopathic

Note: About 20% still remain idiopathic after all investigations.

In case of a diagnostic dilemma, it is best to do contrast-enhanced computed tomography (CECT) of the abdomen within a few hours in the emergency department itself. But if the diagnosis of acute pancreatitis is clear based on blood tests and imaging, then it is wise to delay the CT scan for 3–4 days as necrosis is not picked up early and you will have to repeat a CT scan anyway on day 4 or day 5. Once a diagnosis of acute pancreatitis is established, one should quickly work on two lines first: First, to assess severity so that you can triage the patient and decide whether to send him to the intensive care unit (ICU) or ward. Second, one should try to establish the cause as quickly as possible because some of the etiologies such as stone in the common bile duct (CBD) and hypertriglyceridemia would need early intervention. The most important aspect of managing an acute pancreatitis patient is assessment of severity. It is always a challenge to talk to the relatives about the severity of an attack and the likely outcome, i.e., the prognosis. Various scales are available to assess the severity such as Ranson's, Imrie's, and acute physiology and chronic health evaluation II (APACHE II), but easiest at the bedside is to use BISAP (bedside index of severity of acute pancreatitis) scoring (**Table 2**). The entire exercise of assessment is to know which patients have organ failure because the outcome depends on the number of organs involved (**Table 3**).

TABLE 2: BISAP score.		
BUN	BUN > 25 mg/dL (8.9 mmol/L)	1 point
Impaired mental status	Abnormal mental status with a Glasgow Coma Score <15	1 point
SIRS	Evidence of SIRS (systemic inflammatory response syndrome)	1 point
Age	Age > 60 years old	1 point
Pleural effusion	Imaging study reveals pleural effusion	1 point
Score: 0–2 points: Lower mortality (<2%), 3–5 points: Higher mortality (>15%)		

(BISAP: bedside index of severity of acute pancreatitis; BUN: blood urea nitrogen; SIRS: systemic inflammatory response syndrome)

Management of Acute Pancreatitis

There are certain general measures, the most important of which is aggressive hydration (**Table 4**). Intravenous fluids of lactated Ringer's or normal saline are initially given as bolus 15–20 mL/kg (1,000–1,500 mL), followed by 3 mL/kg/h (200–250 mL/h), to maintain urine output >0.5 mL/kg/h. Serial bedside evaluations are required every 6–8

TABLE 3: Markers of severe acute pancreatitis.	
Risk factors for severity	• Age > 60 years • Obesity, BMI > 30 kg/m^2 • Comorbid disease (Charlson Comorbidity Index)
Markers of severity at admission or within 24 hours	• SIRS—defined by presence of two or more criteria: • Core temperature <36°C or >38°C • Heart rate > 90 bpm • Respirations > 20/min or pCO_2 < 32 mm Hg • White blood cell count > 12,000/μL, <4,000/μL or 10% bands • APACHE II • Hemoconcentration (hematocrit > 44%), admission BUN (>22 mg/dL) • BISAP score ≥3
Markers of severity during hospitalization	• Persistent organ failure • Pancreatic necrosis

(APACHE II: acute physiology and chronic health evaluation II; BISAP: bedside index of severity of acute pancreatitis; BMI: body mass index; BUN: blood urea nitrogen; pCO_2: partial pressure of carbon dioxide; SIRS: systemic inflammatory response syndrome)

TABLE 4: Treatment of acute pancreatitis.	
Airway breathing circulation	Supplemental oxygen, vital signs, and pulse oximetry monitoring (every 2 hourly)
Pain control	Parenteral analgesics and narcotics
Crystalloid therapy	• Ringer's lactate: 250–500 mL/h, 5–10 mL/kg/h (2.5–4 L) • Monitor hematocrit, creatinine, heart rate, MAP of 65–85 mm Hg, and urine output of 0.5–1 mL/kg/h
Electrolyte therapy	Correction of low ionized calcium, low magnesium, and control hyperglycemia
Antiemetics and antibiotics	• Control of nausea and vomiting, NPO status with early resumption of oral feeding, placing of nasogastric tube and suctioning not indicated • Antibiotics not indicated prophylactically or in mild pancreatitis Antibiotics only indicated in strongly suspected infection
Gastroenterologist consultation	In diagnosed biliary obstruction and cholangitis, ERCP is indicated in the first 24 hours

(ERCP: endoscopic retrograde cholangiopancreatography; MAP: mean arterial pressure; NPO: nil per oral)

hours to assess vital signs, oxygen saturation, and changes on physical examination. Lactated Ringer's solution has been shown to decrease systemic inflammation and may be a better crystalloid than normal saline. A target resuscitation strategy with measurement of hematocrit and BUN every 8–12 hours is recommended to ensure the adequacy of fluid resuscitation and monitor response to therapy; less-aggressive resuscitation strategy may be needed in milder forms of pancreatitis. A rising BUN during hospitalization is not only associated with inadequate hydration but is also higher in hospital mortality. A decrease in hematocrit and BUN during the first 12–24 hours is strong evidence that sufficient fluids are being administered. Serial measurement and bedside assessment for fluid overload are continued, and fluid rates are maintained accordingly. Adjustments in fluid resuscitation may be required in patients with cardiac, pulmonary, or renal disease. A central venous catheter with central venous pressure (CVP) monitoring is handy, but assessment of inferior vena cava (IVC) by bedside USG is equally informative and maybe better in expert hands.

Other measures are to keep the patient NPO, give him/her proper analgesics for relief of pain, and close monitoring for oxygen saturation, urine output, blood pressure (BP), and tachycardia. All patients with severe pancreatitis should be managed in the ICU. Pleural effusions and intra-abdominal fluid collections may need USG-guided pigtail drainage. If there is severe respiratory compromise, he/she may require noninvasive ventilation (NIV) or mechanical ventilation. Early enteral feeding is encouraged; hence, if the patient is not able to take orally or is vomiting, then nasojejunal intubation and feeding should be done. If the patient remains oliguric after restoration of intravascular volume, diuretics may be tried but if there is no response, hemodialysis may be required. There are few situations where urgent interventions are required in 48–72 hours such as endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy in case of gallstone pancreatitis with cholangitis (deranged LFT with dilated CBD on USG) or severe hypertriglyceridemia leading to acute pancreatitis wherein you have to start urgent lipid-lowering drugs. All other cases are managed conservatively.

The 1st week is the time for organ failure and the third week is for local complications such as infection/fluid collections and pseudocyst/walled-off necrosis (WON) (**Table 5**). One has to understand that this is a one-time insult and whatever is occurring in the next 4–6 weeks is actually the sequel of that particular attack. It is generally not recommended to start all patients on antibiotics; they are preferably reserved for a documented infection usually in the second or third week, severe necrotizing pancreatitis being an exception. Antibiotics with gram-negative coverage are ideal and imipenem is shown to be having the best penetration. Various anti-inflammatory agents have been tried in several trials, but none has shown good results.

Local complications such as fluid collections, pseudocysts, WON, or IPN should be managed at a dedicated center with a multidisciplinary approach (a team of gastroenterologist, surgeon, and radiologist). All symptomatic collections require drainage and the best way to drain would depend on location, contents, presence of infection, and presence of vessels in wall or vicinity. A good assessment by endosonography and magnetic resonance imaging (MRI) is a must to plan out treatment. In general, collections in head and body with well-defined walls are best drained by endoscopy provided there are no major vessels in the way and those in tail are better drained radiologically. But in any case, sound surgical backup is must. Those with multiple collections are preferably taken up for surgery. Finally, those with biliary pancreatitis will need

TABLE 5: Pancreatic and extrapancreatic complications of acute pancreatitis.

Pancreatic	*Nonpancreatic*
• Necrosis • Sterile • Infected • WON • Pancreatic fluid collections • Pancreatic pseudocyst • Disruption of main pancreatic duct or secondary branches • Pancreatic ascites • Involvement of contiguous organs by necrotizing pancreatitis • Thrombosis of blood vessels (splenic vein, portal vein) • Pancreatic enteric fistula • Bowel infarction • Obstructive jaundice	• Cardiovascular—hypotension, hypovolemia, myocardial dysfunction, myocardial infarction, pericardial effusion • Pulmonary—hypoxia atelectasis, pleural effusion, pulmonary infiltrates, acute respiratory failure • Gastrointestinal—erosive gastritis, GI perforation, GI bleed, bowel obstruction, splenic infarction • Renal—oliguria, azotemia, acute kidney injury, renal vessels, thrombosis • Metabolic—hyperglycemia, hypoglycemia, hypertriglyceridemia

(GI: gastrointestinal; WON: walled-off necrosis)

laparoscopic cholecystectomy as soon as feasible, i.e., when inflammation has subsided.

The overall prognosis depends on the severity of pancreatitis. Those with mild pancreatitis recover in about 1 week, those with moderately severe pancreatitis take several weeks, and those with severe pancreatitis take several months to recover completely. Severe pancreatitis has a mortality of about 30%, the cause being organ failure in the first 2 weeks and infection or bleeding after 2 weeks.

ACUTE CHOLECYSTITIS

Acute cholecystitis means inflammation of gallbladder (GB) which most commonly occurs due to gall stones. It occurs when a stone gets lodged in the neck of GB or cystic duct leading to mechanical distension, ischemia of wall, and bacterial infection. Usual organisms are gram-negative bacteria such as *Escherichia coli* or *Klebsiella*. In emphysematous cholecystitis, it is usually *Clostridium perfringens*. Less often, it could be acalculous cholecystitis, which is seen in patients undergoing nonbiliary major surgeries, severe trauma, burns, sepsis, etc. (**Table 6**). But even in acalculous cholecystitis, >50% of cases are due to small stone/sludge blocking the cystic duct not picked up on imaging.

Diagnosis of Acute Cholecystitis

Presentation of acute cholecystitis is like an extended biliary colic where pain starts in epigastrium, is usually severe, may radiate to right shoulder or back, and may be associated with vomiting often associated with low-grade fever and ileus. The patient may give a history of similar pain in the past which used to subside in 30–40 minutes and his interpretation is usually a "gas block" in the past. On examination, about 50% of patients will have right upper quadrant (RUQ) tenderness and a sudden holding of breath during deep inspiration (Murphy's sign). USG is usually diagnostic showing stone, thickening of GB wall, and pericholecystic collection of fluid (**Table 7**). But a CT scan may be done to rule out complications such as perforation/empyema/emphysematous cholecystitis (**Box 1**). Magnetic resonance cholangiopancreatography (MRCP) or endosonography should be done if there is a suspicion of CBD stone based on LFT.

TABLE 6: Acute acalculous cholecystitis (AAC).

Critically ill patients	• Major surgery • Severe trauma • Sepsis • Total parenteral nutrition • Diabetes • Atherosclerotic disease • HIV infection
Nonhospitalized patients	Elderly male with atherosclerosis

Note: HIDA scan and sampling of luminal contents may help to establish the diagnosis.

(HIDA: hepatobiliary iminodiacetic acid; HIV: human immunodeficiency virus)

TABLE 7: Criteria for diagnosis of acute cholecystitis.

Local examination	*Right upper quadrant mass pain or tenderness, Murphy's signs*
Systemic features	Fever, raised C-reactive protein, elevated WBC count
Imaging	• USG—sonographic Murphy's sign, GB thickening, distension, pericholecystic fluid • CT scan—GB wall thickening, distension, hyperdense, GB wall pericholecystic fluid, and fat stranding
Diagnosis	• One local + one systemic = Suspected • One local + one systemic + imaging finding = Definitive diagnosis

(GB: gallbladder; WBC: white blood cell)

Treatment

Treatment of acute cholecystitis is urgent laparoscopic cholecystectomy unless the patient is unfit for surgery in which case you can plan for an early cholecystectomy within 4–6 weeks. In sick patients, USG-guided PTGBD (percutaneous transhepatic gallbladder drainage) is a good procedure to tide over the crisis. Laparoscopic cholecystectomy in the presence of acute cholecystitis carries a complication rate of 1–3% (c/f interval cholecystectomy: 0.5–1%), but one must understand that perforation/empyema GB with sepsis has a mortality of 15–30%. So, in an acute case, if you decide to go for conservative treatment, the patient can progress to one of these complications. Hence, urgent laparoscopic cholecystectomy is preferred. Complications after laparoscopic cholecystectomy are CBD injury, bile leak, local hematoma, atherosclerosis, biliary stricture, etc., all of which require treatment in

BOX 1: Complications of acute cholecystitis.

- Suppurative cholecystitis (empyema)
- Gangrenous cholecystitis
- Emphysematous cholecystitis
- Hemorrhagic cholecystitis
- Gallbladder perforation
- Fistula formation, cholecystoduodenal, cholecysto-intestinal, cholecystobiliary
- Mirizzi syndrome

Mirizzi syndrome: Gallstone impacts the gallbladder wall and compresses it causing pressure necrosis which further gets adhered to the common bile duct wall leading to jaundice.

Type 1: Compression of CBD without lumen narrowing

Type 2: Compression causing CBD lumen narrowing

Type 3: Compression causing CBD wall necrosis

Type 4: Cholecystocholedochal fistula

(CBD: common bile duct)

specialized centers. There are no long-term complications of removing GB except mild diarrhea in about 10% of patients due to bile acid malabsorption.

SUMMARY

Acute pancreatitis and cholecystitis remain a common reason for hospitalization. The most common etiologies include gallstones, followed by alcohol. It has a significant impact on healthcare resource utilization, morbidity, and mortality. The disease can vary from mild to severe with systemic complications. The cornerstones to management include aggressive early fluid resuscitation, appropriate nutritional supplementation, and management of complications. Patients with mild acute gallstone-related pancreatitis should undergo cholecystectomy prior to discharge to prevent recurrent episodes. Severe acute pancreatitis and pancreatitis with local and systemic complications should be managed in a multidisciplinary approach with the involvement of intensivists, gastroenterologists, hepatobiliary surgeons, and interventional radiologists.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Acute Hepatitis

Amit Mittal, Akanksha Rastogi

INTRODUCTION

In simple terms, acute hepatitis means an acute inflammation of the liver. Various causes can lead to acute hepatitis, e.g., infectious (viral, bacterial, fungal, and parasites) and noninfectious (alcohol, drugs, metabolic diseases, etc.). Acute viral hepatitis is actually a systemic infection which predominantly involves the liver. The terms fulminant hepatic failure (FHF) and acute liver failure (ALF) are used interchangeably and mean jaundice followed by encephalopathy and coagulopathy (hyperacute: <7 days, acute: 8–28 days, or subacute: 29 days to 26 weeks) in the absence of a preexisting liver disease; however, the majority of cases are of much shorter duration.

ETIOLOGY

Viral infections are most common in acute hepatitis. *Common* viruses include hepatitis A, B, E, C, and D (superinfection/coinfection with B) and *uncommon* viruses include cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus (HSV), dengue fever, and transfusion transmitted virus (TTV).

Toxins and drugs: Drug-induced liver injuries (DILI) include paracetamol, carbon tetrachloride, isoniazid, phenytoin, amoxicillin-clavulanate, mushroom (amanita phalloides), ackee fruit, cycasin, aflatoxin (*Aspergillus flavus*), and sea anemone sting (**Table 1**).

Acute liver failure: Causes of ALF include the above-mentioned viruses and toxins, ischemic hepatopathy (cardiogenic shock, hypotension, heatstroke, and cocaine), vascular (Budd–Chiari syndrome, sinusoidal obstruction syndrome), Wilson's disease, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, acute fatty liver of pregnancy, primary graft nonfunction after liver transplantation, and malignant infiltration (breast cancer, small cell lung cancer). HSV hepatitis causes ALF in case of neonates, human immunodeficiency virus (HIV) coinfection, and pregnancy.

In India, 95% causes of ALF are due to viruses (hepatitis E: ~40%, hepatitis B: ~10–15%, hepatitis A: ~1%) and DILI: ~5%; however in America, viruses cause ~10% of ALF.

TABLE 1: Liver toxins and types of injury.

Toxin	*Liver injury*	*Disease*	*Component*
Mushroom	ALF	Liver necrosis	Alpha-amatoxin and phalloidin
Ackee fruit	Steatosis	Jamaican vomiting sickness	Hypoglycin
Cycasin	Acute hepatitis	Liver necrosis	Methylazoxy-methanol
Aspergillus flavus	Acute hepatitis	Liver necrosis and carcinogenic	Aflatoxin B_1
Aspergillus tamari	Acute hepatitis	Liver necrosis	Cyclopiazonic acid

(ALF: acute liver failure)

TABLE 2: Classification of acute liver failure.

Category	*Causes*	*Prognosis*
Hyperacute	Hepatitis A, paracetamol	Fair
Acute	Hepatitis B, drugs	Poor
Subacute	Drugs, indeterminate	Very poor

Acetaminophen (paracetamol) overdose is a suicidal agent and a common cause of ALF (UK: ~57%, USA: ~45%, and France: 22%). It appears that hepatitis C can cause ALF in the presence of hepatitis B coinfection.

PATHOPHYSIOLOGY

Hepatitis A and E infections are mainly noted in areas with poor sanitation and they occur by consuming contaminated water or food and contact with an already infected person. Hepatitis B and C infections spread by exposure to body fluids and blood.

In the chain of events in ALF (**Table 2**), there is significant death of hepatocytes (death exceeds regeneration) due to direct and immune-mediated injury which leads to cytokine storm, release of proinflammatory cytokines [tumor necrosis

factor (TNF)-alpha, interleukin (IL)-beta, IL-6], and systemic inflammatory response syndrome (SIRS). Arterial ammonia levels start rising and lead to raised intracranial pressure (ICP) and cerebral edema in 30% of cases. Gradually, multiple organ damage syndrome (MODS) sets in which include infection; metabolic derangements such as hypoglycemia, hypokalemia, and acid–base changes; hypotension; respiratory depression; gastrointestinal bleeding; renal failure; and ultimately death. Cerebral edema is a very common presentation in the hyperacute category and less common in the acute category. Renal failure and peripheral edema are more common, and cerebral edema is rare in the subacute category.

CLINICAL PRESENTATION

Acute viral hepatitis has an incubation period (2–4 weeks in A, 2–6 weeks in E, and 1–6 months in B and C). Typical features of acute viral infections include variable prodromal symptoms in the form of loss of appetite, nausea, vomiting, tiredness, malaise, photophobia, and coryza followed by jaundice after 1–2 weeks. The acute hepatitis C infection can be symptomatic or subclinical. Serum sickness-like features (fever, rash, joint pain, and angioneurotic edema) may be seen in only 10% of patients with acute hepatitis B. Liver toxins cause abdominal pain, vomiting, diarrhea on day 1–2, and jaundice and renal failure over the next 24–48 hours of consumption. In paracetamol overdose, there is no symptom initially; later, weakness, nausea, and vomiting develop. Initially, ALF can have vague symptoms and signs, i.e., lethargy, nausea, and pain in the abdomen, which eventually becomes more specific, i.e., jaundice, altered sensorium, slurred speech, confusion, seizure, and later coma.

Hepatitis A can have many patterns, i.e., asymptomatic, jaundice <2 months, cholestasis >2.5 months, relapsing pattern (≥2 episodes over 10 weeks), and ALF.

Hepatitis B infection can be occult [detectable hepatitis B virus (HBV) deoxyribonucleic acid (DNA), negative hepatitis B surface antigen (HBsAg)] in few individuals.

Watch for life-threatening causes of jaundice such as acetaminophen overdose and massive hemolysis, e.g., falciparum malaria and FHF (altered behavior or coagulopathy).

Early identification of complications of acute hepatitis B and C should be done [chronic hepatitis, cirrhosis of liver, ascites, portal hypertension, hepatocellular cancer (HCC), and hepatorenal syndrome]. Cushing's triad is a clinical feature of raised ICP suggestive of encephalopathy (respiratory depression, bradycardia, and hypertension).

EVALUATION

History

Age and sex: Type A viral hepatitis in young, type E in pregnant, drugs and alcohol in adults.

Onset: Rapid in hemolysis), *precipitants* (dehydration, fasting), duration of jaundice, *awareness* (who noticed? relative/patient himself/herself), *depth* (maximum recorded level of bilirubin), *progression*, and *fluctuation.*

Acute hepatitis: History of prodromal symptoms (nausea, vomiting, anorexia, myalgia, skin rash, and fever in viral infections), drugs (antibiotics/azathioprine/antitubercular/herbal), toxins (consumption of mushrooms, foodstuffs including grains and nuts contaminated by fungal mycotoxins), injections, blood transfusion, alcohol, and contact with other jaundiced patients.

If acute hepatitis turns into a cholestatic phase: Accumulation of biliary constituents, e.g., itching (site, severity, nocturnal symptoms, and progression), mustard oil-like urine, clay-colored stools, skin darkening, deficiency of bile acids in intestine presenting as fat-soluble vitamin deficiency (night blindness, dry skin, leg cramps, and bleeding).

Past history: Recurrent jaundice (relapsing viral hepatitis A).

*Occupation, place of origin, family history (*hemolysis, congenital hyperbilirubinemias).

Alcohol and smoking can cause HCC. How are the symptoms now? Progression or improvement.

Physical Examination

Look for nutrition, anemia, depth of jaundice, purpura (skin bleed), scratch marks, body hair, liver and spleen size, ascites, flapping tremors, pedal edema, and altered mental behavior. Vesicular skin lesions suggest HSV hepatitis.

General examination: Anemia, bruising, purpura, lymphadenopathy, clubbing, mental state (fetor hepaticus, flapping tremors, intellectual deterioration in hepatocellular jaundice, and hepatic coma).

Abdominal examination: Small liver (hepatitis, cirrhosis), large nodular liver (cancer), tender liver (congestive heart failure, alcoholism), splenomegaly (portal hypertension), ascites (cirrhosis, malignancy).

INVESTIGATIONS

Complete blood count provides complementary information concerning the cause of jaundice. In case of anemia, look for hemolysis or poor oral intake; leukopenia may establish viral etiology; leukocytosis may be a clue to sepsis; and thrombocytopenia (<1.5 lakh/mm^3) may be a clue to cirrhosis or ALF.

Serum biochemical tests: The presence of bilirubin can confirm jaundice and help to know its depth, transaminases [alanine transaminase (ALT) > aspartate aminotransferase (AST) in hepatitis, i.e., >1,000 U/L or >20–25 × normal and AST >2 × ALT, nearly always <300 U/L in alcoholism, but AST > ALT, i.e., >1,000 U/L or >20–25 × normal in cases of drugs or toxins in a patient with an underlying alcoholic liver injury or cirrhosis], and alkaline phosphatase (ALP; elevated in cholestasis). Prothrombin time (PT) is elevated in obstructed biliary tree or ALF [PT/international normalized ratio (INR) > 1.5].

Serologic testing: Viral serologies for hepatitis A, B, C, and E, i.e., anti-hepatitis A virus (HAV) immunoglobulin M (IgM), HBsAg, anti-HBc (anti-hepatitis B core), HBV DNA, anti-HCV (hepatitis C virus), HCV-RNA (ribonucleic acid), anti-HEV (hepatitis E virus) IgM if there is a suspicion of viral hepatitis; HSV DNA, EBV-DNA, and CMV-DNA in nonhepatotropic viruses.

Autoimmune markers: In case of autoimmune hepatitis ANA, ASMA, anti-LKM antibody test should be done. If AST and gamma globulin are elevated the AST:ALP ratio should be >3.

Other laboratory tests: Serum acetaminophen level and urine toxicology screening in suspected overdose cases in ALF.

Serum ceruloplasmin: 24-hour urine copper, genetic testing, and slit-lamp eye examination to look for fulminant Wilson's disease if ALP: Total bilirubin < 4 and AST: ALT > 2.2.

Radiology: Chest film to look for tumor and elevation of diaphragm due to enlarged liver.

Ultrasound: Inexpensive, noninvasive, and portable which allows distinction between intrahepatic and extrahepatic biliary obstruction. Look for vascular disorder, cholelithiasis, intrahepatic space-occupying lesion (SOL), and ascites.

Abdominal computed tomography (CT) scan can detect small SOL, is expensive, and needs normal renal function for contrast.

Liver biopsy: In suspected cases of drug or infiltrative/autoimmune liver disease (after correction of prothrombin time with vitamin K).

Assess severity of liver injury every 8–12 hours early on and daily thereafter in ALF: Complete blood count (CBC), kidney function test (KFT), random blood sugar (RBS), liver function test (LFT), PT/INR, factor V, fibrinogen, arterial blood gas (ABG), ammonia, lactate, blood and urine cultures, peritoneal fluid if ascites, neurological status by bedside neurology examination, Glasgow Coma Score, CT scan of head [if > hepatic encephalopathy (HE) Grade 2, i.e., marked confusion, incoherent speech, sleeping most of the time], ICP monitor if Grade 4 HE, i.e., comatose, unresponsive to pain, decorticate or decerebrate posturing.

TREATMENT

The optimal treatment of jaundice is supportive and treatment of the etiology. Immediate hospitalization is needed if altered mental behavior and coagulopathy, i.e., PT/INR ≥1.5, are present. Prevent and treat the complications of ALF. Paracetamol and mushroom poisoning is treated by N-acetyl cysteine (up to 3 days) 140 mg/kg over 1 hour intravenously followed by 70 mg/kg every 4 hours for at least 12 doses. Supportive treatment is given in acute viral hepatitis. Oral nucleoside analog, i.e., entecavir or tenofovir, is recommended if high jaundice (bilirubin > 20) or high PT/INR or encephalopathy is present. Start steroids in case of autoimmune hepatitis. Keep the patient in the intensive care unit if more careful monitoring is required. Plan to transfer to a liver transplant unit if bilirubin > 17.5, PT/INR > 2, and Grade 2 or more HE develops.

SUMMARY

Multiple clues to the etiology of jaundice can be obtained from the history and examination.

Identify life-threatening causes of jaundice. ALF is a rare but potentially fatal disease. Survival in ALF depends on the cause, urgent management of ALF, and its complications. The treatment approach depends upon the patient, the facilities, and the expertise available. The mortality rate of hepatitis E-related ALF is 15–25% in pregnancy. Also, watch for HELLP and alpha-fetoprotein (AFP) in pregnancy.

Liver transplantation is a rescue therapy in ALF for those who are not recovering or have an advanced disease while milder cases can recover with conservative management. Vaccines can prevent hepatitis A and B. (Vaccine for hepatitis E is not available in India at the time of this publication.) Investigational approaches include extracorporeal treatment, bioartificial support system, and stem cell therapy for ALF.

Many myths exist in India, which practically have no benefit, i.e., role of sugarcane juice, avoidance of yellow-colored food, black magic, and *tantra vidya*.

MULTIPLE CHOICE QUESTIONS

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Chronic Liver Disease and Complications

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CHAPTER

Ravindra Kale

INTRODUCTION

Most patients remain asymptomatic for years when they are affected by hepatitis B or hepatitis C virus infections, or by nonalcoholic fatty liver disease (NAFLD), or by alcoholic hepatitis. During this asymptomatic period, the disease manifests as mild elevation of transaminase levels, NAFLD is identified as fatty liver, there is incidental finding on abdominal ultrasound studies, and pathologically normal liver parenchyma is replaced by scar and fibrotic tissue. When a significant amount of normal liver parenchyma is replaced by scar and fibrotic tissue, cirrhosis develops. Cirrhosis manifests as generalized weakness, abdominal pain, ascites, spontaneous bacterial peritonitis (SBP), electrolyte imbalance, and altered mental status due to the development of hepatic encephalopathy (HE). Cirrhosis is a progressive disease and is initially asymptomatic (compensated cirrhosis). With gradually declining liver functions, decompensation occurs, leading to different complications. Knowledge of these complications may help in prevention and successful treatment and thus improve the quality of life of these patients.

MALNUTRITION

Malnutrition is a common complication. Chronic liver disease leads to sarcopenia and nutrient deficiency due to various factors. Chronic alcohol use leads to reduced caloric and nutrient intake. Anorexia is a frequent symptom of cirrhosis leading to reduced caloric intake. Moreover, there is dietary restriction due to altered taste sensation, tense ascites, and frequent drug-induced nausea. Patients with recurrent encephalopathy suffer from severe caloric and protein undernutrition. During evaluation, each patient should be enquired about dietary caloric and protein intake. On physical examination, one should look for glossitis, pedal edema, peripheral sensation, and muscle wasting. Patients should have dietary counseling. Each patient should be assessed for and receive thiamine, zinc, and B12 supplementation. Preferably vegetarian diet with frequent meals should be given. Salt restriction is needed in case of ascites and edema. Protein restriction is not needed even in the presence of encephalopathy (1–1.5 g protein/kg body weight should be given). Replacement of protein, usually in the form of branched-chain amino acids, is advisable but some patients could not tolerate it due to its taste.

INFECTIONS

Cirrhotic patients are more prone to infections. Common infections are SBP, urinary tract infections, pneumonia, cellulitis, and *Clostridium difficile* colitis. Use of proton-pump inhibitors, frequent use of urinary catheters, and antibiotics during admission make the patient prone to these infections. SBP is diagnosed by the presence of >250 polymorphonuclear leukocytes (PMNs) in ascitic fluid and is monobacterial (**Table 1**). It is usually caused by gram-negative organisms (*Escherichia coli*). Presence of polymicrobial infection or a very high neutrophilic count in patients with localized abdominal symptoms suggests inflammation/perforation of an organ (secondary bacterial peritonitis). The usual presentation of SBP is with abdominal symptoms such as pain, diarrhea, vomiting, or ileus or it may present with worsening of liver function, encephalopathy, gastrointestinal (GI) bleed, or acute kidney injury. Sometimes, it may be asymptomatic; hence, there is a need to do paracentesis of ascitic fluid in all patients on admission. Untreated patients have high mortality. Treatment usually consists of empirically starting third-generation cephalosporin (cefotaxime or ceftriaxone) after sending ascitic and blood cultures. Culture is positive in 40%

TABLE 1: Diagnosis and treatment of spontaneous bacterial peritonitis.

Diagnosis	• Ascitic fluid cytology: 50 mL of ascitic fluid should be sent for cell count, Gram stain, and culture • Ascitic fluid WBC count > 1,000/mm^3 or polymorphonuclear cell > 250/mL or bacteria on Gram stain
Empiric treatment	• Oral fluroquinolone (in mild cases) • Intravenous fluroquinolones • Cefotaxime or ceftriaxone

of patients only. Treatment should be given for 5 days. Repeat tap after 48 hours to demonstrate that at least 25% reduction in PMN count is helpful in assessing response. Prophylaxis of SBP with quinolones (norfloxacin 400 mg/day) should be started in patients with very low ascitic albumin, jaundice, and Child "C" liver [Child–Turcotte–Pugh (CTP) > 9] function status.

Tuberculosis (TB) is very common in cirrhotic patients, especially in India, and is associated with significant morbidity and mortality. Antitubercular therapy is associated with significant hepatotoxicity. Patients with decompensated cirrhosis require a modified antitubercular regimen for a prolonged period.

GASTROINTESTINAL BLEEDING

Gastrointestinal bleeding could be variceal or nonvariceal. Variceal bleed is common and is associated with mortality in 20% of patients. The common precipitating factors are infections, and nonsteroidal anti-inflammatory drug (NSAID) is used. The initial treatment includes gastric lavage, intravenous (IV) fluids, and packed cell transfusion. Bleeding is frequently associated with further hepatic decompensation, sepsis, and acute kidney injury; prophylactic third-generation cephalosporins should be started on admission. Infusion of octreotide (50 μg stat and 50 μg/h) or terlipressin 1–2 mg 6–8 hourly helps in reducing portal pressure. Upper GI endoscopy after hemodynamic stabilization will help in diagnosing and treating the cause of bleed. Esophageal variceal bleed can be managed by endoscopic variceal ligation (EVL) or endoscopic sclerotherapy (EST). Gastric varices are managed by cyanoacrylate glue injection. Placement of a Sengstaken–Blakemore tube or a metallic (Danis–Ella) stent may be needed in persistent severe bleeding. If bleeding still persists, an emergency transjugular intrahepatic porto-systemic shunt (TIPS) can be considered. Balloon retrograde transvenous obliteration (BRTO) is used for gastric variceal bleed. Follow-up EVL/EST needs to be done every 2–3 weeks to obliterate varices.

Every patient of cirrhosis should undergo surveillance endoscopy to check for presence of varices at baseline. If no varices are found on endoscopy, then repeat endoscopy after 3 years and for those with varices yearly endoscopy is advisable. Those with high-risk varices (small varices with red color signs or large varices with or without red color signs) should receive prophylaxis with nonselective beta-blockers (propranolol, nadolol) or carvedilol or prophylactic EVL. The dose of beta-blocker should be adjusted to a heart rate of 50–60 beats/min. Common side effects are dyspnea, hypotension, and fatigue. Carvedilol worsens fluid accumulation and hyponatremia in patients with high MELD (Model for End-stage Liver Disease) score. Those intolerant to drugs or with refractory ascites should undergo prophylactic EVL.

ASCITES

Development of ascites is the most frequent complication of cirrhosis and reflects declining liver function. The initial event in ascites formation appears to be splanchnic vasodilatation secondary to release of local vasodilators (e.g., nitric oxide) in setting of portal hypertension. Consequent to this, hyperdynamic circulation develops. Decreased arterial pressure leads to activation of the renin–angiotensin–aldosterone system with resultant sodium and water retention in the kidney. An increased hydrostatic pressure gradient across the sinusoids lead to weeping of fluid from the liver surface. Systemic inflammation due to intestinal translocation of bacteria and bacterial products contributes to circulatory dysfunction.

Diagnostic ascitic taping should be done in every case and fluid should be sent for routine examination, culture, cytology, and adenosine deaminase (ADA) levels. Depending on the serum ascitic albumin gradient (serum albumin–ascitic albumin; **Table 2**), ascites can be classified as those related to portal hypertension [high gradient, serum albumin ascites gradient (SAAG) > 1.1] or those not related to portal hypertension (low gradient, <1.1). Low SAAG ascites can occur in TB, malignancy, pancreatitis, and nephrotic syndrome while high SAAG ascites occurs in cirrhosis, myxedema, Budd–Chiari syndrome, and cardiac causes. 5% of patients will have mixed ascites (high SAAG ascites with TB or malignancy).

Treatment of ascites involves treatment of the primary cause of liver disease, such as antivirals for hepatitis B and C and D-penicillamine for Wilson disease. Reversal of fibrosis and improvement in ascites may occur. Mild ascites can be treated by moderate salt restriction (2 g/88 μmol/day) and spironolactone 100 mg daily with or without furosemide 40 mg daily. In some patients, ascites persists (refractory ascites) either after using the maximum doses of diuretics (spironolactone 400 mg and furosemide 160 mg) or when adequate dosing of diuretics is not possible due to side effects. In these patients, large-volume paracentesis (5–10 L) along with albumin infusion (8 mg/L of ascites removed) helps in mobilizing ascites. TIPS should be considered if frequent paracentesis is required. It improves ascitic control and quality of life. However, one fourth of patients may develop post-TIPS HE. Elderly patients, poor liver function (Child–Pugh score > 12, MELD > 18, recurrent encephalopathy), and cardiac dysfunction (EF < 60%) preclude use of TIPS. Liver transplant should be considered in a patient who is otherwise a transplant candidate.

PULMONARY COMPLICATIONS

A patient with cirrhosis has a propensity for pneumonia and should be vaccinated for pneumococcus. Pleural effusion is common and is usually improved with ascites control with diuretics and albumin. Pleural drain should be avoided except

TABLE 2: Serum albumin ascites gradient (SAAG).

SAAG > 1.1 g/dL	• Cirrhosis • Heart failure • Alcoholic hepatitis • Hepatic metastasis • Myxedema
SAAG < 1.1 g/dL	• Peritoneal tuberculosis • Peritoneal carcinomatosis • Pancreatitis • Nephrotic syndrome • Bowel obstruction/perforation

for massive hydrothorax and empyema. *Two pulmonary conditions unique to patients with cirrhosis and portal hypertension are hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH), respectively.*

Hepatopulmonary syndrome is characterized by the presence of intrapulmonary vascular dilatation (IPVD) and increased alveolar-arterial oxygen gradient. Patients usually are asymptomatic or have dyspnea. Dyspnea worsens with standing (platypnea) due to predominant vasodilatation in lung bases. Diagnosis requires a high index of suspicion. Arterial blood gas shows a widened alveolar-arterial gradient (>15 mm Hg in those <64 years of age and >20 in those >64 years of age). Pulse oximetry can be used as a screening method. IPVD can be detected by contrast echo and technetium macroaggregated albumin (^{99m}Tc MAA) scan. In contrast echo, agitated saline is given intravenously. Appearance of intravenously injected microbubbles in the left ventricle after three cardiac cycles suggests intrapulmonary shunts. ^{99m}Tc-MAA scan utilizes intravenous injection of 20-μm MAA particles. Normally, these particles get trapped in lung capillaries. But in HPS, some particles cross through abnormal capillaries and reach the brain. Shunt fraction > 6% is termed a positive scan. There is no effective pharmacological treatment of HPS. Multiple drugs and garlic extract have been tried. Liver transplant is effective, but post-transplant mortality is high in severe HPS. POPH is the presence of pulmonary hypertension [mean pulmonary artery pressure (PAP) >25 mm Hg at rest and pulmonary capillary wedge pressure <15 mm Hg in presence of portal hypertension]. POPH can be mild (PAP 25–35 mm Hg), moderate (35–45 mm Hg), or severe (>45 mm Hg). Mortality is high in moderate-to-severe POPH. Treatment is done with vasodilators. Prostacyclin, endothelial receptor agonist (bosentan), and phosphodiesterase 5 inhibitors (sildenafil, tadalafil) are used. The role of liver transplant is controversial.

HEPATORENAL SYNDROME

Acute kidney injury (AKI) in cirrhosis is defined as rise in creatinine >50% over baseline or 0.3 mg more than baseline. It is present in around 20% patients of cirrhosis on admission. The common precipitating factors are infections, dehydration due to diuretics or lactulose overdose, NSAID and other nephrotoxic drugs, and large-volume paracentesis (LVP). Besides this, renal dysfunction may occur due to functional renal failure where no evidence of renal parenchymal abnormality is found and there is no response to initial fluid replacement and diuretic and nephrotoxic drug withdrawal. Functional renal failure is known as hepatorenal syndrome-AKI (HRS-AKI). Previously defined HRS type 1 and 2 terms are abolished now. Pathophysiology of HRS is related to altered hemodynamics in advanced cirrhosis. This consists of splanchnic and systemic vasodilatation and renal vasoconstriction leading to lower renal perfusion. Presence of hypovolemia, infection, and release of cytokines worsens this already compromised renal circulation.

HRS-AKI is diagnosed by the International Ascitic Club AKI criteria (2015) as follows:

- Patient of cirrhosis with ascites and AKI
- No improvement in serum creatinine on volume replacement (decrease to <1.5 mg/dL)
- Absence of shock
- No current or recent nephrotoxic drug use
- Absence of parenchymal kidney disease as indicated by proteinuria (>500 mg/day), microhematuria [>50 red blood cells (RBCs)/high power field (HPF)], and/or abnormal renal findings on ultrasonography (USG)

Treatment of AKI consists of stopping nephrotoxic drugs, NSAIDs, and diuretics; optimizing the dose of lactulose to avoid diarrhea; excluding intrinsic renal disease; treatment of infection; and correction of intravascular volume (1 g albumin/kg body weight—max 100 g/day). If no response to the above measures is seen, then vasoconstrictors should be added. Vasoconstrictors used are terlipressin, norepinephrine, and midodrine. Terlipressin is used in bolus doses of 0.5 mg every 4–6 hourly and increased if there is no response (maximum 2 g 6 hourly for 14 days). Norepinephrine infusion is done to achieve a mean arterial pressure of 10 mm Hg. Treatment is continued till creatinine levels fall below 1.5 mg/dL. Midodrine is an alpha-adrenergic agonist available as 2.5- and 5-mg tablets. Initial doses of midodrine 7.5 mg thrice daily in combination with octreotide 100 μg subcutaneously thrice daily are given. Doses can be increased to achieve a mean arterial pressure of 90 mm Hg.

Those who do not respond should be listed for liver transplant. TIPS can be used as a bridge to transplant in selected patients with a relatively good MELD score.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is one of the most common cancers. It usually develops in a setting of cirrhosis but may develop in noncirrhotic patients. Early diagnosis of HCC is essential to improve survival. However, the usually available screening methods—USG of abdomen and alpha-fetoprotein (AFP)—lack specificity and sensitivity. Screening of HCC should be done every 6 months. Those with recent decompensation and weight loss should also be evaluated for HCC. A nodule < 1 cm should be followed 3–6 monthly for growth. Larger nodules should be evaluated by triple-phase computed tomography (CT) scan or magnetic resonance imaging (MRI).

A small single tumor in patients with good liver function (Child–Pugh A) and no portal hypertension can be resected surgically with good 5-year survival (75%). Solitary HCC <5 cm or three nodules <3 cm size have good post-transplant survival. Percutaneous ablation by ethanol or radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) are good modalities for reducing tumor burden in transplant candidates awaiting transplant and also in those who have multiple nodules. Systemic chemotherapy with sorafenib, lenvatinib, and other newer agents is used in advanced disease.

HEPATIC ENCEPHALOPATHY

Presence of abnormal neuropsychiatric manifestations in cirrhosis is called HE. About 50–75% of patients with cirrhosis develop HE. The terminology used for HE is given in **Table 3**. It can vary from trivial changes in cognitive abilities on psychometric testing [minimal hepatic encephalopathy (MHE)] to overt encephalopathy (lethargy and coma). Encephalopathy can be episodic, recurrent, or persistent. Grading of HE (**Table 4**) is done according

TABLE 3: Current terminology for the classification of HE.

Type	*Description*	*Subcategory*	*Subdivision*
A	Encephalopathy associated with acute liver failure	–	–
B	Encephalopathy with portosystemic bypass and no intrinsic hepatocellular disease	–	–
C	Encephalopathy associated with cirrhosis or portal hypertension/ portosystemic shunts	Episodic HE	• Precipitated • Spontaneous • Recurrent
		Resistant HE	• Mild • Severe • Treatment dependent
		Minimal	

(HE: hepatic encephalopathy)

TABLE 4: West Haven criteria: Clinical stages of hepatic encephalopathy.

Stage	*Features*
I	General apathy
II	Lethargy, drowsiness, altered sensorium, asterixis
III	Hyperreflexia, extensor plantar reflexes, stupor
IV	Coma

to "*West Haven criteria*". Encephalopathy occurs due to increase in ammonia and various other toxins and systemic inflammation. However, blood ammonia levels do not correlate with the grade of encephalopathy. There are several factors which precipitate HE. Constipation, large protein meal, uremia, infections, sedatives, electrolyte imbalance, and GI bleed are the usual precipitating factors given in **Box 1**. Identification and correction of these factors are helpful in treatment. Assessment of a patient with HE is important for adequate treatment (**Box 2**). Nonabsorbable antibiotics (rifaximin 550 mg BD) and lactulose (or lactitol) in adequate doses to cause two to four soft stools daily are given. Overdose of lactulose can cause diarrhea, electrolyte imbalance, and dehydration and may worsen encephalopathy. In comatose patients, feeding by a nasogastric tube should be started to ensure adequate caloric and protein intake. Dietary protein should not be restricted. Branched-chain amino acid can be considered in patients intolerant to dietary protein.

Subclinical or MHE is characterized by abnormal psychometric tests in a patient with otherwise normal clinical, neurological, and mini-mental scale examination. Various psychometric tests such as paper and pencil tests (number

BOX 1: Precipitating factors for hepatic encephalopathy.

- Constipation
- Electrolyte imbalance: Hyponatremia, hypokalemia, alkalosis
- Gastrointestinal bleeding
- Infection:
  - SBP
  - Pneumonia
  - Urinary tract infections
  - Skin and soft-tissue infections
- Sedative drugs, psychotropic medicines, benzodiazepines, morphine
- Renal failure
- Surgery
- Dehydration:
  - Diuretics
  - Diarrhea
  - Vomiting
  - Excessive paracentesis
  - Fluid restriction
- Alcohol

(SBP: spontaneous bacterial peritonitis)

BOX 2: Assessment of acute episodic encephalopathy in cirrhotic patients.

- Assess for nonhepatic causes of altered mental status, such as delirium, intoxication, alcohol withdrawal, and hypoglycemia. Consider noncontrast CT scan of head to assess for acute intracranial process if new focal neurologic findings are found
- Assess for clinical and neurological examination findings consistent with HE. Grade the severity of HE by West Haven criteria or Glasgow Coma Scale
- Triage for patient safety: Consider hospital admission and monitoring in ICU. Consider intubation if the patient is unable to protect airway
- Assess for precipitating causes of HE and treat accordingly: Thorough clinical exam, labs (e.g., electrolytes, glucose, renal function, cell counts, cultures, urine drug screen, stool for *C. difficile*), and imaging
- Treat HE with lactulose (per oral, nasogastric tube, or rectum) ± rifaximin
- Assess the need for long-term therapy for prevention of recurrent HE
- Assess the need for liver transplant evaluation

(HE: hepatic encephalopathy; ICU: intensive care unit)

connection tests, figure connection tests, digit symbol tests), critical flicker frequency, and computerized tests may be used. Patients with MHE may have problems with driving skills and are more likely to progress to overt HE. Treatment of MHE consists of lactulose and/or rifaximin regularly for long term. Treatment steps of hepatic encephalopathy are summarized in **Box 3**.

BOX 3: Treatment of hepatic encephalopathy.

- Supportive care of unconscious or confused patient
- Identification and treatment of concomitant disease
- Careful search for and correction of precipitating factors
- Reduction of ammonia production and absorption:
  - Lactulose, lactitol, lactose orally or in enema form
  - Restriction of dietary protein
  - Disaccharide inhibitors
  - Probiotics
- Promotion of nitrogen excretion:
  - L-ornithine, aspartate IV, and PO
  - Sodium benzoate IV and PO
- Correction of neurotransmitter abnormalities in the brain:
  - Flumazenil
  - Branched-chain amino acid–enriched formulations
  - Zinc replication (many possible modes of action)
- Portosystemic shunt suppression
- Liver support systems
- Liver transplantation

SUMMARY

Chronic liver disease and cirrhosis are progressive disorders with many associated complications. These can be prevented and treated early. Treatment of the basic cause of liver disease is important in delaying decompensation and sometimes reverses fibrosis. Prophylaxis for infections; avoidance of drugs such as proton-pump inhibitors, NSAIDs, nephrotoxic drugs, and sedative-hypnotics; prophylaxis for variceal bleed; and secondary prophylaxis for HE are important to improve the quality of life in these patients. Liver transplantation should be considered in the end-stage liver disease.

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CHAPTER

End-stage Liver Disease

Uday Sanglodkar, Neeraj Mangla

INTRODUCTION

The occurrence of complications in patients with cirrhosis such as jaundice, ascites, encephalopathy, infection, renal dysfunction, or variceal bleeding requiring hospitalization alters the natural history of the disease with an increase in 5-year mortality as high as 40–50%. A significant proportion of these patients with acute decompensation require management in the intensive care unit (ICU) with organ support and have a high rate of in-hospital mortality. End-stage liver disease (ESLD) means that liver function has deteriorated to the point where the damage cannot be reversed other than with liver transplant. We are discussing here the management of these critically ill patients, However, before that, it is important to know few definitions and scoring systems related to the ESLD which will help in risk stratification at the emergency.

DEFINITIONS

Cirrhosis of liver [chronic liver disease (CLD)]: Chronic liver damage from a variety of causes leading to scarring (end stage of fibrosis) and liver failure

Compensated CLD (C-CLD): Patients diagnosed with CLD but asymptomatic in terms of complications such as ascites, encephalopathy, and acute kidney injury (AKI).

Decompensated CLD (D-CLD): Patients diagnosed with CLD, who previously suffered from complications

Acute on chronic liver failure (ACLF): This is the most commonly encountered entity in the emergency department. As per the APASL (Asia Pacific Association of Study of Liver) guideline, it is defined as an acute hepatic insult manifesting as jaundice [serum (S) bilirubin ≥5 mg/dL] and coagulopathy [international normalized ratio (INR) ≥ 1.5] complicated within 4 weeks by clinical ascites and/or hepatic encephalopathy (HE) in a patient with previously known or unknown CLD and associated with a high 28-day mortality.

There are various scores used to define the severity of CLD which also help in prognosticating, such as MELD (model of end-stage liver disease), Child-Turcotte-Pugh (CTP), CLIF-C ACLF (chronic liver failure consortium acute on chronic liver failure), and CLIF-OF (chronic liver failure organ faiure) (**Tables 1** to **3**).

Model for end-stage liver disease (MELD): The original MELD score is a prospectively developed and validated CLD severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the INR for prothrombin time

TABLE 1: Child–Turcotte–Pugh scoring.

Variables	*1 point*	*2 points*	*3 points*
Encephalopathy	None	I–II	III–IV
Ascites	None	Mild	Moderate-to-large
Serum bilirubin (mg/dL)	<2	2–3	>3
Albumin (mg/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged or INR)	<4 sec or INR <1.7	4–6 sec or INR 1.7–2.3	>6 sec or INR >2.3
Child class A = 5–6, Child class B = 7–9, Child class C = 10–15			

(INR: international normalized ratio)

TABLE 2: Chronic liver failure—sequential organ failure assessment scoring.

Organ system	*Variable*	*Score = 1*	*Score = 2*	*Score = 3*
Liver	Bilirubin	<6	6 to ≤ 12	>12
Kidney	Creatinine	<2	2 to <3.5	≥3.5 or RRT
Brain	Encephalopathy grade (West Haven)	0	1–2	3–4
Coagulation	INR	<2	2 to <2.5	≥2.5
Circulation	MAP	≥70	<70	Vasopressors
Respiration	PaO_2/FiO_2 or SpO_2/FiO_2	>300 >357	≤300 >200	≤200 ≤214

(INR: international normalized ratio; MAP: mean arterial pressure; RRT: renal replacement therapy)

TABLE 3: ACLF grading as per the CLIF-SOFA scoring system.	
ACLF grade	***Acute liver damage associated with***
Grade 1	Single kidney failure or liver failure, coagulopathy, circulatory failure, respiratory failure, serum creatinine 1.5–1.9 mg/dL, and/or brains failure with creatinine 1.5–1.9 mg/dL
Grade 2	Two-organ failure
Grade 3	Three or more organ failure

(ACLF: acute on chronic liver failure)

TABLE 4: West Haven criteria: Clinical stages of hepatic encephalopathy.	
Stage	***Features***
I	General apathy
II	Lethargy, drowsiness, altered sensorium, asterixis
III	Hyperreflexia, extensor plantar reflexes, stupor
IV	Coma

to predict 3-month survival. The score is useful for listing the patient for liver transplant (MELD ≥14) and prioritize for the same.

CTP: Epidemiologic work shows that the CTP score may predict life expectancy in patients with advanced cirrhosis. A CTP score of 10 or greater is associated with a 50% chance of death within 1 year (**Table 1**). CLIF-C, sequential organ failure assessment (SOFA) score or (CLIF OF) risk score is given in **Table 2**.

CLIF-C ACLF score: $10 \times [0.033 \times CLIF\ OFs + 0.04 \times Age + 0.63 \times Ln(WBC)\ 2]$.

The above-mentioned score has more impact as compared to others. The European Foundation for the study of chronic liver failure (CLIF-C) ACLF score had the best predictive value for 28-day mortality compared with all other scores.

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Pathophysiology

Mechanisms behind neurological dysfunction, mostly which is caused by HE in hospitalized cirrhotic patients, are varied and are often overlapping with concurrent or precipitating illnesses such as infections and electrolyte abnormalities. Despite the growing understanding of the multifactorial pathophysiology of this disease, ammonia continues to be thought to play a central role. In the brain, ammonia and glutamate are converted into glutamine and the resultant high levels of glutamine then act as an osmolyte, causing astrocyte edema and neuronal dysfunction. Critical care assessment: Severity of HE is given as per West Haven criteria as given in **Table 4**.

Approach and Management for Hepatic Encephalopathy

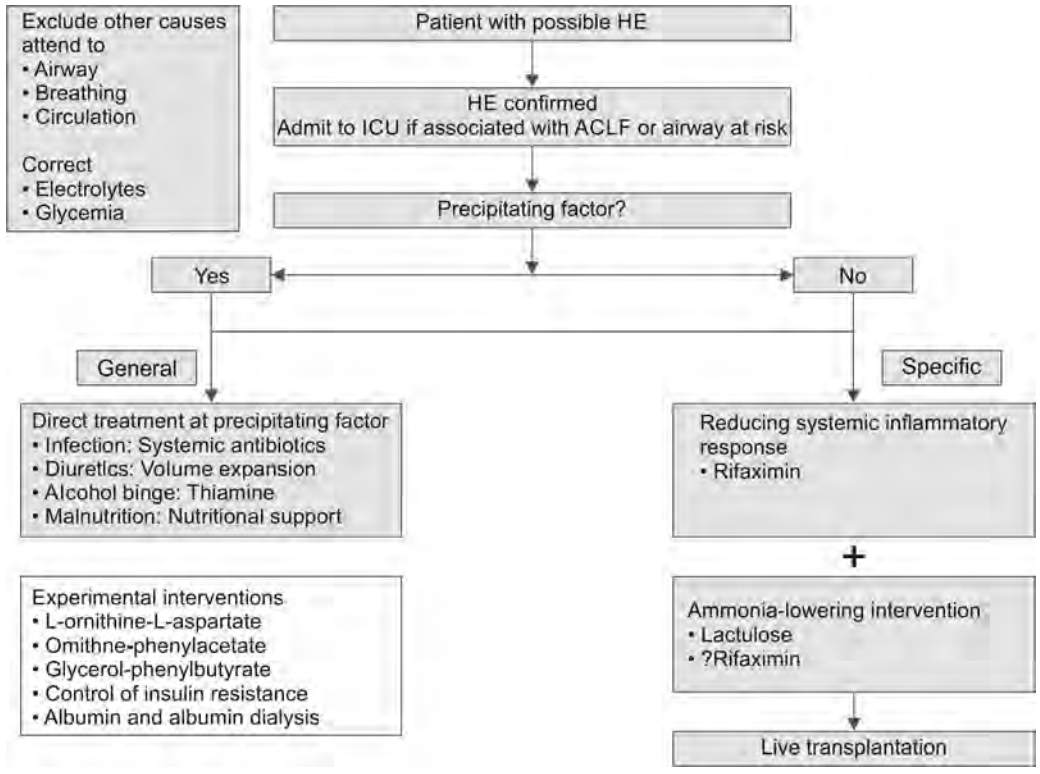
On examination, patients with severe HE may exhibit hyporeflexia or hyper-reflexia, rigidity, myoclonus, ataxia, dilated pupils, and even transient decerebrate posturing. Grading of HE is important in defining the further plan of action. Usually, arterial ammonia level in combination with clinical assessment is recommended in case of doubt of HE. Precipitating factors of HE in ESLD patient are recurrent infections, constipation, electrolyte imbalance, gastrointestinal bleeding and diuretic overdose. ESLD are at high risk for numerous disease state that may cause altered mental status, e.g., sepsis uremia, alcohol withdrawal and intracerebral hemorrhage. As such, an ESLD patient with altered mental status should not be presumed to have HE until other causes have been systematically considered and ruled out.

A patient with grade I or II HE usually does not require airway protection. All patients with grade III or IV HE should be evaluated thoroughly with arterial blood gas (ABG) and ammonia levels. These two parameters usually give an idea about the severity and need of an aggressive treatment such as airway protection. Once the airway is secured, management should be correction of precipitating factors such as dyselectrolytemia, infection, and dehydration. It has been found that early use of lactulose enema and hydration improves encephalopathy. There are various drugs such as rifaximine, L-ornithine L-aspartate (LOLA), and branched-chain amino acids (BCAA) which can be used for early recovery from encephalopathy. Specific points to be remembered in management of HE are as follows (**Flowchart 1**):

- Recognition of the underlying cause of HE and correction of the same should be the primary aim of treatment, e g., correction of dyselectrolytemia.
- Use of lactulose (oral or enema) is highly effective and hence it is recommended. The dose for oral suspension is 30 mL q8h and for enema is 300 mL.
- Serial ammonia monitoring may help in prognosis of HE. Moreover, when the patient is intubated, the response to treatment can be assessed on ammonia levels.
- Other drugs, such as LOLA, BCAA, and zinc, can be used along with the above-mentioned treatment.
- Finally, no response to medical therapy even after correcting the underlying cause is an indication to do electroencephalogram (EEG)/brain imaging and other etiologies should be ruled out.
- Continuous renal replacement therapy (CRRT) is rarely useful in ESLD patients as compared to acute liver failure.

MANAGEMENT OF GASTROINTESTINAL BLEED

The occurrence of GI bleeding in cirrhotic patients is always pointed toward upper GI bleed unless proven otherwise. The incidence of upper gastrointestinal (UG) bleed is 60% amongst all the complications. Patients with CLD usually come to the emergency room (ER) with a history of melena or hematemesis. The history will be short and may refer toward coffee ground vomitus. Most commonly, the source of bleeding is the upper GI tract (i.e., above the second part of duodenum) and is usually related to portal hypertension. The site of occurrence of GI bleed in CLD is 80% variceal and 20% nonvariceal. The most common cause for variceal bleed in cirrhotic patients is increased portal hypertension. The cause for this is severity of liver disease such as MELD



(ACLF: acute on chronic liver failure; HE: hepatic encephalopathy; ICU: intensive care unit)

FLOWCHART 1: Management of hepatic encephalopathy.

>14 or CTP-C. Other causes for bleeding are portal vein thrombosis, development of hepatocellular carcinoma (HCC), infections, etc.

Emergency Critical Care Assessment and Management

In the emergency, one should suspect the GI bleeds if it is not obvious. These patients may have collected altered blood in the stomach which might be too early to manifest as melena or hematemesis. The patient may present with drowsiness, shock, giddiness, or perspiration. There are various clinical criteria to assess for the severity of bleeding and which decide the need of urgent endoscopy and ICU or ward admission and also prognosticate the condition, e.g., clinical Rockall score, Glasgow Blatchford score (GBS), AIMS-65, and T-Score.

Initial assessment and resuscitation–oxygenation. Secure two wide-bore intravenous (IV) lines. If required airway protection IV fluids and blood transfusion packed red blood cells (PRBC), prophylactic antibiotics (ciprofloxacin 400 mg BD or ceftriaxone 1 mg BD), and role of nasogastric (NG) tube placement is controversial. Basic investigations and brief history about known or unknown CLD, past history of similar episodes, latest endoscopy report infection, and medications are required. Drugs used in patients with GI bleed are as follows:

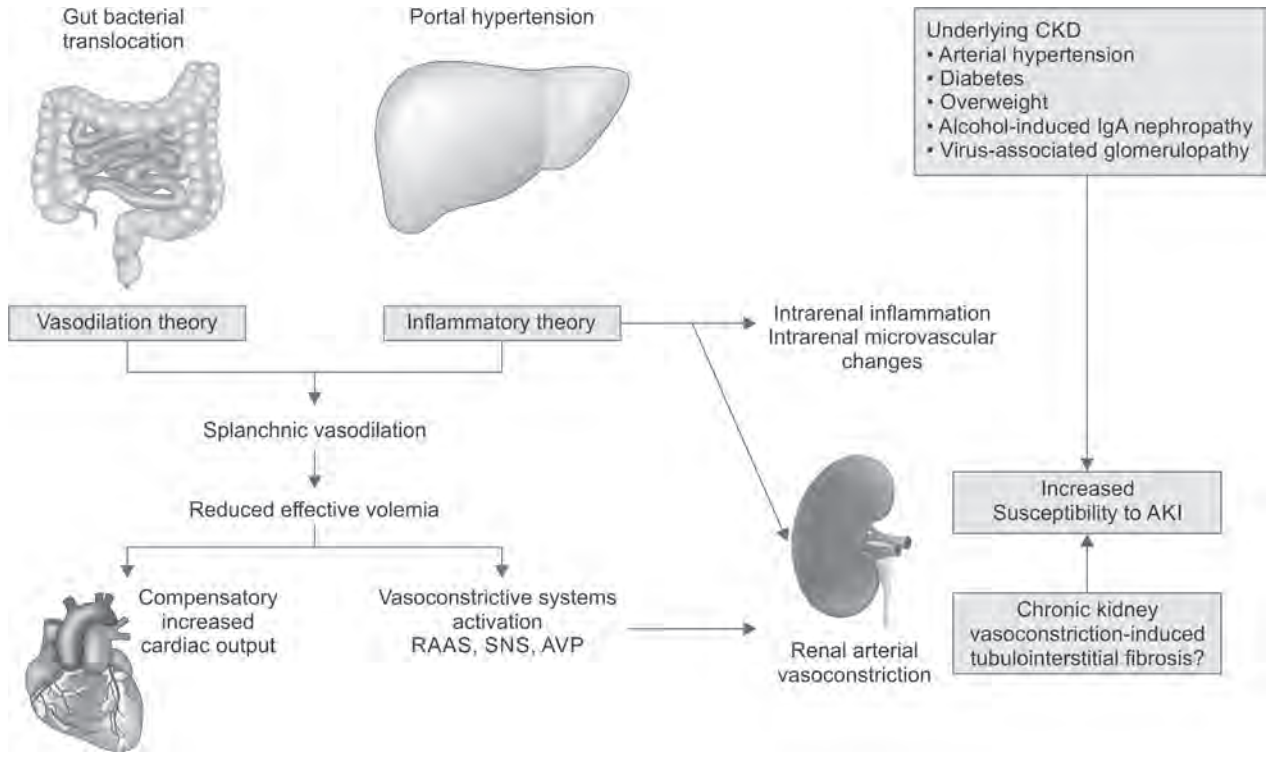
- *Terlipressin* 2 mg q6h [contraindications are coronary artery disease (CAD), peripheral vascular disease (PVD), bradycardia, etc.]

  or
- *Octreotide* 50 μg stat followed by 50 μg/h infusion (as such no obvious contraindications).
- Role of proton-pump inhibitors (PPIs) in variceal bleed is controversial. Still, injectable PPI should be given stat dose till endoscopy is done. 80% of GI bleed are due to varices.
- Endoscopic variceal ligation (EVL)/sclerotherapy/glue 20% nonvariceal—adrenaline injectable/coagulation therapy
- If bleeding is torrential, always insert a Sengstaken–Blakemore (SB) tube as a bridge to further intervention. The primary aim should be reduction of portal pressure.
- Other modalities should be considered when conventional therapy fails such as TIPSS (transjugular intrahepatic portosystemic shunt) or BRTO (balloon-occluded retrograde transvenous obliteration). Vascular surgeries are rarely done nowadays; however, liver transplant is the last resort.

MANAGEMENT OF ACUTE KIDNEY INJURY

Acute kidney injury occurs in 50% of patients who get admitted with cirrhosis, which represents one of the important criteria that defines ACLF and also has the maximum impact factor in the MELD score. The pathophysiology of AKI in CLD is multifactorial (**Flowchart 2**). However, important physiological changes in cardiovascular and the renin–angiotensin–aldosterone system (RAAS) mechanisms are responsible for the same.

The current definition of AKI depends on absolute or relative changes in serum creatinine and urine output. Urine output has been found to be sensitive and an early marker of AKI in ICU patients. There are various criteria or grading systems used for diagnosis of AKI in cirrhotic patients such as acute kidney injury network (AKIN), kidney diseases improving global outcomes (KDIGO), acute dialysis quality initiative (ADQI). Following are various definitions and criteria



(AKI: acute kidney injury; AVP: arginine vasopressin; CKD: chronic kidney disease; SNS: sympathetic nervous system; RAAS: renin–angiotensin–aldosterone system)

FLOWCHART 2: Pathophysiology of acute kidney injury in chronic liver disease.

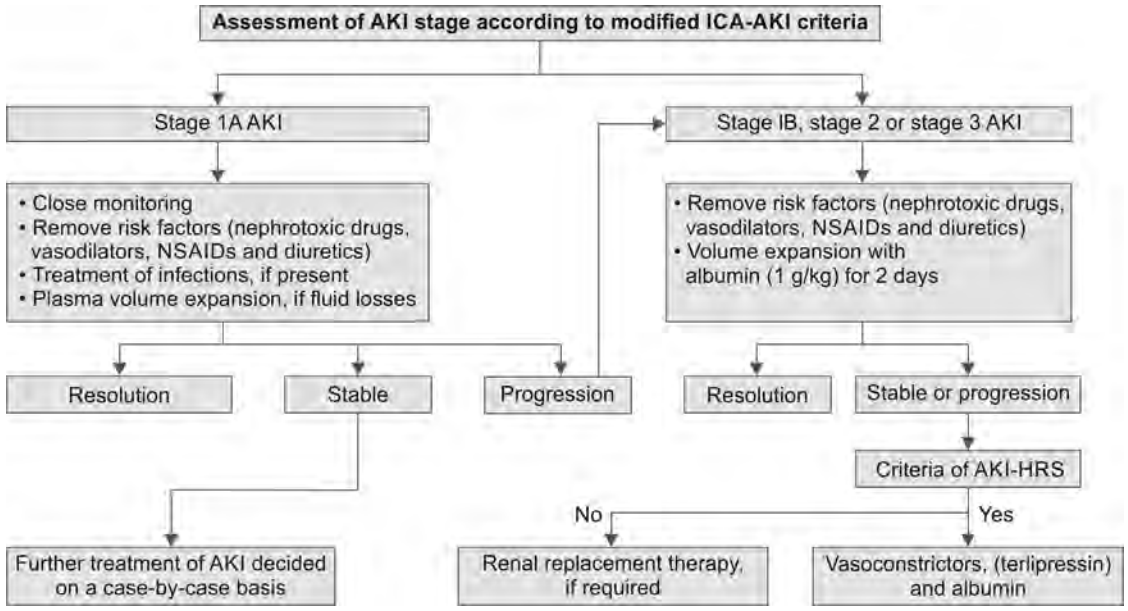
TABLE 5: Definition/Grading/Staging of AKI and HRS.	
RIFLE (2004)	• Increase SCr ≥1.5 times of baseline within 7 days • Or GFR decrease >25% or urine output <0.5 mL/kg/h for 6 h
AKIN (2007)	• Increase SCr ≥0.3 mg/dL within 48 h • Or increase SCr ≥1.5 times of baseline within 48 h • Urine output <0.5 mL/kg/h for 6 h
ADQI (2015) AKI in cirrhosis	• Increase SCr ≥1.5 times of baseline within 48 h • Or SCr percentage increase ≥50% of baseline
ICA-AKI staging	• *Stage 1*: Increase SCr ≥0.3 mg/dL within 48 h • *Stage 2*: Increase SCr 2–3 times of baseline • *Stage 3*: Increase SCr >3 times of baseline
HRS-AKI	• Presence of cirrhosis and ascites • AKI according to ICA-AKI criteria • Absence of shock • No response following 2 days of 1 g/kg albumin volume expansion and diuretics • No signs of structural kidney injury (proteinuria >500 mg/day, microhematuria, and abnormal findings on renal ultrasound)

Note: Baseline SCr: SCr value obtained in the previous 3 months should be used if available; if multiple SCr level is available, value close to admission should be used; if no SCr level is available, admission SCr level should be used.

(ADQI: acute dialysis quality initiative; AKI: acute kidney injury; AKIN: acute kidney injury network; HRS: hepatorenal syndrome; ICA: International Club of Ascites; RIFLE: risk, injury, failure, loss of kidney function, and end-stage kidney disease)

for AKI. Also, there is a specific terminology called hepatorenal syndrome (HRS), the definition of which is also included in the **Table 5**. **Flowchart 3** will help in managing the AKI in CLD hospitalized patients. Specific points to be remembered in CLD patients (recommendations) are as follows:

- Replacement of isotonic crystalloid is recommended in case of volume loss due to diarrhea, overdiuresis, or blood loss in case of GI bleed. Moreover, use of 20–25% albumin in case of infections, HRS, or where etiology of AKI is unclear is strongly recommended.
- To start treatment with vasoconstrictors such as terlipressin, noradrenaline, or combination of octreotide with midodrine. All these drugs to be used with 20%


Assessment of AKI stage according to modified ICA-AKI criteria
Stage 1A AKI
Stage IB, stage 2 or stage 3 AKI
• Close monitoring
• Remove risk factors (nephrotoxic drugs, vasodilators, NSAIDs and diuretics)
• Treatment of infections, if present
• Plasma volume expansion, if fluid losses
• Remove risk factors (nephrotoxic drugs, vasodilators, NSAIDs and diuretics)
• Volume expansion with albumin (1 g/kg) for 2 days
Resolution
Stable
Progression
Resolution
Stable or progression
Criteria of AKI-HRS
No
Yes
Further treatment of AKI decided on a case-by-case basis
Renal replacement therapy, if required
Vasoconstrictors, (terlipressin) and albumin

(AKI: acute kidney injury; HRS: hepato-renal syndrome; ICA: International Club of Ascites; NSAIDs: nonsteroidal anti-inflammatory drugs)

FLOWCHART 3: Steps in management of acute kidney injury in chronic liver disease.

albumin (1 mg/kg on day 1 followed by 20–40 mg/day) in patients with type 1 HRS or persistent AKI.

- Consider as nonresponder to medical treatment when no reduction in serum creatinine happens even after 3 days. Finally, the ultimate treatment option is renal replacement therapy (RRT) like hemodialysis (HD) or CRRT depending on volume status and vitals.

MANAGEMENT OF SEPSIS

Pathophysiology

The risk of infections, especially bacterial infection, is very high in cirrhotic patients because of multiple factors. **Figure 1** depicts the causative factors and pathophysiology of the same. Basically, immune defect facilitates bacterial translocation, induced by increased intestinal permeability and gut bacterial overgrowth. The most common infections in decreasing frequency are spontaneous bacterial peritonitis (SBP), subacute bacterial endocarditis (SBE), respiratory tract infections, urinary tract infections, cellulitis, and others.

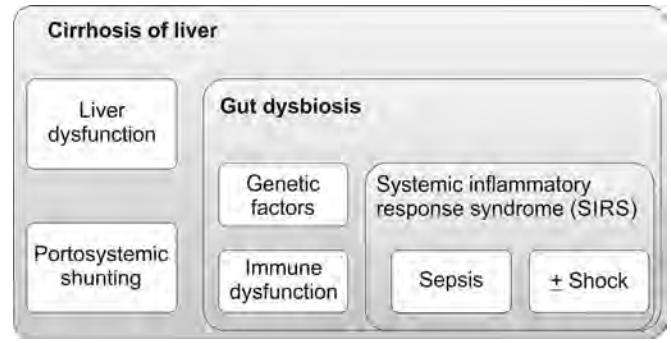
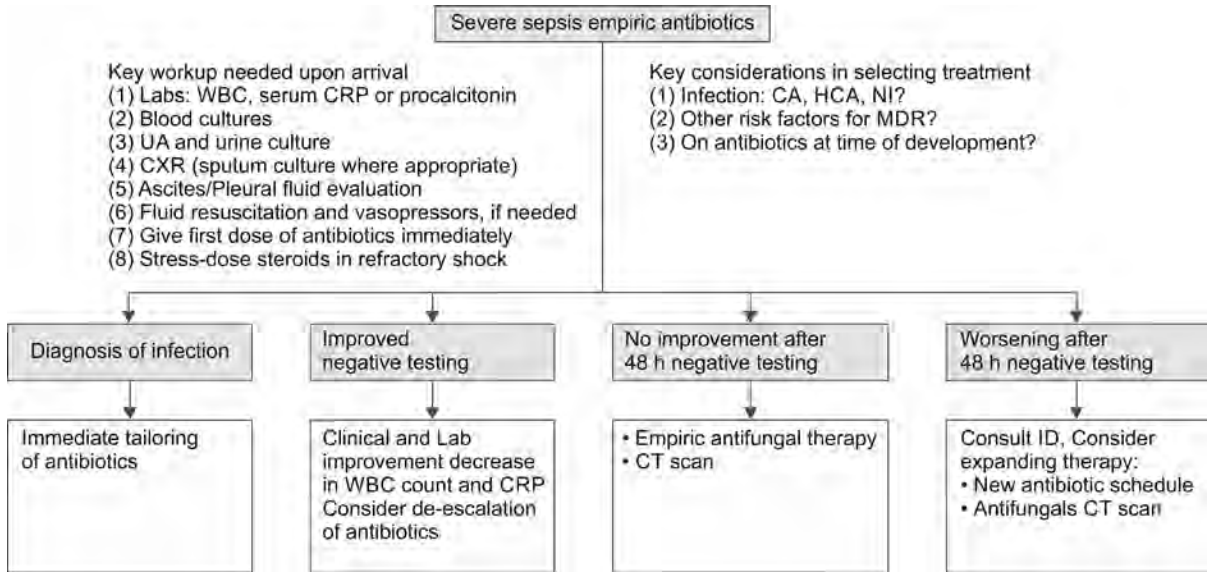


FIG. 1: Pathophysiology of sepsis in chronic liver disease.

Critical Care Assessment and Approach

Sepsis management in CLD is summarized in **Flowchart 4**. Specific points to be remembered in the management of sepsis and SBP are as follows:

- Diagnosis of SBP should be suspected clinically when the patient complains of abdominal pain and/or fever. Also, the presence of AKI should immediately raise a suspicion towards the presence of SBP in selected cases.
- All patients should undergo diagnostic tapping if clinically indicated. Diagnosis is based on the presence of polymorphonuclear (PMN) counts >500 cells/μL in ascitic fluid analysis or culture positivity.
- After the diagnosis of SBP, it should be classified into community acquired (C-SBP), nosocomial (N-SBP), and health care–associated (H-SBP) because it defines the prognosis and helps in selecting the use of antibiotics.
- All patients should be given antibiotics as per hospital policy and sensitivity, e.g., injectable ceftriaxone (third-generation cephalosporin) 1 mg BD is recommended. Also, injectable albumin 20% 1.5 g/kg on day 1 followed by 1 g/kg on day 3 should be given in patients with low creatinine (>1 mg/dL), [blood urea nitrogen (BUN) 30 mg/dL], or bilirubin (>4 mg/dL).
- Primary prophylaxis should be given in those where ascitic fluid total protein <1.5 g/dL and at least two of the following are met: Creatinine ≥1.2 mg/dL, BUN ≥25 mg/dL, serum sodium ≤ 130 mEq/L, or CTP class ≥ 9 with bilirubin ≥3 mg/dL (norfloxacin 400 mg OD).
- Secondary prophylaxis should be given to all patients [norfloxacin 400 mg OD or alternately sulfamethoxazole-trimethoprim (SMP-TMX), ciprofloxacin, or levofloxacin].


Severe sepsis empiric antibiotics
Key workup needed upon arrival
(1) Labs: WBC, serum CRP or procalcitonin
(2) Blood cultures
(3) UA and urine culture
(4) CXR (sputum culture where appropriate)
(5) Ascites/Pleural fluid evaluation
(6) Fluid resuscitation and vasopressors, if needed
(7) Give first dose of antibiotics immediately
(8) Stress-dose steroids in refractory shock
Key considerations in selecting treatment
(1) Infection: CA, HCA, NI?
(2) Other risk factors for MDR?
(3) On antibiotics at time of development?
Diagnosis of infection
Improved negative testing
No improvement after 48 h negative testing
Worsening after 48 h negative testing
Immediate tailoring of antibiotics
Clinical and Lab improvement decrease in WBC count and CRP Consider de-escalation of antibiotics
• Empiric antifungal therapy
• CT scan
Consult ID, Consider expanding therapy:
• New antibiotic schedule
• Antifungals CT scan

(WBC: white blood cell count; CRP: C-reactive protein; UA: urine analysis; CXR: chest X-ray; MDR: multi-drug resistant; CA: community acquired; HCA: healthcare associated; NI: nosocomial infection; ID: infectious disease)

FLOWCHART 4: Approach to management of sepsis in chronic liver disease.

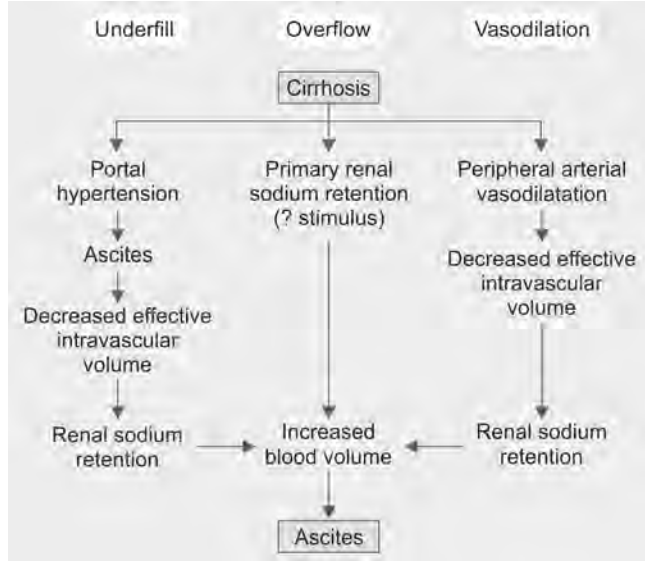
MANAGEMENT OF ASCITES

Ascites is the most common cause of decompensation in cirrhosis and in 5–10% of patients with compensated cirrhosis per year. The mainstay of ascites formation is renal sodium retention due to the activation of sodium-retaining systems, such as the RAAS and the sympathetic nervous system. The resulting positive fluid balance ultimately leads to extracellular fluid volume expansion. Reduced effective volume secondary to splanchnic arterial vasodilation is the main determinant of these alterations. The underfill and overfill theory define the development of ascites (**Flowchart 5**). Grading of ascites is as follows:

Grade 1: Mild ascites—it is only detected by ultrasonography.

Grade 2: Moderate ascites—it is manifested by moderate symmetrical distension of abdomen.

Grade 3: It is characterized by large gross ascites with marked abdominal distension.



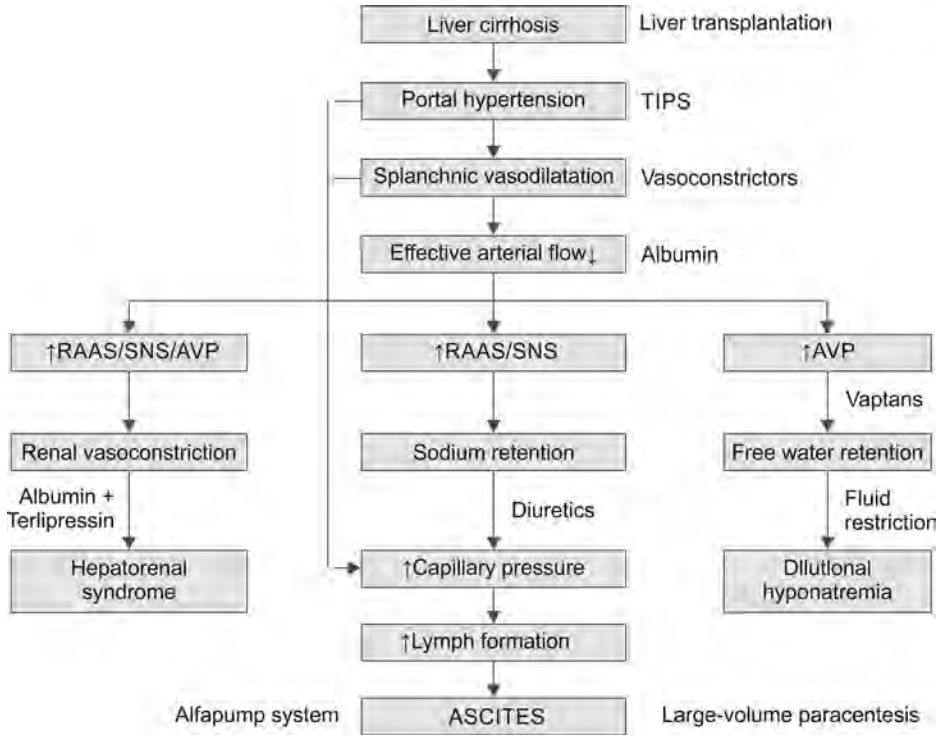
FLOWCHART 5: Underfill and overfill theories of ascites formation in chronic liver disease.

Management of Ascites in End-stage Liver Disease

Once the pathophysiology is understood, it is easier to hit the targets and manage ascites. Various modalities are available in refractory cases such as TIPS, vasopressors, vaptans, and liver transplantation. Management of ascites starts with salt restriction (<5 g/day) that means 1 teaspoon. As per the guidelines, the patient should be started on spironolactone and followed by furosemide if no response. The response is defined as weight reduction of at least 0.5–1 kg in a week. A maximum dose of spironolactone up to 400 mg and furosemide 160 mg is recommended. Finally, those who do not respond to medical therapy need paracentesis. Usually, LVP (large volume paracentesis) is indicated in refractory ascites.

*Management of ascites in Emergency (**Flowchart 6**)*:

- LVP is the first-line therapy in patients with large ascites (grade 3 ascites), which should be completely removed in a single session.
- LVP should be followed with plasma volume expansion to prevent postparacentesis circulatory dysfunction (PPCD).
- In patients undergoing LVP of >5 L of ascites, plasma volume expansion should be performed by infusing albumin (8 g/L of ascites removed), as it is more effective than other plasma expanders, which are not recommended for this setting.
- In patients undergoing LVP <5 L of ascites, the risk of developing PPCD is low. However, it is generally agreed that these patients should still be treated with albumin because of concerns about the use of alternative plasma expanders.
- After LVP, patients should receive the minimum dose of diuretics necessary to prevent reaccumulation of ascites.
- When needed, LVP should also be performed in patients with AKI or SBP.



(AVP: arginine vasopressin; RAAS: renin–angiotensin–aldosterone system; SNS: sympathetic nervous system; TIPS: transjugular intrahepatic portosystemic shunt)

FLOWCHART 6: Pathophysiological rationale for the treatment of patients with ascites and other related complications.

MANAGEMENT OF HEPATIC HYDROTHORAX

It is defined as transudative pleural effusion in patients with decompensated liver disease that is not secondary to cardiopulmonary failure, renal failure, malignancy, or another primary process. It occurs in 5–10% of patients, usually right-sided (85%), left-sided (13%), and bilateral (2%). Similar to SBP, bacterial translocation may cause infection in the pleural fluid which is called SBE. Usually, patients are asymptomatic due to chronicity and customization to ascitic fluid. However, if hepatic hydrothorax is moderate to severe, e.g., fluid quantity >500 mL, it may cause symptoms such as breathlessness and tightness of chest. On examination, the patient might have tachypnea, tachycardia, and hypoxia-reduced air entry on auscultation. Fever and pain should suspect toward the development of SBE. Usually, 50% of patients will have ascites at the same time. Assessment should start with SpO_2 monitoring, ABG, and X-ray of chest in the emergency to decide the severity and admission to ward or critical care unit.

Management of Hepatic Hydrothorax

Usually, management guidelines to be followed for hepatic hydrothorax are similar to that of ascites. In the ER, one should assess the quantity of fluid; if it is moderate to or severe, one should plan for tapping (thoracentesis). Treatment options may include TIPS, pleurodesis, or liver transplantation in refractory cases.

Management of hydrothorax in emergency:

- Patients who are severely symptomatic should undergo therapeutic thoracocentesis.
- Care should be taken to limit fluid removal to 1–2 L on initial thoracentesis, owing to concerns of precipitating negative pressure pulmonary edema or even HRS.
- For each 1 L of fluid drained, albumin 100 mL (20%) should be replaced slowly to prevent re-expansion pulmonary edema or HRS.
- Patients presenting with SBE should be administered ceftriaxone 2 g every 24 hours, with levofloxacin as an alternative agent in penicillin-allergic patients.
- Occasionally, chest tube placement may be necessary in patients with SBE with frank pus or loculations; however, chest tubes should not be placed routinely for the treatment of hepatic hydrothorax.
- Chest tube placement in these patients can result in massive protein and electrolyte losses, and there is no clear endpoint for chest tube removal because of continuous reaccumulation of fluid.
- Chest tube placement in ESLD patients with hepatic hydrothorax has been associated with numerous complications including infection, renal failure, empyema, bleeding, and an increased risk of death.

LIVER TRANSPLANTATION IN CRITICALLY ILL ESLD PATIENTS

Liver transplantation remains the ultimate cure for critically ill ESLD patients. However, risk and benefit should be

weighed before advising the liver transplant. Most of the times, these patients are critically ill and if transplant is considered, the morbidity and mortality intraoperatively and postoperatively are very high. Those patients who have an ACLF (grade 1 or 2) like scenario as mentioned earlier in this chapter might benefit if transplanted early in the course of disease. However, the most common complications of ESLD such as sepsis, AKI, refractory HE, severe sarcopenia, and poor nutrition are responsible for refuting the patients for transplantation.

SUMMARY

The knowledge of the key pathophysiologic mechanisms makes it possible nowadays to counteract the progression of cirrhosis and thus to prevent its complications. ESLD is a syndrome associated with multiorgan/system failure(s) (liver, kidney, brain, coagulation, circulation, and/or respiration) and with extremely poor survival. These patients often require ICU care. Critical care assessment in emergency and management of these patients cautiously might help in bridging the gap for liver transplantation which is a definitive cure for ESLD patients.

MULTIPLE CHOICE QUESTIONS

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101 CHAPTER

Liver Transplant and Related Complications

Amit Ganguly

INTRODUCTION

Liver transplant has evolved from an experimental procedure to a curative procedure for end-stage liver disease (ESLD). From the first paper published by Starzl et al. which had 5 cases to 1,400 cases in India alone in 2014, liver transplant has come a long way. While various complications of portal hypertension such as variceal bleed, ascites, and encephalopathy can be managed medically, endoscopically, or by radiological interventions, liver transplant remains the only curative option, which aims to restore normal physiology.

INDICATIONS

Indications for liver transplant can be easily summarized as follows:

- Where the estimated survival of the patient is <1 year because of liver disease
- Quality of life is unacceptable because of liver disease

However, it is often difficult to assess these in many patients; therefore, more objective criteria were sought. Two such scoring systems which are often used are Child–Turcotte–Pugh and MELD (Model for End-stage Liver Disease) score, respectively. Computed tomography perfusion (CTP) has been in use for assessment of liver function. But it has subjective criteria (e.g., ascites and encephalopathy). The MELD score, on the other hand, is based on the mathematical regression model, which takes serum creatinine, international normalized ratio (INR), and serum bilirubin into consideration. Thus, it is more objective and dynamic. It has been validated as a predictor of 3-month mortality for chronic liver disease (CLD) as per the allocation criteria for deceased donor liver transplantation (DDLT) proposed by the National Organ and Tissue Transplant Organization (NOTTO). The MELD score of <15 is a contraindication for liver transplant. Few common indications are described below.

Chronic Liver Disease

In an Indian setup, the most common indications for transplant in adult are ESLDs related to hepatitis C and B, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD).

Viral hepatitis-induced ESLD remains one of the most common indications for transplant. In cases of hepatitis C-related CLD, it is essential to know the viral load and genotype as this helps in predicting the prognosis after transplant. Antiviral drugs and pegylated interferon are often started before transplant to decrease the chances of recurrence of disease in graft. However, these patients have high chances of recurrence.

The outcome of hepatitis B-related CLD has improved with the availability of hepatitis B immunoglobulin (HBIg) and antiviral drugs. Reinfection of graft is rare, though the duration of treatment is still controversial.

Liver transplant for alcoholic liver disease is offered to the patient who is abstinent for a period of 3–6 months. It is believed that a patient who has been abstinent for a particular period is less likely to suffer from recidivism and thus will have a good outcome. Survival rates are similar to any other cirrhotic patients. The role of transplant in patients with alcoholic hepatitis is controversial, with few centers offering transplant.

In India with a large diabetic population, *CLD secondary to NAFLD* is emerging as an important indication for transplant.

Transplant for hepatocellular carcinoma in the presence of cirrhosis definitively provides survival benefits. It is not only curative but also decreases the chances of recurrence as the cirrhotic liver is replaced by healthy liver. Most of the centers are expanding the criteria for transplant, from the Milan criteria to the University of California San Francisco (UCSF) criteria. The UCSF criteria is also accepted by NATTO. These patients may need priority points as their MELD scores may be low.

Cholestatic liver diseases, such as *primary biliary cirrhosis (PBC)* and *primary sclerosing cholangitis (PSC)*, are other indications where quality of life issues such as repeated cholangitis, intractable pruritus, and bone diseases are the indications for transplant. In pediatric population, biliary atresia is a common indication for transplant.

Metabolic diseases which cause irreversible damage and decompensation are an indication for transplant. There is a long list of diseases which can be corrected by liver transplant including *Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency*. Transplant for vascular conditions such as Budd–Chiari syndrome should be considered when portal

decompensation has failed and cirrhosis with decompensation is well established.

Other uncommon indications for transplant include *complicated polycystic liver disease* (with or without kidney disease) and *Caroli's disease.*

Acute Liver Failure

Fulminant liver failure is characterized by encephalopathy, coagulopathy, and jaundice. Common causes of acute liver failure (ALF) in an Indian setting are viral hepatitis (hepatitis A, B, and E), idiosyncratic drug-induced liver injury, and indigenous medications administered for a variety of different etiologies. Antitubercular drug-induced ALF seems to have worse outcomes than hepatitis E, which is a common cause for ALF in India. In the western population, acetaminophen toxicity is a common cause for ALF. Timely identification and referral for transplant are essential in these cases, otherwise the patient may succumb to sepsis and cerebral edema. There are many different scoring systems, e.g., King's college criteria, for urgent transplantation in these patients. The chance of these patients getting an organ in emergency in absence of robust brain-dead declaration and organ donation drive often leaves living donor liver transplant (LDLT) the only likely option.

CONTRAINDICATIONS

Absolute contraindications for liver transplant are as follows:

- Severe cardiopulmonary disease
- Extrahepatic malignancy
- Uncontrolled systemic sepsis originating from a source other than liver
- Active substance abuse

Other relative contraindications are advanced age (>70 years), uncontrolled human immunodeficiency virus (HIV) disease, and diffuse thrombosis of vein.

BRAIN DEAD DONOR AND OPTIMIZATION

An ideal donor is a young, hemodynamically stable patient who is pronounced brain dead. Most of these patients are victims of road traffic accidents. After two separate brain stem death declarations at an interval of 6 hour, the process of organ retrieval is started.

Brain death induces multiple physiological responses in the body, mostly because of dysfunction of the hypothalmo–pituitary axis. As the time of organ procurement from declaration of brain dead increases, there is a possibility of loss of potential donor. While waiting for organ donation, these patients should be carefully managed in the intensive care unit (ICU) in consultation with an intensivist. The cardiorespiratory support is continued so as to maintain sinus rhythm with adequate blood pressure with a mean arterial pressure (MAP) of 60–80 mm Hg. Respiratory targets are to maintain pH of 7.35–7.45, with minimum FiO_2, to have partial pressures of oxygen (PaO_2) >100 mm Hg, oxygen saturations >95%, and partial pressure of carbon dioxide ($PaCO_2$) 35–40 mm Hg. Hypothermia is to be avoided. Hemoglobin is to be maintained at >9 g/dL and if coagulation is deranged, then it should be corrected with fresh frozen plasma (FFP)/platelets. Some other physiological derangements and their management are listed in **Table 1**.

TABLE 1: Correction of physiological derangement.

Hypovolemia	***Corrected with isotonic crystalloid fluid***
Hypotension	Volume correction and use of dopamine and vasopressin
Diabetes insipidus ($Na^+ > 155$)	Desmopressin
T3 deficiency	Thyroid supplementation
Failure of hypothalamic-pituitary-adrenal axis	Low-dose steroids
Hyperglycemia	Insulin

LIVER TRANSPLANT PROCEDURE

The standard liver transplant involves removal of the entire liver from a brain-dead donor and placement of it at the place of native diseased liver which is removed, hence the word orthotopic liver transplant. Most of the centers preserve native inferior vena cava (IVC; piggyback technique), and donor suprahepatic cava is anastomosed with recipient IVC, following which portal vein, hepatic artery, and bile duct are reconstructed end to end. In most the European countries, deceased donor liver transplant accounts for majority of cases.

However, in many Asian countries including India, due to lack of organ donation, living donor transplant accounts for a greater number of cases. This involves removal of the right lobe of liver (VI–VIII) from a healthy donor after workup and implanting it. The minimum size of the graft required is 8% of the recipient to ensure viability of graft and patient. In comparison to DDLT, LDLT requires meticulous right hepatectomy on a healthy, voluntary donor and more demanding reconstruction on the recipient. It also exposes a healthy donor to the morbidity and mortality of major hepatectomy. For a pediatric patient, a left lobe graft (I–IV) can be used, which is less morbid for the donor.

COMPLICATIONS OF LIVER TRANSPLANT

Primary Nonfunction

The exact etiology is not clear; it is most probably multifactorial without any technical complications. The clinical presentation is altered sensorium with diminished bile production, coagulopathy, elevated transaminases, and acidosis. Multiorgan failure occurs and in the absence of pretransplant the outcome is poor. Some of the factors identified are increased cold and warm ischemia time, donor steatosis, intraoperative hypotension, and renal failure in the recipient.

Vascular Complications

Arterial: Hepatic artery thrombosis occurs between 1 and 7% of cases. The common presentation is graft dysfunction. This needs immediate either radiological intervention, revascularization, or retransplant.

Venous: Outflow obstruction due to stenosis of IVC anastomosis is rare with the piggyback technique.

Portal vein thrombosis is also more common in a patient who has a past history of partial or complete thrombus in the

portal vein; however, it can occur in patients with no previous history also.

Biliary: Bile leaks and biliary stricture are the common biliary complications.

- *Ischemic type*: These are due to because of hepatic artery thrombosis, ischemia-reperfusion injury, or ABO incompatibility. These present with diffuse intrahepatic strictures, producing a beaded appearance along with stenosis and dilatation. The clinical presentation is with pruritus and recurrent cholangitis. These may need retransplant.
- *Anastomotic type*: These are often associated with surgical technical issues and bile leak. The first line of management is often endoscopic retrograde cholangiopancreatography (ERCP) with balloon dilatation with endoprosthesis.
- *Associated with partial graft*: Anastomotic strictures are more common with patients undergoing a live donor or split graft. One of the factors proposed for this increased incidence is the size of the duct, which is smaller.

Infections in Liver Transplant

Infections are one of the most common causes of death in liver transplant, which is understandable as these patients are immunosuppressed, malnourished, and have undergone major complex surgical procedures. These can occur immediately postoperatively or subsequently after discharge from the hospital. A brief list of infections and their causing organisms are mentioned in **Table 2**.

IMMUNOSUPPRESSION AND REJECTION

Post liver transplant immunosuppression is in many ways similar to other solid organ transplant except that liver recipients are maintained at lower dosage. Liver transplant does not require human leukocyte antigen (HLA) typing between the host and donor. The long-term aim is to have decreased rejection episodes and also to avoid infection, malignancy, and other side effects of these drugs. The commonly used drugs postoperatively are as follows:

- *Corticosteroid*: It remains the mainstay of treatment. It is used for both induction and treatment of rejection. It is started during the hepatic phase and continued postoperatively.
- *Calcineurin inhibitor (CNI)*: Introduction of cyclosporine in the 1970s improved the long-term survival of liver transplant. Along with tacrolimus (TAC), it has considerably improved the results of transplant. Because of its excellent graft-protecting function, TAC is used by most of the transplant centers and started early to achieve TAC trough level between 5 and 10 ng/dL. Cyclosporine is no longer the first choice among CNIs.
- *Mycophenolate mofetil*: Introduced in the 1990s, this immunosuppressive drug is used in combination with TAC. It is a purine synthase inhibitor with antiproliferative activity against T and B cells.
- *Azathioprine*: It is another purine synthase inhibitor. The use of antimetabolite drugs [mycophenolate mofetil (MMF) and azathioprine (AZA)] has increased due to the need to decrease the dose of CNI, which causes nephrotoxicity. The immunosuppression regimen needs to be tailored for renal impaired patients, hepatitis C virus (HCV) transplanted patients, and patients showing signs of rejection.

Three types of rejections are known following liver transplant:

1. *Hyperacute*: It is rarely seen today. It typically occurs in the setting of ABO incompatibility. It is mediated by preformed antibodies in the recipient.
2. *Acute*: It usually occurs within the first 4 weeks of transplant. It is often detected by raised transaminases. Biopsy is needed to establish the diagnosis, which shows portal inflammation with mononuclear cells, bile duct inflammation and injury, and centrilobular necrosis and lobular inflammation. Treatment consists of bolus dosage of corticosteroid. Steroid-resistant rejection is treated by antithymocyte globulins (ATGs) after review of liver biopsy.
3. *Chronic*: It is multifactorial. It is characterized by progressive loss of bile duct, obliteration of small- and large-sized arterioles, and cellular portal infiltration.

The prevalence of both acute and chronic rejection has been declining steadily with the advent of new immunosuppressive drugs. Acute rejection is seen in 15–30% of cases. This can be treated with increasing immunosuppression. In contrast, chronic rejection (ductopenic) can result in graft loss.

TABLE 2: Common infections related to liver transplant and recommended treatment.

Bacterial	***Gram-negative bacilli Gram-positive cocci (vascular catheter-related)***	***Routine use of broad-spectrum antibiotics Culture-based antibiotics***
	Another bacteremia—pneumonia, biliary, and wound infections	
Viral	• Cytomegalovirus (CMV) • Epstein–Barr virus	Ganciclovir
Fungal	• *Candida* • *Aspergillus/Cryptococcus*	• Fluconazole routinely • Culture-based
Protozoal	*Pneumocystis carinii*	Trimethoprim + sulfamethoxazole

OUTCOME

The results of liver transplant have improved worldwide. The majority of death occur within the early postoperative period. Infections and intra- or postoperative complications are the cause of death or graft loss in 60% of cases in the first year. In long-run cardiovascular diseases, renal failure, infection, and de novo malignancy are other important causes of death. Survival after transplant for fulminant liver failure remains below average.

In most high-volume centers, 1- and 5-year survival rates are close to 90% and 70%, respectively. Some paper has reported 10-year survival close to 60%. In patients with HCV and hepatocellular carcinoma (HCC) recurrence of disease does affect long-term survival, while those patients transplanted for biliary atresia have 10-year survival >75%.

SUMMARY

Despite the rapid strides made in the field of hepatology, liver transplant still remains the final solution to the large number of patients with ESLD. The progress made in the field of immunosuppression, better perioperative care, and refined anesthetic and surgical skills all have greatly contributed to the improved outcome.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Bowel Obstruction

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INTRODUCTION

Bowel obstruction is defined as the impairment of passage of intestinal content. It is classified according to a couple of characteristics that are the site of obstruction, the degree of obstruction, and the presence of irrigation impairment (ischemia). The sites of obstruction in general terms are the small bowel and the large bowel, which have an additional subclassification, which can be extrinsic or intrinsic (intraluminal and intramural). The degree of obstruction can be either partial or complete. In a partial obstruction, there is still some passage of intestinal content and gas which could result in constipation; in a complete obstruction, there is no passage of intestinal content and the patient might present with obstipation (incapability of passing gas or stool). We can further classify bowel obstruction on its peristaltic characteristics (dynamic or adynamic). When the obstruction is nonmechanical or adynamic, there is an impairment in the transmission of neuromuscular innervation to the myenteric plexus, which results in paralytic ileus (aperistalsis) and colonic pseudo-obstruction. Dynamic obstruction occurs when there is a mechanical obstruction of the bowel lumen, which impairs peristalsis functionality. These obstructions can be extrinsic or intrinsic (intraluminal or intramural) as determined earlier. It can be challenging to establish a diagnosis due to unspecified symptomatology, radiological, and laboratory results. Learning these classifications can help to identify these differences which have an important outcome in decision-making regarding treatment choices. Mechanical obstruction will be widely discussed in this chapter.

ETIOLOGY

Bowel obstruction can be classified according to their etiology as being intrinsic (intraluminal, intramural) and extrinsic (**Table 1**). The location and onset of obstruction guide us toward a specific etiology; it is important to determine if the obstruction is in the small or large bowel to be able to establish a precise diagnosis. Postoperative adhesions are the most common etiology of small bowel obstruction (SBO) in 60–85% of cases approximately, followed by hernias in 30% cases which result in surgery due to incarceration and obstructive malignancy. The large bowel is most frequently obstructed by a malignant etiology; rectosigmoid tumors are the most common manifestation of these; the benign etiology that obstructs the large bowel more frequently is the presence of sigmoid volvulus, followed by a stricture because of diverticulitis. Other causes of large bowel obstruction (LBO) are presented in **Box 1**.

TABLE 1: Causes of small bowel obstruction.

Intraluminal lesions	• Intussusception • Gallstones • Congenital atresia, duplication, and congenital bands • Neoplasm • Parasites • Bezoars • Foreign body • Strictures due to NSAID enteropathy • Feces • Meconium • Food bolus
Intramural lesions	• Neoplasm • Hematoma • Crohn's disease • Postoperative stricture ring • Radiation enteritis
Extrinsic lesions	• Adhesions (congenital and acquired) • Hernia (congenital and acquired) • Volvulus • Endometriosis • Carcinomatosis • Superior mesenteric artery syndrome • Abscess

(NSAID: nonsteroidal anti-inflammatory drug)

BOX 1: Causes of large bowel obstruction.

- Neoplasm (colorectal cancer)
- Adhesions
- Strictures (diverticular disease, ischemic colitis, Crohn's disease)
- Volvulus (sigmoid volvulus)
- Hernia
- Fecal impaction
- Inflammatory bowel disease
- Bezoars
- Intussusception
- Gallstone ileus
- Endometriosis

PATHOPHYSIOLOGY

Small bowel obstruction occurs when there is a blockage of its lumen, preventing the normal passage of intestinal content through the bowel, impairing its normal functionality. When this happens, the small bowel starts to dilate proximal to the site of obstruction provoking bacterial accumulation and fermentation. Swallowed air, gas, and bacterial fermentation lead to intestinal distention, bowel wall edema, and loss of absorptive function; translocation of bacterial fermentation may lead to sepsis. As this process continues, there is loss of electrolyte-rich fluid by emesis and transudation, this may result in metabolic alkalosis and hypovolemia. Continued bowel distention leads to vascular compromise, loss of perfusion, ischemia, and eventually necrosis and perforation.

Large bowel obstruction occurs in 60% of cases because of a neoplasm. Tumors that tend to cause obstruction with greater frequency are those located at the splenic flexure. Ischemia, necrosis, and perforation in LBO occur due to an inflammatory reaction provoked by tumor invasion. The ileocecal valve plays an important role in the physiopathology of LBO, when the ileocecal valve is competent and a closed-loop obstruction (presence of two obstruction sites) occurs due to the incapability of decompression of the bowel, resulting in ischemia or necrosis.

CLINICAL PRESENTATION

The clinical presentation of SBO and LBO differ slightly from one another, and its symptomatology varies depending on the onset of instauration. These differences will be explained in **Table 2**.

Careful evaluation of symptomatology progress must be done; abdominal pain can evolve from being an intermittent cramping pain to a constant and more severe pain, which might indicate clinical complications such as ischemia and perforation. Nausea and vomiting might be more severe in patients with a proximal SBO and abdominal distention might be minimal. In distal SBO, vomiting might be infrequent and abdominal distention important. Most concerning features (red flag) are shown in **Figure 1**.

TABLE 2: Clinical presentation of small bowel and large bowel obstruction.

Small bowel obstruction (SBO)	*Large bowel obstruction (LBO)*
Acute onset: • Periumbilical pain (colicky, cramping) • Nausea • Vomiting • Abdominal distention • Obstipation	*Acute onset*: • Hypogastric pain • Abdominal distention • Obstipation • Diarrhea • Rectal tenesmus • Rectal obstruction • Nausea and vomiting (may or may not be present)
Chronic onset: Develop same symptomatology of acute onset SBO, but with varying severity	*Chronic onset*: • Weight loss • Weakness • Anorexia • Rectal bleeding • Develop same symptomatology of acute onset LBO, but with varying severity

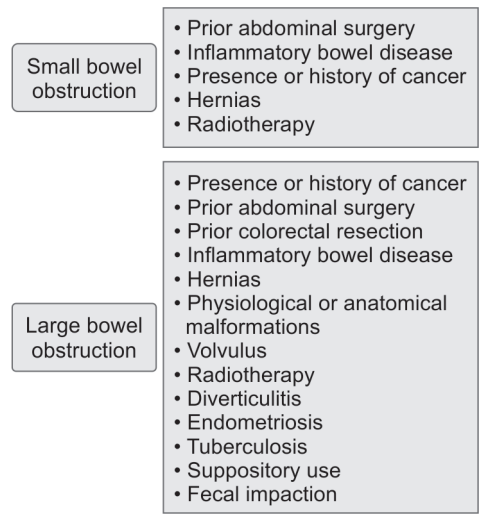


FIG. 1: Most concerning clinical features: "Red flag" bowel obstruction.

EVALUATION: HISTORY AND PHYSICAL EXAMINATION

History

Performing a complete medical history is a crucial step to meet to obtain sufficient information that leads us to an accurate diagnosis. Even though a thorough medical history is necessary, if a patient arrives in the emergency room, there are five main clinical features we should always have in mind. These are the (1) presence of abdominal pain, (2 and 3) constipation/obstipation, (4) abdominal distension, and (5) vomiting. Acknowledging if the patient has had a previous surgical procedure is of equal importance.

Abdominal Pain

When carrying out a physical examination in a patient with abdominal pain, careful attention must be paid to the location and onset of pain. Abdominal pain is the most common complaint. SBO pain usually is in the periumbilical area and is described as a colicky or cramping pain which is generally of severe and acute instauration. In LBO, hypogastric pain is frequently present and generally described as a cramping pain which recurs every 20 minutes approximately. When there is a closed-loop obstruction in LBO, pain can be constantly increasing. In any of these cases, if pain becomes constant and fixed in a specific area the possibility of ischemia or perforation is greater.

Constipation/Obstipation

These clinical manifestations might be present in SBO and LBO, although they are generally indicative of a LBO. Incapability to pass gas or stool might be present in an acute onset of LBO and usually occurs in a distal obstruction. Past surgical history should be acquired as well as changes in intestinal functioning or unprogrammed weigh changes in the last few months.

Abdominal Distension

Once the obstruction develops, peristaltic activity increases in an effort to release the blockage; this process continues until intestinal motility starts to decrease due to relaxation of the bowel wall and dilation. This should be considered, since changes in peristaltic motility might be indicative of ischemia, necrosis, and perforation. In both SBO and LBO, abdominal distension is present, although usually greater in LBO, since vomiting helps alleviate this manifestation in SBO.

Vomiting

Vomiting might appear in both SBO and LBO, even though it is more frequently present in SBO as an early onset manifestation. The characteristics of the vomit are an important clue toward finding out the site of obstruction. Unprocessed food usually indicates a proximal SBO and feculent vomit is generally indicative of a distal obstruction.

Physical Examination

A thorough physical examination should always be performed. In bowel obstruction, even though there are similar physical manifestations between SBO and LBO, paying close attention to these and other systemic features are imperative for an optimal diagnosis and treatment choice. Vital signs should be monitored. The presence of fever might be indicative of an infection or other systemic complications. Heart rate monitoring is important since vomiting in SBO is usually present and this could lead to dehydration, tachycardia, hypotension, and oliguria. Abdominal inspection is a key step, since in its fulfillment we might be able to find some previous surgery marks that could guide us toward the diagnosis. Abdominal auscultation should also be considered; in an acute onset bowel obstruction, as previously mentioned, peristalsis might be increased and accompanied by a hyper-resonant percussion differing from a chronic process in which peristalsis and percussion might be absent or hypoactive. During abdominal palpation, we can be able to identify abdominal masses such as tumors or hernias that could be provoking the symptomatology. A rectal examination should be performed to evaluate rectal obstruction that might be caused by fecal impaction.

Interpretation of Finding

- Persistent and increasing abdominal pain—might be indicative of a closed-loop obstruction or/and ischemia, necrosis, or perforation
- Increased peristalsis—may indicate an early or recent obstruction
- Decreased or absence of peristalsis—may indicate ischemia, necrosis, or perforation
- Persistent and increasing abdominal distension—the presence of LBO must be evaluated
- Active vomiting—could be a sign of early proximal SBO
- Bilious vomiting—main manifestation of intestinal malrotation and duodenal duplication cyst
- Feculent vomiting—might be indicative of a distal obstruction
- Presence of fever—systemic complication, bacteremia, sepsis
- Oliguria, hypotension, and tachycardia—may be found in dehydrated patients due to constant vomiting in SBO
- Rectal obstruction—might be due to fecal impaction.

INVESTIGATIONS

After a general examination has been achieved, special attention should be paid to the abdominal (inspection, auscultation, percussion, and palpation) and digital rectal examination. A full cardiovascular evaluation is recommended; blood pressure, pulse and capillary refill time should be considered. To detect or prevent the presence of systemic inflammatory response syndrome (SIRS), the body temperature and respiratory rate must also be monitored.

Laboratory Studies

Complete blood count with differential, electrolytes, blood urea nitrogen (BUN), creatinine, amylase, arterial blood gas, serum lactate, and blood cultures (if systemic features) should be done.

Imaging Studies

Plain Radiography (X-ray)

Because of its practical use, easy availability, and low cost, it is preferred as the first evaluation diagnostic tool. It can help determine whether an emergent procedure should be performed or not, and it can also help in evaluating the location and type of obstruction (partial or complete).

A plain supine abdominal radiography and an upright chest film should be done. Findings include:

- Small dilated bowel loops that can be indicative of a LBO with an ileocecal valve that is incompetent in about 30% of cases. A dilated colonic diameter above 8 or 10 cm or more dilation of the cecum is considered pathological
- If there is a dilation of the proximal bowel (>2.5 cm) with collapse of the distal bowel, it might be indicative of SBO
- An abdominal radiograph that shows a gasless abdomen might be indicative of a small bowel that is fluid-full. The sign of "*string of pearls*" might be present

- If volvulus is present, pneumoperitoneum, "*northern exposure and coffee bean signs*" might be present in LBO
- In an upright chest film, hydroaerial levels are found in the same levels in adynamic obstruction (paralytic ileus) while in mechanical obstruction these appear at different intestinal levels.

Multidetector Computed Tomography Scan

Multidetector computed tomography (MDCT) scan can find the cause of obstruction in approximately 70–95% of cases and determine the specific location of the obstruction and evaluate any other masses that might be present. Performing a CT scan using contrast might be useful, but not essential, since retained fluid in the bowel can help function as contrast. Contrast imaging might be done by administering oral or rectal contrast; a nasogastric tube can also be used. Intravenous contrast is another possibility although renal pathology patients are not candidates. Some findings obtained can be the presence of submucosal hemorrhage and/or edema, thickening of the abdominal wall, and ascites. A CT scan can also contribute in finding specific signs related to the diagnosis. For example, in volvulus a "whirlpool sign" might be found in SBO, while in LBO there might be a separation of the sigmoid wall which is described as a "split-wall" sign and "X marks the spot" which is found when there are two transition points present; in intussusception, there is a "target sign" and the "cut-off sign," which is found in thrombosis. In a study made in 62 patients with bowel obstruction, it was found that the use of a CT scan for determining the site of obstruction was accurate in 91.9% of cases, while an abdominal ultrasound predicted it accurately in 82% of cases and a plain abdominal radiograph in 90.3%, thus concluding that an abdominal CT scan is the most effective tool for obstruction location.

Ultrasonography and Magnetic Resonance Imaging

These diagnostical imaging approaches are not the best tools for diagnosis of bowel obstruction. These imaging options are used in pregnant women and children.

TREATMENT

General Measures

- Fluid restoration should be done using isotonic fluid
- A Foley catheter must be applied to assure adequate renal function and fluid restoration
- Electrolyte imbalance should be corrected as soon as possible
- Nasogastric tube placement is ideal for decompression.

Small Bowel Obstruction

In SBO, a prompt diagnosis and initial treatment can lead to a nonsurgical management in approximately 73% of cases which consists of fluid restoration and stomach decompression that must be done within 48 hours of diagnosis. If there is evidence of strangulation, ischemia, perforation, or a decline in clinical symptomatology, a surgical management is the treatment of choice. In the case of intussusception in kids, the use of contrast enemas guided by X-rays and hydrostatic pressure is the treatment of choice. When intussusception occurs in adults, surgical resection is the treatment of choice due to its high probability of being caused by a malignant process. The surgical approach for SBO involves a laparotomy or laparoscopic management. Laparotomy is usually preferred because of the possibility of a thorough abdominal examination and is the treatment of choice when there are previous abdominal injuries, dense adhesions, or complicated symptomatology. A laparoscopic approach, even though it has been increasing in popularity, is reserved for well-trained doctors, due to challenging abdominal exploration. Hospital stay, morbidity, and mortality are lower in the laparoscopic approach.

Large Bowel Obstruction

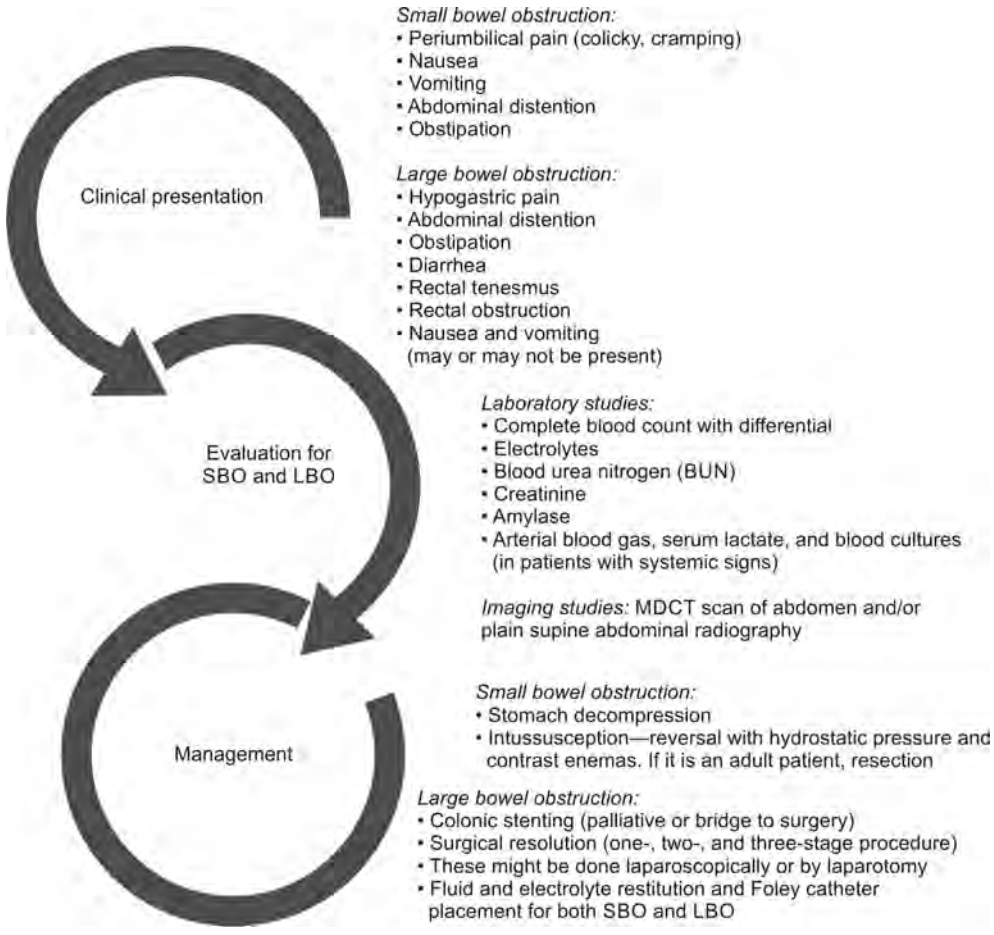
Large bowel obstruction treatment varies depending on the cause of the obstruction, evolution, and clinical condition of the patient. First of all, as in SBO, the patient's fluid and electrolyte imbalance should be managed; this is crucial as a beginning step in treatment. Stomach decompression can also be performed. Around 75% of LBO will require a surgical intervention eventually, but there are a series of treatment alternatives that help "make a bridge" between having to perform and emergency surgery and an elective one. These will be discussed below. In case the patient presents a sigmoid volvulus in the emergency room, a flexible sigmoidoscopy for colonic decompression can be performed initially in order to have a programmed surgery; this procedure is successful in about 90% of the cases, even though the recurrence rates are about 50%. If the patient is in an adequate clinical condition, the first treatment should be elective resection. Colonic stenting might be done for the same two reasons: decompression and having additional time for an elective procedure. When it is used to evade an emergency procedure, colonic stenting which is done laparoscopically can allow resection and anastomosis to be done rather than having an ostomy done. This procedure may also be used as palliation, even though it is not a resolutive treatment; it is successful for deobstruction in the short term. Complications of this procedure might be reobstruction, perforation, and migration of the stent.

Surgical resolutions for LBO might be done at different times (one-stage, two-stage, and three-stage) and with different purposes (curative and palliative). A one-stage procedure should always be preferred; when it is used as a curative solution, the bowel where the obstruction and dilated wall are localized is resected and reanastomosed. This procedure usually has an anastomotic leak of about 2.2–6.9%. When the one-stage procedure is used for palliation, bowel decompression and stenting are the best options. Stenting is usually done endoscopically, and decompression is done by performing a transverse loop colostomy. Cecostomy done with local anesthetics and fluoroscopic guidance might be performed in short life expectancy patients. The two-stage procedure involves the resection of the obstructed and dilated bowel followed by doing a colostomy or reanastomosing the bowel with a diverting loop ostomy, which is then reversed in a second step to re-establish continuity. A three-stage procedure starts with a Hartmann's procedure in which colon decompression is done by proximal diversion. After this is done, the second step consists in removal of the obstructed colon. Anastomosis can be done with an end colostomy or by a proximal diverting ostomy. To finish the three-staged surgeries, reversal of the ostomy and re-establishment of gastrointestinal continuity are done.

SUMMARY

Bowel obstruction is a syndrome characterized by a blockage of the intestinal content, gas, and liquid, through a small or a

large bowel. The block must be complete and permanent. The diagnosis of bowel obstruction usually is made on the basis of the patient's history, symptoms, and physical signs and is then confirmed by plain abdominal X-rays. There are several data that can diversify the intestinal obstruction syndrome. The first is the etiology based on a large number of factors that allow the subdivision into mechanical and functional/paralytic obstruction. The other feature characterizes the syndrome: the seat of the obstruction along the bowel—upper small gut, distal small gut, and large bowel. Finally, the cause of obstruction can involve the vascular supply of an intestinal segment, giving rise to strangulation obstruction that should be differentiated from simple obstruction. Evaluation and management of bowel obstruction are summarized in **Figure 2**.


Clinical presentation
Small bowel obstruction:
• Periumbilical pain (colicky, cramping)
• Nausea
• Vomiting
• Abdominal distention
• Obstipation
Large bowel obstruction:
• Hypogastric pain
• Abdominal distention
• Obstipation
• Diarrhea
• Rectal tenesmus
• Rectal obstruction
• Nausea and vomiting
(may or may not be present)
Evaluation for SBO and LBO
Laboratory studies:
• Complete blood count with differential
• Electrolytes
• Blood urea nitrogen (BUN)
• Creatinine
• Amylase
• Arterial blood gas, serum lactate, and blood cultures (in patients with systemic signs)
Imaging studies: MDCT scan of abdomen and/or plain supine abdominal radiography
Management
Small bowel obstruction:
• Stomach decompression
• Intussusception—reversal with hydrostatic pressure and contrast enemas. If it is an adult patient, resection
Large bowel obstruction:
• Colonic stenting (palliative or bridge to surgery)
• Surgical resolution (one-, two-, and three-stage procedure)
• These might be done laparoscopically or by laparotomy
• Fluid and electrolyte restitution and Foley catheter placement for both SBO and LBO

(LBO: large bowel obstruction; MDCT: multi-detector computed tomography; SBO: small bowel obstruction)

FIG. 2: Summary—evaluation and management of bowel obstruction.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Acute Appendicitis

Mukund Khetan

INTRODUCTION

Acute appendicitis is the most common general surgical emergency, and early surgical intervention improves the final outcome. The diagnosis is at times deceptive, and a high index of suspicion is important to prevent serious complications.

ANATOMY

Embryologically, the appendix and cecum develop as outpouchings of the caudal limb of the midgut loop. At birth, the appendix is located at the tip of the cecum, but the adult appendix typically originates from the posteromedial wall of the cecum. The appendix measures 5–9 cm in length, with its outside diameter ranging from 3 to 8 mm and lumen ranging from 1 to 3 mm. The base of the appendix is consistently found by following the teniae coli of the colon to their confluence at the base of the cecum. The arterial supply of the appendix comes from the appendicular branch of the ileocolic artery. Lymphatic drainage flows to the lymph nodes along the ileocolic artery (**Fig. 1A**). The appendicular tip, however, can vary significantly in location (**Fig. 1B**).

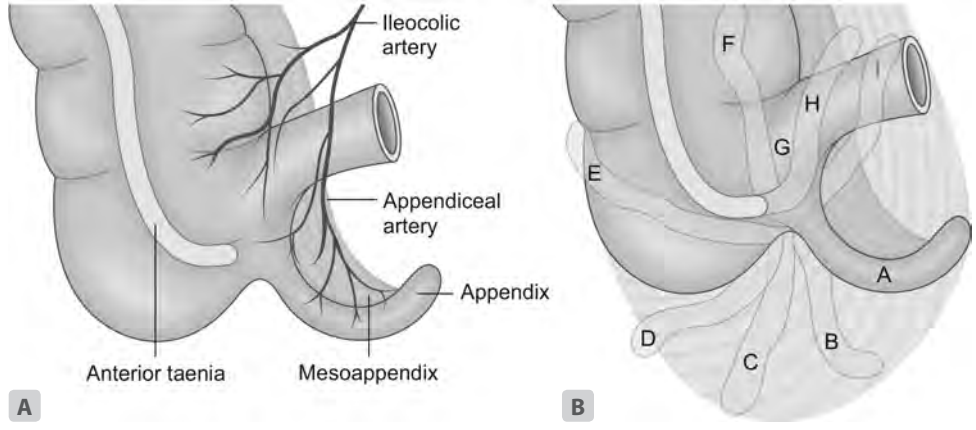
HISTORY

The first description of the appendix dates to the 16th century. The appendix was formally described in 1524 by da Capri and in 1543 by Vesalius. The first description of a case of appendicitis was by Fernel in 1554. Amyand is credited with the first appendectomy in 1736. Lawson Tait in London presented in 1880 the first successful transabdominal appendectomy for a gangrenous appendix. In 1886, Reginald Fitz of the Harvard Medical School first described the natural history of the inflamed appendix, coining the term "appendicitis."

In 1889, Chester McBurney described characteristic migratory pain as well as localization of the pain along an oblique line from the anterior superior iliac spine to the umbilicus. Laparoscopic appendectomy was first reported by the gynecologist Kurt Semm in 1982.

ETIOPATHOGENESIS

Obstruction of the appendiceal lumen is believed to be the major cause of acute appendicitis. This may be secondary to inspissated stool (fecalith or appendicolith), lymphoid



FIGS. 1A AND B: (A) Anatomy of appendix; (B) Variations in locations of appendicular tip (A to I).

hyperplasia, vegetable matter, parasites, or a neoplasm. A fecalith is typically composed of inspissated fecal material, calcium phosphates, bacteria, and epithelial debris.

Obstruction of the appendiceal lumen contributes to bacterial overgrowth, and continued secretion of mucus leads to increased intraluminal pressure and distension. Luminal distension produces typical periumbilical pain. Further impairment of lymphatic and venous drainage leads to mucosal ischemia. This in turn promotes a localized inflammatory process that may progress to gangrene and perforation. Perforation, although there is much variability, occurs after at least 48 hours from the onset of symptoms and is accompanied by an abscess cavity walled off by the surrounding omentum and small intestine.

Although appendiceal obstruction is widely accepted as the primary cause of appendicitis, evidence suggests that this may be only one of many possible etiologies. First, some patients with fecalith have a histologically normal appendix, and the majority of patients with appendicitis show no evidence for a fecalith.

The flora in the normal appendix is very similar to that in the colon, with a wide variety of facultative aerobic and anaerobic bacteria. *Escherichia coli*, *Streptococcus viridans*, *Bacteroides,* and *Pseudomonas* are frequently isolated.

PRESENTATION

Perhaps the most common surgically correctable cause of abdominal pain, the diagnosis of acute appendicitis still remains difficult in many instances and various abdominal conditions need to be differentiated (**Table 1**).

The *classic presentation of acute appendicitis* begins with crampy, intermittent abdominal pain which may be either periumbilical or diffuse and difficult to localize. This is typically followed shortly thereafter with nausea. If nausea and vomiting precede the pain, patients are likely to have another cause for their abdominal pain. Classically, the pain migrates to the right lower quadrant (RLQ) due to inflammation of the peritoneal lining in RLQ due to transmural migration from the appendix. This usually occurs within 12–24 hours from the onset of the symptoms. The character of the pain thus changes from dull and colicky to sharp and constant.

Movement or the Valsalva maneuver often worsens the pain, so the patient typically desires to lie still. Patients may report low-grade fever up to 101°F (38.3°C). Patients who have appendicitis commonly report anorexia; appendicitis is unlikely in those with normal appetite.

TABLE 1: Differential diagnosis.

Children	Gastroenteritis, mesenteric enteritis, Meckel's diverticulitis, intussusception, Henoch–Schonlein purpura, lobar pneumonia
Adult	Regional enteritis, ureteric colic, perforated peptic ulcer, torsion of testis, pancreatitis, rectus sheath hematoma
Adult female	Pelvic inflammatory disease, pyelonephritis, ectopic pregnancy, torsion of ovarian cyst, endometriosis
Elderly	Diverticulitis, intestinal obstruction, colonic carcinoma, torsion appendix epiploic, mesenteric infarction, leaking aortic aneurysm

Typically, *two clinical syndromes of acute appendicitis* can be apprehended: (1) *acute catarrhal (nonobstructive) appendicitis* and (2) *acute obstructive appendicitis*. The latter is characterized by a much more acute course.

The surgeon is constantly reminded that the classic presentation is not present in all patients. Patients may have none or only few symptoms just described. When the pain becomes constant, it may localize to other quadrants of the abdomen due to an alteration in appendiceal anatomy as in late pregnancy or malrotation. In patients with a retrocecal appendix, the pain may never localize until generalized peritonitis from perforated appendicitis occurs. Urinary or bowel frequency may be present due to appendiceal inflammation irritating the adjacent bladder or rectum.

Perforated Appendicitis

It is a not uncommon that if left untreated, appendiceal inflammation will progress inevitably to necrosis and then to perforation. The time course of this progression varies among patients. A longer duration of prehospital delay is the major contributor to perforation. Perforation after presenting to surgical attention appears to be uncommon.

The pain usually localizes to RLQ if perforation has been walled off but may be diffuse if generalized peritonitis occurs. Patients with perforation often have rigors and high fevers to 102°F (38.9°C) or above. Other rare presentations do occur, most likely in the very young and very old, who cannot express their symptoms and often present late in the course of their disease. Abscesses can also form in the retroperitoneum due to perforation of the retrocecal appendix or in the liver from hematogenous spread of infection through the portal venous system. Pylephlebitis (septic portal vein thrombosis) presents with high fevers and jaundice and can be confused with cholangitis.

EVALUATION

History and Physical Examination

The patient should be asked about the classic symptoms of appendicitis, but the surgeon should not be deterred by the absence of many of the symptoms. A previous appendectomy does not exclude the diagnosis of appendicitis, as "stump appendicitis" (appendicitis in the remaining appendiceal stump after appendectomy), although rare, has been described.

On examination, the patient looks slightly ill and may have mildly elevated temperature and pulse. The clinician should systematically examine the entire abdomen, starting in the left upper quadrant. Maximal tenderness is typically in the RLQ, at or near *McBurney's point*, located one third of the way from the anterior superior iliac spine to the umbilicus. This tenderness is often associated with localized muscle rigidity including rebound, shake, or tap tenderness. RLQ tenderness is the most consistent of all signs of acute appendicitis (**Table 2**).

The patient is asked to point to where the pain began and where it moved (*pointing sign*). Pain in the RLQ on palpation of the left lower quadrant results from localized peritoneal inflammation (*Rovsing's sign*). Pain with the flexion of the leg at the right hip can be seen with a retrocecal appendix due to inflammation adjacent to the psoas muscle (*psoas sign*). Pain with rotation of the flexed right thigh internally indicates inflammation adjacent to the obturator muscle (the obturator sign).

In case of perforated appendicitis, if sepsis has developed, blood pressure can be depressed. Perforation walled off by the surrounding structures can create abscess or phlegmon leading to palpable mass. Free intraperitoneal rupture can lead to signs of generalized peritonitis with diffuse rebound tenderness.

INVESTIGATIONS

Laboratory Studies

The white cell count is typically slightly elevated in nonperforated appendicitis but may be quite elevated in the presence of perforation. A completely normal leukocyte count and differential is found in about 10% of patients with acute appendicitis, particularly in early cases.

A urinary tract infection is not uncommon in patients with appendicitis. Its presence does not exclude the diagnosis of acute appendicitis, but it should be identified and treated.

Measurement of serum liver enzymes and amylase can be helpful in diagnosing liver, gallbladder, or pancreatic disease in patients with mid-abdominal pain. In women of child-bearing age, the urine beta-human chorionic gonadotropin (β-HCG) should be checked to alert the clinician to the possibility of ectopic or concurrent pregnancy.

TABLE 2: Clinical presentation of acute appendicitis.

Symptoms	*Signs*	*Signs to elicit*
Periumbilical pain	Pyrexia	Pointing signs
Pain shifting to right iliac fossa	Local tenderness, right iliac fossa	Rovsing's signs
Anorexia	Muscle guarding	Psoas signs
Nausea	Rebound tenderness	Obturator signs

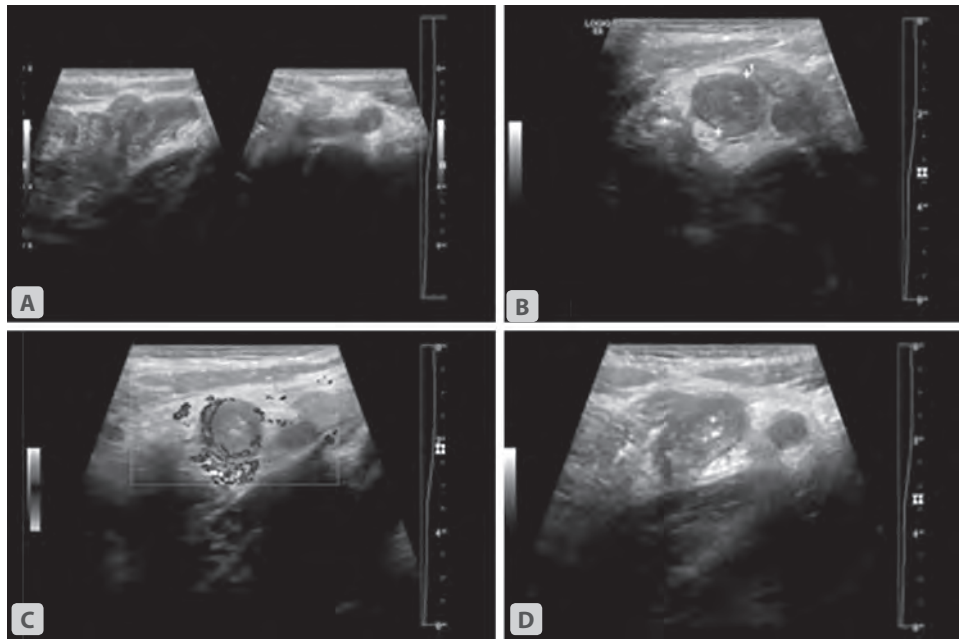
Diagnostic Scores

Diagnostic scoring systems have been developed in an attempt to improve the diagnostic accuracy of acute appendicitis. The most widely used scoring system is the Alvarado score. This scoring system gives point for symptoms (migration of pain, anorexia, and nausea), physical signs (RLQ tenderness, rebound tenderness, and pyrexia), and laboratory values (leukocytosis with a left shift). With the recent improvement in imaging studies, these scores play a smaller role in diagnosis.

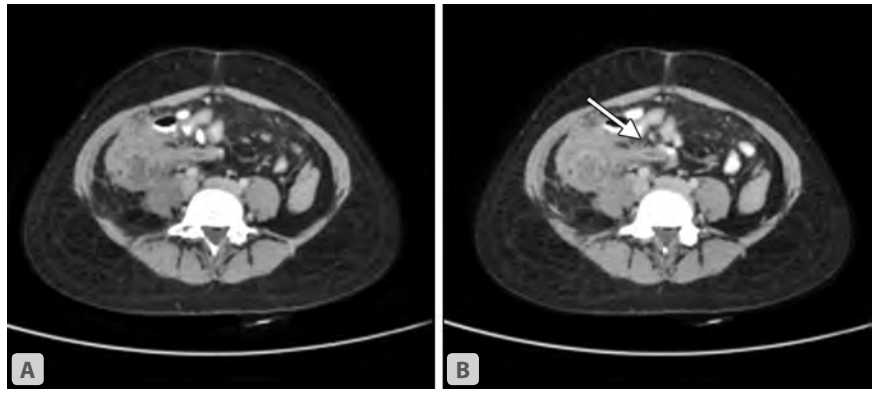
Imaging Studies

The potential imaging modalities for diagnosis of acute appendicitis include plain radiographs, ultrasound (US), and computed tomography (CT). On plain radiographs, fecaliths are nonpathognomonic for appendicitis. Plain radiographs are indicated in elderly patients with severe abdominal pain, in whom a perforated viscus is included in the differential diagnosis. Abdominal *ultrasonography is a popular imaging modality, and findings that suggest appendicitis* include thickening of the appendiceal wall with increased blood flow (leading to the so-called ring-of-fire appearance), loss of wall compressibility, increased echogenicity of the surrounding fat, and loculated pericecal fluid (**Figs. 2A** to **D**). Noncompressible luminal structure seen in cross section as a target lesion. US is highly operator-dependent, and it is frequently unable to visualize the normal appendix.

Computed tomography benefits from a high diagnostic accuracy for appendicitis and visualization and diagnosis of many of the other causes of abdominal pain that can mimic appendicitis. *The radiographic findings of appendicitis on CT* include a dilated (>6 mm), thick-walled appendix that does not fill with enteric contrast or air as well as surrounding fat stranding to suggest inflammation (**Figs. 3A** and **B**). CT demonstrated a sensitivity of 0.94 and a specificity of 0.95.



FIGS. 2A TO D: Ultrasonography findings of acute appendicitis. (A) Thickening of the appendiceal wall and increased blood flow (ring of fire appearance); (B) Loss of wall compressibility; (C) Increased echogenicity of the surrounding fat; (D) Loculated pericecal fluid. ***(For color version, see plate 11)***



FIGS. 3A AND B: Computed tomography findings of acute appendicitis. (A) These include a dilated (>6 mm), thick-walled appendix that does not fill with enteric contrast or (B) Air as well as surrounding fat stranding to suggest inflammation.

Mural stratification referring to the layers of enhancement and edema within the wall is known as target sign.

APPENDICITIS IN SPECIAL POPULATION

Children

Appendicitis most commonly affects children aged 10–19 years. Infants aged 0–4 months have the lowest incidence, but up to two thirds will present with perforation. In children with an equivocal history and physical examination, imaging with either a CT scan or US can significantly reduce the negative appendectomy rate. As with adults, both CT and US have been shown to be highly accurate in diagnosing appendicitis in children, although a CT scan is believed to have a higher specificity and sensitivity.

Elderly

Because of a diminished inflammatory response, the elderly can present with less impressive symptoms and physical signs, longer duration of symptoms, and decreased leukocytosis. Perforation is thus more common, occurring in as many as 50% of patients older than 65 years of age. A prompt CT scan is advocated when the diagnosis is in dilemma.

Pregnancy

The diagnosis can be challenging, as nausea, anorexia, and abdominal pain may be symptoms of both appendicitis and normal pregnancy. The gravid uterus can displace the abdominal viscera, shifting the location of appendix. It can occur in any trimester, with perhaps a slight increase in frequency in the second trimester. Perforation is more common in the third trimester. US is accurate in pregnancy and is a useful first radiological tool. Rectal contrast CT has also been shown to be highly accurate. Although ionizing radiation has risks to the fetus, the radiation from a typical abdominopelvic CT is below the threshold of 5 rad at which teratogenic effects can be seen. Additionally, magnetic resonance imaging (MRI) has been recently used to aid in the diagnosis of appendicitis in the pregnant patient when US results are equivocal. To date, however, no adverse effects of MRI on the developing fetus have been reported.

Immunocompromise

The immunocompromised state alters the response to acute infection and wound healing. Appendicitis affects all types of patients and must be considered in those who have undergone organ transplant, are receiving chemotherapy, or are infected with the human immunodeficiency virus (HIV).

TREATMENT

Nonoperative or Medical Management

Appendicitis has long been a surgically treated disease; recently, few studies of nonsurgical management dot the surgical literature. Based on a higher rate of failure with antibiotics alone, nonoperative management of acute appendicitis has not been recommended. Nevertheless, antibiotic treatment may be a useful temporizing measure in environments with no surgical expertise. Intravenous antibiotics have been shown to reduce the incidence of postoperative wound infection and intra-abdominal abscess. Antibiotics should be administered 30 minutes prior to skin incision. As the typical flora of appendix resembles that of colon, a second-generation cephalosporin or a combination of antibiotics directed at gram negatives and anaerobes will suffice. In nonperforated appendicitis, a single preoperative dose, and in cases of perforation, an extended course of at least 5 days of antibiotics are advocated.

Operative Management: Open or Laparoscopic Appendectomy

Once the diagnosis of appendicitis is confirmed, the surgeon must decide whether to perform an open or laparoscopic appendectomy. Meta-analysis and systematic reviews have addressed the controversy. Based on the data available, one cannot convincingly recommend either open or laparoscopic appendectomy over the other. One situation in which laparoscopic appendectomy may be advisable is when the diagnosis of appendicitis is in doubt.

Open Appendectomy

If an open approach is chosen, the surgeon must then decide on the location and type of incision. If a mass representing

the inflamed appendix can be palpated, the incision must be centered at that location. If the appendix cannot be visualized, it can be located by following the teniae coli of the cecum to the cecal base. Care should be taken to avoid perforation of appendix, with spillage of pus or enteric contents into the abdomen. In excising the appendix, the surgeon must decide whether or not to invert the appendiceal stump. Recent studies show no advantages to appendiceal stump inversion. No matter how the appendix is divided, the residual appendiceal stump should be no longer than 3 mm to minimize the possibility of stump appendicitis in the future. If the base of the cecum is also inflamed but there is sufficient uninflamed cecum between the appendix and the ileocecal valve, an appendectomy with partial cecectomy can be performed using a stapling device.

Laparoscopic Appendectomy

Multiple port placements for laparoscopic appendectomy exist. The authors utilize a three-port technique, with one umbilical and one suprapubic port and the third port can be placed in either the left lower quadrant or RLQ. The appendix should be placed in a retrieval bag and removed through the umbilical port site to minimize the risk of wound infection (**Figs. 4A** to **D**).

Postoperative Care

Patients with nonperforated appendicitis require a shorter (24–48 h) hospital stay. Postoperative care for both the laparoscopic and the open approaches is similar. Patients can be started on a clear liquid diet after 4 hours, and their diet can be advanced as tolerated. Patients can be discharged when they tolerate a regular diet.

SPECIAL CONSIDERATIONS DURING APPENDECTOMY

Perforated Appendicitis

When appendicitis progresses to perforation, management depends on the nature of the perforation. If perforation is contained, it can lead to a mass or phlegmon or may result in a pus-filled abscess cavity. Appendectomy proceeds as described earlier. Peritoneal drains are not necessary, as they do not reduce the incidence of wound infection or abscess, but the final decision is of the operating surgeon. Patients are often continued on broad-spectrum antibiotics for 5–7 days and should remain in hospital until they tolerate a regular diet.

In patients with a solid inflammatory mass in the RLQ, without evidence of abscess cavity, suggesting a phlegmon, appendectomy can be difficult due to dense adhesions and inflammation.

In such circumstances, to reduce potential complications, many support an initially nonoperative approach. Conservative treatment failure, as evidenced by bowel obstruction, sepsis, persistent pain, or leukocytosis, requires immediate appendectomy.

Normal Appendix

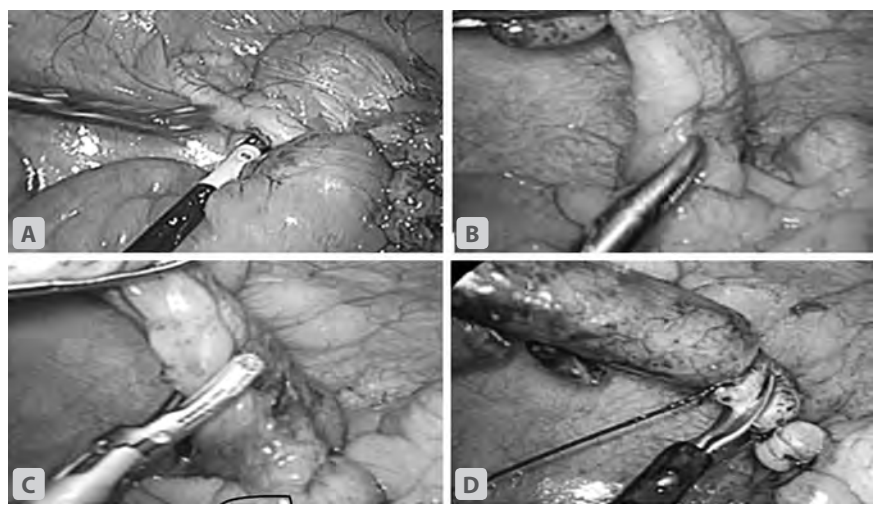
Because of the difficulty in diagnosing appendicitis, it is not uncommon for a normal appendix to be found at appendectomy. This can occur >15% of the time, with considerably higher percentage in infants, the elderly, and young women. For many reasons, it is advisable to remove the grossly normal appendix. When a normal appendix is discovered at appendectomy, it is important to search for other possible causes of the patient's symptoms.

Interval Appendectomy

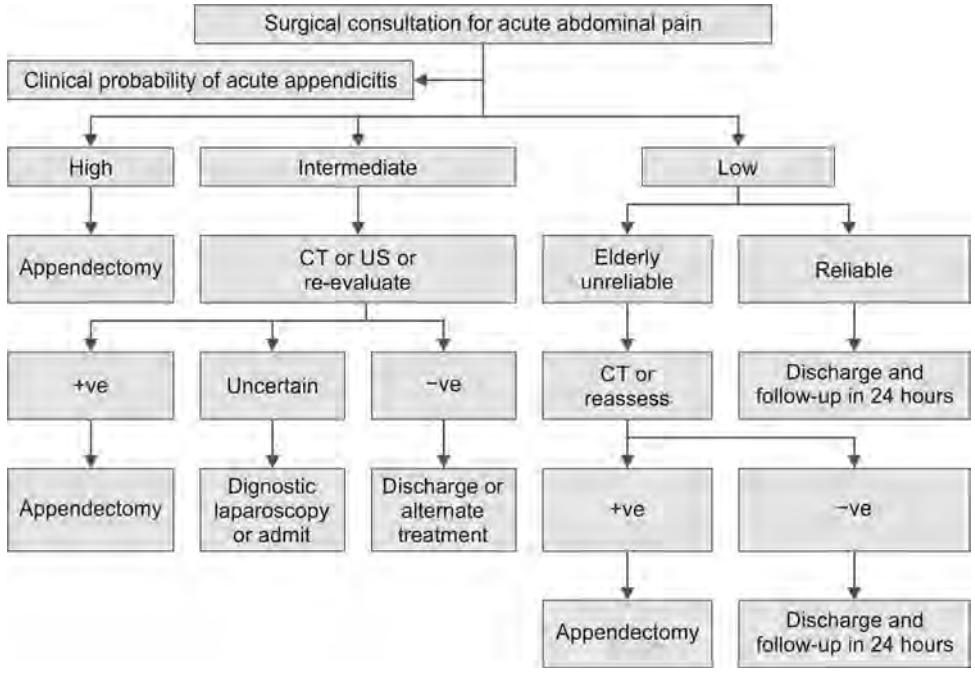
Factors to be considered when advising patients on interval appendectomy include a relatively low incidence of future appendicitis (8–10% and often associated with an appendicolith) and a morbidity associated with an interval appendectomy of approximately 11%.

Chronic or Recurrent Appendicitis

Patients do not present with the typical symptoms of acute appendicitis. Instead, they complain of recurrent and infrequent RLQ pain. When questioned, they may describe an initial episode with more classic symptoms of acute



FIGS. 4A TO D: Laparoscopic appendectomy. (A) Localization; (B) Dissection of mesoappendix; (C) Harmonizing mesoappendix; (D) Endo-loop ligation and division of appendix. ***(For color version, see plate 11)***



(CT: computed tomography; US: ultrasound)

FLOWCHART 1: Algorithm for the evaluation and management of patients with possible acute appendicitis.

appendicitis, with no treatment delivered. Because the diagnosis is often uncertain preoperatively, laparoscopy is a useful tool to allow exploration of the abdomen.

RECENT ADVANCES

Literature Review

Appendectomy versus antibiotic treatment for acute appendicitis, a Cochrane review, was prepared and maintained by the Cochrane Collaboration and published in the Cochrane Library 2011, Issue 11. Authors conclude that appendectomy remains the standard treatment for acute appendicitis. Antibiotic treatment might be used as an alternative treatment in a good-quality randomized controlled trial (RCT) or in specific patients or conditions where surgery is contraindicated.

New data show that pure transvaginal appendectomy is emerging as a safe and well-tolerated procedure for women with acute nonperforated appendicitis that reduces the burden of pain and has faster recovery times when compared with laparoscopic approaches.

Guidelines

The American College of Surgeons, the Society for Surgery of the Alimentary Tract, and the World Society of Emergency Surgery all describe appendectomy (either laparoscopic or open) as the treatment of choice for appendicitis. Regarding an antibiotic-first strategy, the American College of Surgeons patient information guide indicates that it "may be effective, but there is higher chance of recurrence"; the Society for Surgery of the Alimentary Tract patient care guidelines suggest that it is "not a widely accepted treatment"; and the World Society of Emergency Surgery states that "this conservative approach features high rates of recurrence and is therefore inferior to the appendectomy.... Nonoperative antibiotic treatment may be used as an alternative for specific patients for whom surgery is contraindicated."

SUMMARY

Appendicitis is one of the common causes of abdominal pain of less than a week duration presenting to the emergency department. Appendicitis can occur at any age. In spite of advances in imaging accuracy, appendicitis remains a high-risk disease for delayed or missed diagnosis, because of its varied presentation, absence pathognomonic sign or symptom, and poor predictive value of associated laboratory testing. Appendicitis continues to be a high risk for missed and delayed diagnosis, especially in extremes of young and elderly. Delayed or missed diagnosis in the emergency department and ruptured appendix are the important causes for increase in morbidity and mortality. No specific history, physical finding, or laboratory test can make the definitive diagnosis of appendicitis. US is helpful when positive but not accurate in excluding appendicitis or identifying the rupture. CT is accurate and also helpful in identifying the other causes of abdominal pain. Combination of findings can increase the likelihood of disease diagnosis and is helpful in further management. An algorithmic approach is helpful for evaluation of patients with suspected acute appendicitis (**Flowchart 1**).

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CHAPTER

Anorectal Diseases

Ashok Kumar Puranik, Devendra Richhariya

INTRODUCTION

Anorectal diseases are sensitive in nature and the patient often presents in the later stage of the disease because he may feel embarrassed while giving history. An emergency physician should be aware of the presenting features, onset, frequency, character, recurrence, and systemic manifestation of various anorectal diseases. Physical examination requires proper positioning of the patient, adequate lighting, and visualization. Digital rectal examination (DRE) and anoscopy are helpful in further evaluation. It is important for the emergency physician to be more familiar with history and clinical findings of various anorectal complaints. The anorectal junction is the point where the rectosigmoid part of the intestine joins the skin (**Fig. 1**). This transition area is called dentate line, and 1–2 cm distal to the dentate line is the anal canal and distal to the anal canal is the anal verge which consists of skin, hair follicle glands, and subcutaneous tissue. The rectum above the dentate line is supplied by the superior hemorrhoidal artery and below the dentate line is supplied by the middle and inferior hemorrhoidal arteries.

HEMORRHOIDS

Hemorrhoidal disease is one of the most chronic diseases in the history of mankind. Ancient texts date back to Babylonian, Egyptian, Greek, and Hebrew cultures. Although very few people have died after hemorrhoids, this chapter will guide the practitioners in following a more humane approach to treat hemorrhoidal disease patients.

Pathophysiology

Hemorrhoids are submucosal cushions containing venules, arterioles, and smooth muscle fibers in the anal canal. These cushions are primarily located at right anterolateral (11 o'clock), right posterolateral (7 o'clock), and left lateral (3 o'clock) positions. Hemorrhoids are thought to have a role in anal continence and they aid in complete closure of anal canal at rest. Hemorrhoidal disease occurs as a result of abnormality in the constituents of these cushions leading to bleeding which may or may not be associated with the prolapse of the hemorrhoidal tissue. This can occur as a result of excessive strain, chronic constipation due to low-fiber diet, and increased internal anal sphincter tone. Diarrhea may also cause hemorrhoids because of recurrent straining. Pregnancy is also a significant risk factor for hemorrhoids, which can be reversed after delivery.

Classification of Hemorrhoids

Hemorrhoids are classified on the basis of their presence below (external hemorrhoids) and above (internal hemorrhoids) the dentate line (**Fig. 2**).

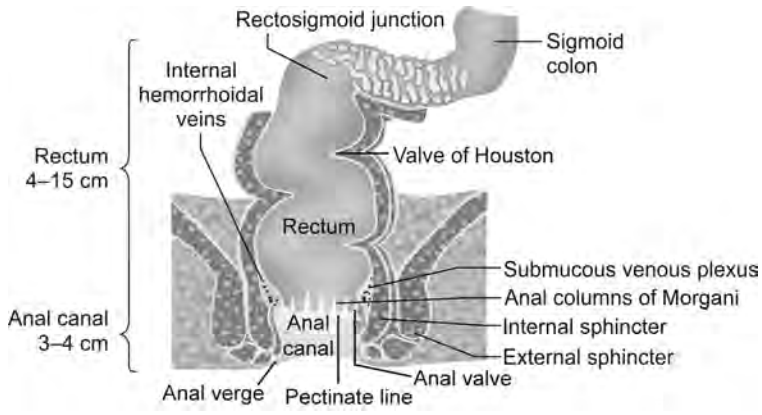


FIG. 1: Anatomy of the anorectal area.

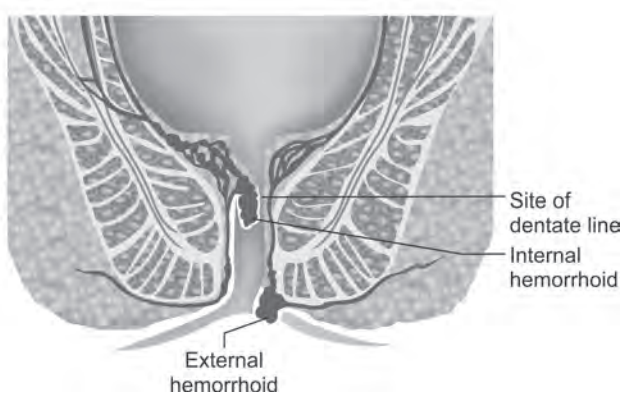


FIG. 2: Anatomy of external and internal hemorrhoids.

TABLE 1: Standard classification of internal hemorrhoids.	
Grade 1	Bleeding only
Grade 2	Prolapse with spontaneous reduction
Grade 3	Prolapse requiring manual reduction
Grade 4	Prolapsed and cannot be reduced (are at high risk for strangulation)

- *External hemorrhoids*: These are located distal to the dentate line and are covered by anoderm and because anoderm is highly innervated, the thrombosis of external hemorrhoids can be extremely painful. So, external hemorrhoids should not be ligated or excised without adequate anesthesia. Skin tag at anal verge often represents the thrombosed, fibrotic external hemorrhoids. It can cause itching and difficulty in maintaining hygiene. Treatment of external hemorrhoids and skin tag is only indicated for symptomatic relief.
- *Internal hemorrhoids*: These are located proximal to the dentate line and are covered by insensate anorectal mucosa. Internal hemorrhoids can bleed and prolapse but are rarely painful. They can become painful if severe thrombosis and necrosis occur which are usually related to severe prolapse, incarceration, and strangulation. Internal hemorrhoids are further classified clinically as given in **Table 1**.
- *Combined internal and external hemorrhoids*: These are located at the dentate line and have features of both external and internal hemorrhoids. Hemorrhoidectomy is often needed for this type of hemorrhoid.

Clinical Features

Bleeding and protrusion are the most important symptoms of hemorrhoids. Bleeding from hemorrhoids is typically bright red, either on toilet paper or into the commode after bowel movements; this is usually painless. If it is painful, then most of the time it is associated with fissure-in-ano. Although bleeding is the most common symptom, anemia is rare in these patients. Feeling of rectal fullness and perineal irritation are also associated features. Thrombosed external hemorrhoids can present as blue tender mass. Internal hemorrhoids are generally not visualized or palpated on rectal examination unless they are enlarged, prolapsed, and thrombosed.

Examination

The preferred position for examination is left lateral position with knees drawn up toward the chest as high as possible. This approach allows the patient relative comfort and the ability to clearly inspect the perineal skin and perform DRE unless he/she is thrombosed. On proctoscopy, hemorrhoids are seen as masses prolapsing into the scope.

Treatment

Medical Management/Conservative Management

Bleeding from grades 1 and II often improves by giving bulk laxatives, such as psyllium and stool softeners, and avoidance of straining. It is very important to increase the daily water intake along with fibers. Failure of conservative management is an indication for some surgical intervention.

Sclerotherapy

It was first advocated by Mitchell in 1871. The principle of sclerotherapy is scaring of submucosa which results in atrophy and fixation of the hemorrhoidal complex to the wall of the anal canal. A variety of solutions are available such as 5% phenol, sodium morrhuate, and sodium tetradecyl sulfate (STD). The procedure is performed in a patient with left lateral decubitus position. An anoscope is inserted to identify symptomatic hemorrhoids; then 1–2 mL of sclerosant is injected into the submucosal plane using a 25-gauge spinal needle. Before injection, the syringe should be aspirated to avoid intravascular injection. Accidental injection into the prostate in a male is very painful as it causes chemical prostatitis. Not more than two hemorrhoids should be injected in one sitting to avoid anal stenosis.

Rubber Band Ligation

Barron was the first to describe hemorrhoidal banding using a rubber band in 1963. It is often applied in patients with grade II and III hemorrhoids. The mucosa over the hemorrhoids, 1–2 cm above the dentate line, is grasped and pulled into the rubber band applicator. The procedure is usually well tolerated if the band is applied above the dentate line. It is important to ask the patient if he/she experiences any pain before deployment of the band. If he/she has pain before deployment of the band, it will worsen after banding. Other complications of banding include urinary retention, infection, and bleeding. Urinary retention occurs in nearly 1% of patients. Necrotizing infection is an uncommon but life-threatening complication. Severe pain, fever, and urinary retention are early signs of infection and should prompt immediate evaluation of the anal canal under anesthesia. Treatment includes debridement of necrotic tissue, drainage of associated abscess, and broad-spectrum antibiotics. Bleeding may occur 7–10 days after banding when ligated pedicles necrosed and sloughed. Bleeding is usually self-limiting, but persisted bleeding may require examination under anesthesia and outer ligation of the pedicle.

Infrared Coagulation and Ultroid (Direct Current) Therapy

The infrared coagulation technique uses a tungsten–halogen lamp that generates heat for 1.5 seconds leading to destruction

of mucosa and submucosal hemorrhoids. Ultroid uses direct current and is applied for 10 minutes over the hemorrhoidal complex.

Excisional Hemorrhoidectomy

Excisional hemorrhoidectomy requires a mutual decision by the physician and the patient. The physician must explain that medical and nonexcisional options are either not appropriate or law failed. The usual clinical symptoms that require surgical excision are frequent prolapse and anal seepage or hemorrhoids making anal hygiene difficult to maintain.

Milligan and Morgan Hemorrhoidectomy (Open Hemorrhoidectomy)

It was originally described in 1973 and is widely practiced in Europe. In this procedure, the entire enlarged hemorrhoidal complex is excised with ligation of the vascular pedicle and preservation of the intervening anoderm. While dissecting, the internal anal sphincter should be brushed away to preserve it. The wound is left open and allowed to heal by secondary intention.

Ferguson Hemorrhoidectomy (Closed Hemorrhoidectomy)

This technique was proposed as an alternative to open hemorrhoidectomy, as open hemorrhoidectomy has prolonged discomfort and morbidity. In this technique, an hourglass-shaped excision of internal and external hemorrhoids is done with ligation of the vascular pedicle. The center of the hourglass is anoderm. After excision, the wound is closed by an absorbable suture. It is crucial to identify the internal and external anal sphincters and preserve them. In this technique, all the primary hemorrhoids can be removed in a single sitting, although care should be taken to avoid resecting a large area of perianal skin to avoid postoperative anal stenosis.

Whitehead Hemorrhoidectomy

This technique was devised in 1982 to excise internal hemorrhoids circumferentially and relocate the prolapsed dentate line which is often a component of prolapsed hemorrhoids. In this technique, the enlarged internal hemorrhoids are excised circumferentially just proximal to the dentate line and after excision the rectal mucosa is advanced and sutured to the dentate line. But this technique has been abandoned by most surgeons because of its complications such as anal stenosis and mucosal ectropion (Whitehead's deformity).

Procedure for Prolapsed Anal Hemorrhoids or Stapled Hemorrhoidectomy

The term procedure for prolapsed hemorrhoids (PPH) has largely replaced the term stapled hemorrhoidectomy (SH) because in this procedure, the hemorrhoid tissue is not excised; instead, the redundant mucosa is fixed above the dentate line. In this procedure, a short segment of rectal mucosa proximal to the dentate line is removed circumferentially using a circular stapler. This causes the ligation of feeding venules of the hemorrhoid plexus along with fixation of redundant mucosa higher in the anal canal. But this technique is only appropriate for internal hemorrhoids and cannot be used for external or combined hemorrhoids.

Complications of Hemorrhoidectomy

Postoperative pain is the most common complication following hemorrhoidectomy. It is usually managed by oral/intravenous (IV) narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, topical analgesics, and comfort measures such as sitz bath.

Urinary retention is another common complication after hemorrhoidectomy and occurs in 10–50% of patients. The incidence can be reduced by minimizing the intraoperative and perioperative IV fluids and providing adequate analgesics.

Fecal impaction is also a complication of postoperative pain which can be minimized by adequate analgesia and liberal use of laxatives.

Bleeding is also a common complication after hemorrhoidectomy. A small amount of blood with stool is suspected, but massive bleed requires urgent examination and pedicle ligation under anesthesia in the operation theater (OT). Bleeding can occur after 7–10 days when necrotic mucosa overlying the vascular pedicle sloughs, although some of the patients can be safely observed; however if the bleeding is massive, it may require examination and suture ligation of the vessel in the OT.

Infection is a rare complication after hemorrhoidectomy but necrotizing soft-tissue infection, mostly in immunocompromised individuals, can be devastating. Severe pain, fever, and urinary retention are the early signs of such infection. In this condition, emergency examination and debridement should be done under anesthesia. Long-term complications include anal stenosis and ectropion (after Whitehead's hemorrhoidectomy).

ANAL FISSURE

Anal fissure is a tear in anoderm distal to the dentate line, which may be acute or chronic. Acute fissure is a simple laceration, whereas a chronic anal fissure is an ulceration with scarred edges and visible internal sphincter muscles at its base with anal tag and hypertrophied papilla at the dentate line. Anal fissure almost always occurs in midline with posterior location predominance (90% in women and 99% in men). Fissures located at other than these sites often indicate some serious systemic pathology such as Crohn's disease, human immunodeficiency virus (HIV), leukemia, and other immune deficiency syndromes.

Etiology

The etiology of anal fissure is probably trauma because of passing hard stool or prolonged diarrhea. Prior anal injury or surgery leading to stenosis, stricture, or scarring is a predisposing factor. Various theories about the cause have been proposed; among them, the theory of vascular anatomy of the internal anal sphincter is most compelling. In 1989, Klosterhalfen et al. reported the anatomical detail of the branches of the inferior hemorrhoidal artery. In this study, they found that in 85% of cadaveric specimens, the posterior commissure of anal canal was not directly perfused; rather they received blood supply from end arterioles. So, there is poor perfusion of mucosa in the posterior midline along with this sphincteric spasm and hypertonicity which is common in this disease and may further decrease blood flow in the posterior midline. Schouten et al. have shown a correlation between increased anal tone and decreased vascularity by using a laser Doppler flowmeter.

Infections also cause anal fissure over the last century. Sexually transmitted infections and infections associated with an immunocompromised state may be a cause of anal fissure. Chancroid, herpes virus, and cytomegalovirus usually present as multiple superficial ulcers, while syphilitic ulcers have purulent discharge with granulation at the base. So, it is very important to properly diagnose the disease because treatment of these conditions is different.

Diagnosis

A burning pain or tearing pain while defecation is the most common symptom of anal fissure. Bleeding is usually only detected on toilet paper. Pain may last for minutes to hours. The examination should be gentle by separating the buttocks. Patients are often intolerant to DRE and proctoscopy. Topical anesthesia does not provide free examination. Atypical location of fissure requires more intensive history-taking and investigation to rule out Crohn's disease, HIV, and other immunodeficiency diseases.

Management

Nonsurgical Management

- *Conservative management*: The first-line treatment for simple, acute fissures-in-ano is warm sitz bath with stool softeners. Warm water reduces the discomfort by muscle relaxation, while stool softeners prevent trauma to the mucosa by loosening the stool. Stool softeners, such as psyllium, bran, and fiber, draw water and retain it in stool, thus making it soft. Furthermore, bran has been shown to be effective in preventing recurrence of acute anal fissure. Topical creams and steroids have a limited role in management and are not routinely recommended. This conservative management successfully heal 90% of acute fissure and 40% of chronic fissure.
- *Nitroglycerine*: It is a nitric oxide donor and nitric oxide is a potent smooth muscle relaxant, leading to vasodilatation. In view of etiology of anal fissure: Increase in anal tone and poor vascularity in posterior anal canal, nitric oxide provide immediate relief (5 min) of pain and spasm and also promote healing of fissure.

Headache is a significant side effect of nitroglycerine, which limits its use. Other side effects are orthostatic hypotension, syncopal attack, and tachyphylaxis. These are uncommon side effects.

- *Calcium channel blockers*: Nifedipine and diltiazem can be used as agents of "chemical sphincterotomy." Topical nifedipine reduces sending anal tone and then facilitates healing and relieves pain. About 2% topical diltiazem is equally effective as nitroglycerine. Topical diltiazem can heal up to 75% of anal fissures that have failed to heal by nitroglycerine alone. This class of drug supersedes nitroglycerine in the treatment of chronic anal fissure because of better effectiveness and better side-effect profile.
- *Botulinum toxin (Botox)*: Another alternative for "chemical sphincterotomy" is botulinum toxin A, an exotoxin produced by *Clostridium botulinum* that prevents the release of acetylcholine from presynaptic vesicles leading to muscle paralysis. It is an effective treatment option for chronic anal fissures. In one study, 75% of chronic anal fissures healed at 8 weeks with no recurrence in 16 months' follow-up. Complications of this form of treatment are infrequent and include transient incontinence, mainly flatus and perianal hematoma formation.

Surgical Management

Lateral internal anal partial sphincterotomy (LIS) is done in patients who fail to respond to nonsurgical management options. This procedure was originally described by Eisenhammer in 1951 as a midline posterior incision through the fissure. But subsequent studies found problems with wound healing and formation of a "keyhole" deformity. "Keyhole" deformity is a persistent groove in the midline after the posterior division of sphincter; it causes problems such as anal seepage and incontinence. Subsequent modifications to this procedure lead to repositioning of the incision to the right or left lateral position, which has effectively eliminated the complication of this deformity. *Fissurectomy* is the excision of the anal fissure. This procedure results in a defect in anoderm, which can be covered with a rotational or advancement flap to avoid "keyhole" deformity.

Calibrated balloon dilation is also an effective technique for the management of chronic anal fissures. A study comparing LIS with pneumatic balloon dilation found the healing rate of fissures to be 83.3% in the pneumatic balloon dilation group and 92% in the LIS group. At 24 months' follow-up, incontinence was 0 in the pneumatic balloon dilation group and 16% in the LIS group. So, pneumatic balloon dilation is also a safe and efficacious method.

ANORECTAL ABSCESS

Anorectal suppuration can present with acute or chronic manifestation. Anorectal abscess forms the acute presentation and anal fistula represents the chronic form. Depending on the anatomical location of abscess, the etiology and management vary (**Fig. 3**).

Etiopathogenesis

The most widely accepted theory for the development of anorectal suppuration is the cryptoglandular theory of anal

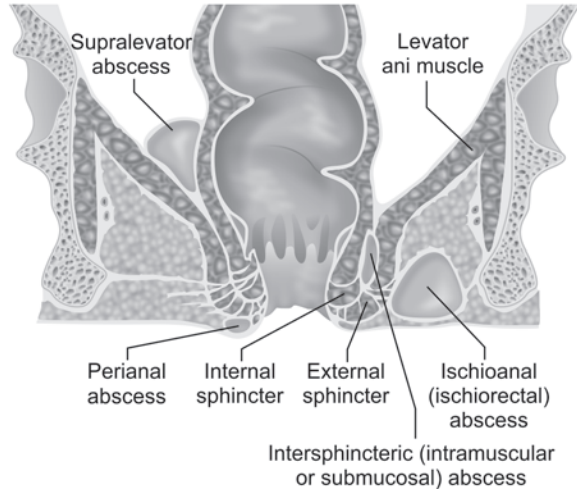


FIG. 3: Anorectal abscess.

sepsis. Anal glands are located in the intersphincteric space and their ducts traverse the internal sphincter and open into the anal crypts at the level of dentate line. Blockage of ducts with fecal bacterial plugging leads to infection of anal glands and abscess formation. The abscess usually originates in the intersphincteric space and can remain isolated or spread vertically upward or downward, horizontally or circumferentially, to any of the perianal or perirectal spaces. Other factors include immunodeficiency due to malignancy (anorectal/hematological) or HIV infection, tuberculosis, actinomycosis, trauma, foreign body, postoperative infection, inflammatory bowel disease, hidradenitis suppurativa, intra-abdominal pathology (in supralevator abscess), etc. Both aerobic and anaerobic bacteria are implicated. Most common aerobes include *Staphylococcus aureus*, *Streptococcus*, *Escherichia coli,* etc., and anaerobes include *Bacteroides fragilis*, *Peptostreptococcus*, *Clostridium,* etc. Recently, Methicillin-resistant *Staphylococcus aureus* strains have also been identified in some abscesses in immunocompromised and recurrent cases.

Types of Anorectal Abscess

Anorectal abscess is classified based on anatomical location into:

- Intersphincteric abscess
- Perianal abscess
- Ischiorectal abscess
- Postanal abscess and horseshoe extension
- Supralevator abscess

Intersphincteric Abscess

Intersphincteric space is found between internal and external anal sphincters. Intersphincteric abscesses are usually difficult to diagnose due to no visible evidence of inflammation (hidden abscess). They present with severe anal pain that may preclude a DRE. Examination under general anesthesia is usually required for diagnosis. Management is by draining the abscess via posterior internal sphincterotomy.

Perianal Abscess

Intersphincteric abscess may spread vertically downward to the perianal space. Perianal abscesses constitute the most common (60%) type of anorectal abscesses. They present with painful swelling at the anal verge. The incision for drainage is placed close to the anal verge, and a disc of skin is usually removed to prevent premature closure. Care must be taken to prevent damage of the underlying sphincter muscle. No packing is required. Sitz bath is initiated from the next day.

Ischiorectal Abscess

Intersphincteric abscess may spread laterally beyond the external sphincter to involve the ischiorectal space. The ischiorectal space is bounded medially by the external sphincter, laterally by the ischium, superiorly by levator ani, and inferiorly by the transverse perianal septum. Ischiorectal abscess may expand slowly till the roof of fossa without much signs and later present with a large, indurated mass in buttock. Simple ischiorectal abscesses are drained through an incision in the overlying skin. Vigorous debridement of abscess cavity is usually avoided to prevent injury to the inferior rectal branch of the internal pudendal nerve, which supplies the external anal sphincter and levator ani muscles.

Postanal Abscess and Horseshoe Extension

Deep postanal space lies posterior to anus and anterior to sacrum, deeper to the anococcygeal ligament, and superficial to the levator ani muscles. Trans-sphincteric extension of an intersphincteric abscess to the posterior midline forms a postanal abscess. They usually present with tenderness posterior to anus without obvious signs of inflammation (hidden abscess) and can be diagnosed by needle aspiration or examination under general anesthesia. A horseshoe abscess is produced when the ischiorectal abscess of one side spreads to the contralateral side via the deep postanal space. It is managed by a modified Hanley procedure in which a posterior midline incision is made over the postanal abscess by incising the anococcygeal ligament, and counter-drainage incisions are made over each ischiorectal space.

Supralevator Abscess

The supralevator space lies superior to levator ani and lateral to rectum and communicates posteriorly. Supralevator abscess occurs following an upward extension of the intersphincteric abscess or secondary to intra-abdominal or pelvic pathology such as appendicitis, diverticulitis, pelvic inflammatory disease, and ruptured viscus. An indurated, bulging mass is found above the anorectal ring on DRE. Management of supralevator abscess depends on its etiology. If it is secondary to upward extension of the intersphincteric abscess, drainage is performed internally through the rectum. Drainage through the ischiorectal fossa is avoided in such cases to prevent the formation of a complicated suprasphincteric fistula. If the abscess is secondary to ischiorectal abscess, then the incision is placed over the ischiorectal fossa and this may lead to the formation of an extrasphincteric fistula. Abscesses secondary to intra-abdominal or pelvic pathology require treatment of the underlying condition and direct drainage of the abscess transabdominally.

Clinical Presentation

The presentation varies depending on the anatomical location. Classically, patients present with severe anal pain out of proportion to physical examination findings. Some patients, especially immunocompromised, may present with fever, urinary retention, or life-threatening sepsis. 20–33% of patients provide a history of previous anorectal suppuration. A palpable mass may be found in the perianal area or by DRE, depending on the location of abscess. Tenderness may be present; however, fluctuation is very rarely elicited in the perianal region. Sometimes, no signs of inflammation may be found, especially in hidden abscesses.

Diagnosis

Diagnosis is made clinically by local examination. Examination under general anesthesia may be required in complex, deep-seated abscesses and in immunocompromised. Pelvic imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), and fistulography are usually indicated in complex and recurrent abscesses following inadequate drainage, immunosuppression, presence of fistula, etc.

Management

Management consists of incision and drainage of abscess, usually under local anesthesia, as an office procedure. Complex abscesses may require exploration and drainage under general anesthesia. Timely management is required to prevent extensive necrosis and life-threatening sepsis, especially in immunocompromised. Antibiotics and abscess culture are indicated if there is a history of immunosuppression, associated systemic illness such as diabetes mellitus, extensive cellulitis, etc. Biopsy to rule out leukemic infiltration is also performed.

ANAL FISTULA

Anal fistula is a chronic manifestation of anorectal abscess. In simple words, anal fistula represents a communication between the anal canal and the perineal skin. The most common cause of anorectal abscess is infection of the anal glands. This is called cryptoglandular theory of anal sepsis. Fecal bacterial plugging of the duct of the anal glands leads to infection in the gland and subsequently abscess formation, leading to anal fistula. Other etiological factors include trauma, Crohn's disease, malignancy, radiation, and unusual infections such as tuberculosis, chlamydia, or actinomycosis. These factors should be considered in the complex, recurrent, or nonhealing fistula.

Classification of Anal Fistula

The classification done by Park et al. in 1967 is the most commonly used classification system, which is as follows:

- *Intersphincteric*: The fistula is confined to the inter-sphincteric plane.
- *Trans-sphincteric*: The fistula traverses the external sphincter, communicating with the ischiorectal fossa.
- *Suprasphincteric*: The fistula extends cephalad over the external sphincter and perforates the levator ani.
- *Extrasphincteric*: The fistula extends from the rectum to the perianal skin, external to the sphincter apparatus.

Clinical Features

Most patients have a history of perineal abscess. Patients usually present with complaints of purulent discharge from the external opening in the perineal region. This discharge is usually intermittent. Classically, the symptom of discharge may also be associated with build-up of pain, mild fever, and pain on defecation, followed by mucopurulent discharge with relief of pain.

Physical Examination

On careful examination of the perineal region, an external opening is often easily seen. It can be identified as a small pit surrounded by localized fibrosis. Active discharge may or may not be present. On DRE, the internal opening may be felt as an indurated nodule or a small area most often at the level of dentate line. The indurated tract may also be palpable. If the external opening is close to the anal verge, the fistula is usually intersphincteric. Trans-sphincteric and other complex fistulas usually open far away from the anal verge. At times, there could be multiple external openings due to multiple complex fistula tracts. This condition is called watering-can perineum.

Clinical examination described nearly 100 years ago by Goodsall and Miles tells about the internal opening in relation to the external opening. The rule states that the external opening anterior to the imaginary transverse line in the coronal plane most likely communicates with an internal opening lying at the end of a radial line drawn to the nearest crypt at the dentate line. If the external opening is posterior to this line, the internal opening will most likely be located in the posterior midline following a curved tract. Exception to this is an anterior opening more than 3 cm away from the anal verge and the presence of multiple external openings. The internal opening in this condition will most likely be in the posterior midline.

Investigations

Sigmoidoscopy and colonoscopy: Sigmoidoscopy should be performed in all patients with anorectal fistula to rule out associated conditions such as neoplasm, inflammatory bowel disease, or secondary tract in the rectum.

Fistulography: It may be done in patients with recurrent fistulas when the prior procedure has failed to identify the internal opening. In this procedure, the external opening is cannulated through which contrast material is injected with minimal pressure, and multiple X-ray images are taken at different angles. However, a study by Kuijpers and Schulpen found that fistulography is unreliable when compared to intraoperative findings. They also found that it gives high false-positive results, and this leads to unnecessary and harmful surgical exploration.

Anorectal ultrasonography: It can delineate the muscle anatomy of anal sphincters and its relation to the fistula tract. Internal opening is usually not identified, but it can be accurate in localization of the fistula tract and/or abscess. The injection of hydrogen peroxide into the tract acts as an image enhancer and is helpful in detecting the complex fistula. Now, three-dimensional endoanal ultrasonography can reliably and accurately diagnose fistula-in-ano with or without hydrogen peroxide enhancement.

Magnetic resonance imaging: MRI is an accurate method of imaging an anal fistula disease. With great accuracy, it can identify the internal opening dose of the fistula tract and its external opening. MRI is particularly very useful in cases of complex fistula and secondary extension of tract. In a study by Beets-Tan et al., the sensitivity of MRI done preoperatively is 100% and specificity is 86%. When combined with endoanal ultrasound, the accuracy of diagnosis is further enhanced.

Computed tomography: The use of CT scan is limited in diagnosis of fistula-in-ano because of its poor visualization of levators and sphincteric complex.

Anorectal manometry: Manometry helps in identifying the patients who are at a greater risk of postoperative incontinence. This can help in tailoring the surgical management for improved clinical and surgical outcomes. This is especially indicated in patients requiring a division of the substantial portion of anal sphincter for its cure, in multipara women, and in women with a history of forceps delivery, third-degree perineal tear, and prolonged second stage of labor.

Fistuloscopy: This, done by using urethroscopy, is a helpful technique in the intraoperative evaluation of fistula openings,

identifying tracts, and iatrogenic tracts. Newer flexible ureteroscopes are in developmental stages. This could be of great help in diagnosing and treating an anal fistula.

Treatment

The treatment and outcome of an anal fistula depend on various factors such as classification of fistula, identification of internal and external openings, course of the fistulous tract, and amount of the sphincter involved. The external opening is usually visible as an indurated, elevated, granulomatous tissue with purulent discharge. The identification of the internal opening is difficult. Injection of hydrogen peroxide and methylene blue mixture is helpful identification of the internal opening. A simple intersphincteric fistula can be managed by fistulectomy (opening the tract) followed by curettage, and the wound is left open to heal by secondary intention.

Treatment of fistula that involves <30% of sphincter complex can be treated by sphincterotomy without having much risk of incontinence. A fistula that involves >30% of sphincter or high intersphincteric fistulas usually require placement of seton. It is placed loosely through the tract to facilitate drainage of any sepsis and to preserve the sphincter. Later, it can be converted to cutting seton which is periodically tightened to cut through the involved sphincter and to promote fibrosis. This avoids the resulting incontinence.

Other methods for a complex anal fistula include fibrin glue and porcine-derived fistula plug. Both are biological products used for fistula healing without division of the sphincter complex. They cause healing of the tract by providing an extracellular matrix which serves as a scaffold which allows cellular ingrowth and remodeling leading to tract obliteration. Successful obliteration of the tract by fibrin glue was seen in 14–60% of cases. A high fistula or persistent fistula can be treated by sliding advancement flap of mucosa, submucosa, and circular muscle to cover the internal opening.

The new technique in treatment of anal fistula is LIFT (ligation of intersphincteric fistula tract). In this technique, dissection is done in the intersphincteric plane, and the fistula tract is identified and ligated. This leads to obliteration of the communication with the anal canal. The success rate of this technique is 60–94%.

PILONIDAL DISEASE

Pilonidal disease is a condition of the intergluteal cleft in which hair containing sinus or abscess develops. The sinus may be a single tract or may be branched. It can spread laterally which emerges as granulation tissue-lined openings over the skin, usually in midline. The incidence of pilonidal sinus is 26 per 100,000 people. The morbidity associated with this disease is high due to its nature, wound complications after surgery, and high recurrence rate, thus generating a challenge for the surgeon.

Etiopathogenesis

Pilonidal disease was first described by M Hodges in 1880 as a sinus containing nest of hair. Earlier, it was considered to be of congenital origin. Gage in 1935 proposed that sinus disease was secondary to anomalous embryonic development of the medullary canal. Many theories thereafter have attributed pilonidal disease to be more of an acquired disease. Hardaway noted that pilonidal disease was "apparently much common in the military service than in civilian life." He attributed this to the poor hygienic conditions. He postulated that compression and irritation of the coccyx during field activities, such as jeep driving, was the cause of the disease. Thus, it was also called "jeep disease." Patey and Scarff in 1946 compared the histology of congenital dermoid and pilonidal sinus. He noted that the dermoid had epithelialized tracts while the pilonidal sinus had granulation tissue-lined tracts which were formed by foreign body granulomatous reaction to surface hairs. Hair follicles are almost never seen in the wall of the sinus. Dead hair is usually present within the sinus cavity. Bascom further explained that a vacuum force is created by the intergluteal cleft that directs hair into the subcutaneous tissue. This forms the basis behind Bascom cleft lift procedure.

Karydaki in 1992 described three main factors for the development of pilonidal disease. The factors are: (1) Invasion of loose hair, (2) Hair embedding, and (3) Vulnerability of the affected skin. These factors were considered in the Karydakis flap reconstruction where a more resistant gluteal skin flap was used. These theories suggest that pilonidal disease is caused due to local irritation from embedded loose cut hairs. The presence of the interdigital pilonidal disease in hairdressers and of the pilonidal disease in other sites such as umbilicus supports the acquired nature of the disease. Rarely, a carcinoma can arise from a chronic pilonidal disease.

Histologically, the pilonidal sinus tract is lined by chronic granulation tissue. The midline pits have a squamous epithelial lining whereas the tract has no epithelium. Foreign body giant cells are seen associated with hair shafts within a background of chronic granulation tissue. Microbiology gram-negative and anaerobes are mostly seen in pilonidal disease. In recurrent disease, gram-positive and aerobic bacteria are present.

Clinical Presentation

Pilonidal disease is seen 2.2 times more frequently in men as compared to women. It is seen in the second to third decade of life. Rarely it occurs in <15 or >40 years of age.

Risk factors include obesity, degree of hair growth, family history of pilonidal disease, local trauma, sedentary occupation, and dark-haired individuals. It is more commonly seen in whites and non-Hispanic populations. It is rarely seen in Asian and Pacific populations.

In 50% of pilonidal diseases, acute presentation is seen. In acute cases, the pilonidal disease presents as an abscess. It is present over the sacrococcygeal region causing pain over the area, fluctuating mass with overlying cellulitis on examination. It lies just cephalad to the midline pit above the gluteal cleft.

In chronic cases, a cavity develops which drains into single or multiple sinuses. These sinuses are located in the midline and lie between the sacrococcygeal joint and the tip of the coccyx. The cavity and sinus openings usually run cephalad, thus differentiating it from a perianal fistula.

Diagnosis

Pilonidal disease is a clinical diagnosis due to its characteristic appearance. Differential diagnosis includes hidradenitis suppurativa, furuncle, perianal abscess or fistula, sacral osteomyelitis, syphilis, tuberculosis, and actinomycosis. Malignant degeneration can occur in 0.1% cases. Squamous cell carcinoma is most commonly seen. It occurs in middle-

aged men with long-standing disease. Hence, histopathological evaluation of an excised specimen is necessary.

Treatment

Earlier when pilonidal disease was considered to be of congenital origin, complete excision of sinus tract up to the sacral fascia was done. With recent theories suggesting an acquired form of disease, complete resection with primary closure is done attending to the offending tissue and the underlying mechanism. The goal of treatment is complete wound healing with minimum morbidity and low recurrence rate. In a Cochrane review, there is no clear benefit of primary closure over an open approach with regard to healing time and infection rates. Primary closure techniques where the incision is placed laterally are considered best. Taking all factors into consideration, an individualized approach should be adopted by the surgeon for treatment of the pilonidal disease.

Acute Pilonidal Abscess

A definitive resection with abscess excision results in higher recurrence rates; hence, a stages approach is used. It can be done in an outpatient setting in the emergency room. Prone jackknife position is given and buttocks are taped apart. A paramedian longitudinal incision is made over the abscess. All debris and hair are curetted from the cavity. Unroofing and fulguration of the tract are done. Sitz bath has to be done daily to maintain hygiene. The wound is evaluated weekly to check for healing and to ensure that it is free of debris and hair. The retained hair is a major factor for nonhealing and recurrence. This procedure has a recurrence rate of 2%.

Chronic Pilonidal Disease

Chronic pilonidal disease is seen in 15–40% of patients treated for acute abscess. Recurrence following previous surgeries is also high. There is no single ideal technique for the treatment of pilonidal sinus. Various techniques are available for the treatment. Antibiotics against anaerobic bacteria may improve healing as suggested in some studies.

Conservative Approach

It consists of hair control by shaving or laser therapy, maintaining perineal hygiene. Limited lateral incision and drainage of abscess are required.

Midline Follicle Excision and Lateral Drainage—Bascom Technique

In this technique, the midline sinus pits are excised using a fine scalpel blade up to the presacral cavity and left open. An incision is made laterally 1 cm from the midline to expose the presacral cavity deep to the pits. The cavity is opened, and debridement of necrotic material, hair, and granulation tissue is done. The wound is then left for secondary healing. Frequent follow-up is required for hair removal. The advantages of this technique are minimal morbidity and a short healing time. In modified Bascom's technique, the midline excised pits are closed using a nonabsorbable suture. The lateral incision helps in curetting out the granulation tissue and hairs. It also releases the midline skin from the presacral fascia, thus preventing tethering. In the modified technique, it prevents any tension on the primary closure of the pits. Fibrin glue can be applied after excision and curettage of the sinus tract.

Incision and Curettage with Marsupialization or Saucerization

In this technique, the sinus tract is identified and deroofing of the tract is done along with curettage. The fistula probe is used to identify secondary tracts which are also deroofed. In saucerization, the skin edge is beveled to allow drainage. In marsupialization, the skin is sutured to the base of the wound. Negative pressure wound therapy can be used over the raw area to improve healing. This procedure has a recurrence rate of 1–19%, low complication rate, short operative time, and early return to work.

Excision with or without Closure

The pilonidal sinus along with the surrounding inflammatory tissue is excised up to the sacral fascia. The wound can then be primarily closed or left open for secondary healing. Data from a meta-analysis suggest rapid healing with primary closure as compared to secondary healing. There is no difference in infection rates between the two techniques. The recurrence rate was, however, lower in secondary healing. In midline and lateral incision comparison studies, lateral incisions had better healing rates, lower infection rate, and lower recurrence rates.

Karydakis Flap

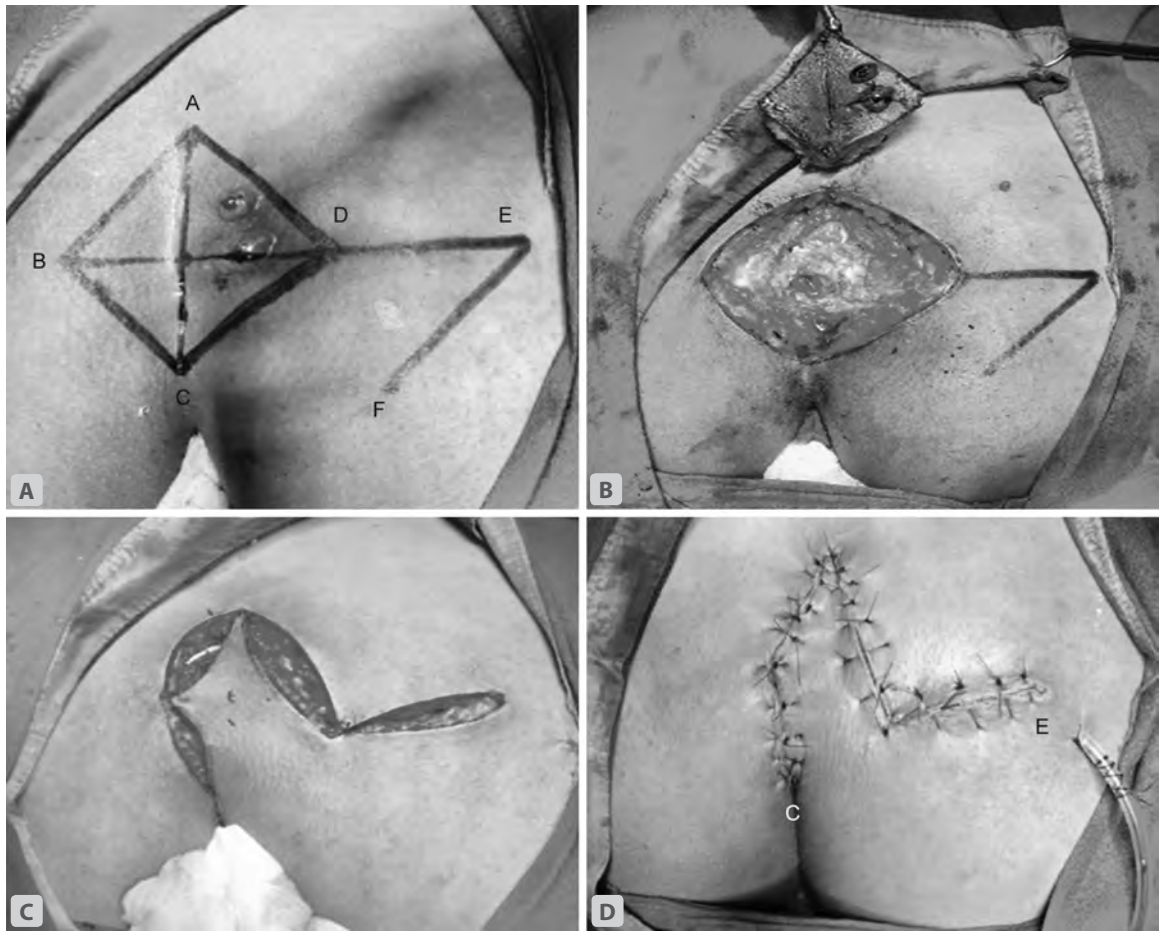
In this technique, an elliptical incision is given. Skin and subcutaneous fat are excised up to the fascia. The ellipse is placed away from the midline. The medial side should just cross the midline and should include the diseased tissue. The medial end is then mobilized by undercutting. Sutures are then placed between the limit of undercutting and the sacral fascia in the midline. This creates a shallow midline sulcus. The subcutaneous tissue is then closed by interrupted sutures after placing a suction drain. The skin is then closed using interrupted sutures. As a result, the incision line lies lateral to midline. This technique cannot be used in bilateral sinus disease.

Limberg Flap

A rhomboid area containing the diseased tissue is marked. The flap that will be utilized for cover is also marked prior to incision. Points A, B, C, D, E, F are marked as shown in **Figure 4**. Line A–C should lie in the midline. C should lie toward the perianal region. Line B–D should intersect line A–C at right angles. Line B–D is extended up to point E. The length of D–E should be equal to A–B. The length of E–F should be equal to A–D and parallel to D–C. Rhomboid excision of the diseased tissue is then done. The flap is then raised containing the skin and subcutaneous tissue up to the fascia. The flap is then rotated over the defect. Point E is sutured to point A. A suction drain is placed. Subcutaneous tissue and skin are then closed by interrupted suture.

Cleft Lift Procedure

This technique is used for a chronic, nonhealing midline wound. The midline wound is excised in a triangular shape. A full-thickness skin flap is raised to overlap the skin edges of



FIGS. 4A TO D: (A) Rhomboid excision with Limberg flap. (B) Rhomboid area to be excised and flap to be taken is marked. (C) Rhomboid excision of diseased tissue is done. (D) Flap created and fixed at points A, B, C, D suction drain in situ. ***(For color version, see plate 12)***

the wound on the opposite side. The skin is then closed over a suction drain. As a result, the superior gluteal cleft is eliminated and incision is displaced laterally.

Recurrent Pilonidal Disease

These patients require a radical approach. A wide excision of the tract along with the diseased tissue is done. It results in creation of a large defect. This defect can then be closed by Z-plasty, V-Y flap, rhomboid excision and Limberg flap, Karydakis flap, or cleft lift procedure. This procedure carries higher morbidity.

RECTAL PROLAPSE

Protrusion of rectal wall through anal orifice is termed rectal prolapse. It is relatively rare condition and malnourished children and elderly mostly affected. Elderly females commonly present with another pelvic organ involvement, e.g., uterine, vaginal prolapse, rectocele urethrocele, or enterocele. The risk factors associated with rectal prolapse are constipation, recurrent or massive diarrhea, fecal incontinence, and rectal ulcers.

Most common complaints are fullness of rectal area; associated symptoms are pain, constipation, and abdominal pain. Careful examination is required by the emergency physician as this condition is misdiagnosed as prolapsed hemorrhoids. Management strategies depend on careful evaluation of incarceration, thrombosis, and strangulation and depend on the presence of ischemia. If signs of ischemia are present, prolapse should be reduced by the surgeon in the operating room. Manual reduction can be attempted in the emergency department (ED) if signs of ischemia are not present. Gentle pressure is sufficient to reduce the prolapse, if edema is present; application of granulated sugar (which causes desiccation of mucosa) can reduce the edema. Once reduction is successful, the patient can be discharged home with follow-up in the surgery outpatient department. Stool softener fiber supplements should be prescribed to the patient with instruction to stay well hydrated to avoid constipation.

RECTAL TRAUMA/FOREIGN BODY

Rectal trauma is less common, mostly due to penetrating injuries, shooting, and road traffic accident. Rectal blunt injury is less common than penetrating injury.

Rectal trauma may occur due to foreign bodies also but is less reported to the ED. The incidence of rectal foreign bodies is reported due to voluntary insertion for sexual stimulation and autoeroticism; however, sexual assault is also reported. Prisoners and psychiatric patients can also hide sharp objects or drugs in their rectum. Obtaining history from a patient with rectal foreign bodies is quite difficult; rectal fullness, rectal pain, rectal bleeding, abdominal discomfort, and constipation are common complaints.

Rectal trauma or rectal foreign body need clinical as well as radiological assessment. Secondary survey is also necessary to assess pelvic fracture, peroneal or transpelvic injuries, and rectal or urethral bleeding. Assessment of rectal trauma with higher sensitivity is possible with rigid proctosigmoidoscopy which also detects extraperitoneal injuries. A CT scan with contrast is the gold standard with high sensitivity and specificity for detecting rectal trauma. *There are five grades of rectal injury* are described by the American Association of Surgery for Trauma (Grade I: Contusion/partial thickness laceration, Grades II–IV: Laceration of varying degree from <50% of circumference to full thickness, Grade V: Devascularized segment).

A plain radiograph has poor sensitivity and specificity and is only helpful in detecting the foreign body. Lateral and anteroposterior plain radiology film is sufficient to detect a rectal foreign body. The number, size, shape, location, and orientation of foreign body can be detected. Colonic perforation, bowel obstruction, hemorrhage, deep mucosal tear, abscess, and peritonitis are the complications of a rectal foreign body.

The general surgeon should be consulted for rectal trauma as multiple concomitant injuries may need attention. Rectal foreign bodies above the rectosigmoid junction should be removed by the surgeon. If a rectal foreign body is palpable on rectal examination, the emergency physician may attempt to remove it. Enema and anal dilatation followed by digital extraction can be attempted. 1% lidocaine or 0.5% of bupivacaine can be used during extraction to relax the anal sphincter. An anoscope or sigmoidoscope is helpful in direct visualization of foreign objects and also prevents iatrogenic injuries. Foreign bodies are difficult to extract by the trans-anal route if the size of the object is >10 cm, it is a sharp object, it has slipped to sigmoid, or it is older than 2 days. Proctosigmoidoscopy should be arranged and performed after removal of foreign body to assess bleeding by mucosal tear bowel injury and residual foreign bodies. The patient should be observed in the ED if a mucosal tear is confirmed.

PROCTITIS

Proctitis is present with nonspecific features such as irritation, itching, burning, and tenesmus and is characterized by inflammation of the rectal mucosa within 15 cm of the dentate line. Proctitis can be acute or chronic and secondary to various other diseases, e.g., sexually transmitted diseases, radiation, medication (antibiotics), autoimmune diseases (Crohn's disease, ulcerative colitis, celiac), iatrogenic (chemicals, trauma, rectal instrumentation), and idiopathic. In response to various irritants, the inflammatory process develops, e.g., loss of mucosal cell, eosinophilia, and endothelial edema. Acute reaction progresses to fibrosis of connective tissue, arteriolar endarteritis, and tissue ischemia leading to bleeding, ulceration, stricture, and fistula. The patient presents with nonspecific complaints and nonspecific examination findings such as mucosal erythema and mucosal friability. Symptomatic supportive care is important in proctitis. Sitz bath, antispasmodic medication, stool softener, and high-fiber diet are recommended. Treatment should be started if any systemic cause of proctitis is identified. Antibiotics (infectious cause), antiviral (viral etiology), and steroids (autoimmune/radiation cause) can be prescribed by the gastroenterologist/colorectal surgeon on follow-up.

PRURITUS ANI

The burning and itching sensation in the perianal region is pruritus ani. After hemorrhoids, it is the most common condition and most of the people do not take medical advice for this condition. 50–90% of cases are primary or idiopathic (no obvious cause), and secondary causes are given in **Table 2**. The problem starts with mild itching and burning which progress to intolerant soreness and itchiness and lead to scratching and excoriation causing skin injury (stage 0: normal skin, stage 1: red and inflamed skin, stage 2: white and lichenified skin, stage 3: lichenified skin, coarse ridges, and may ulcerate).

For primary and idiopathic pruritus ani, symptomatic treatment is started. Maintain dry clean and intact perineal skin. Loose-fitting undergarments are advised. Inflammation is reduced by zinc oxide and corticosteroid topical barriers. Medicated soap and topical anesthesia are discouraged. Treatment of the underlying cause should be initiated for secondary pruritus ani. Intractable pruritus ani is treated with low-dose capsaicin cream. Severe and resistant cases are treated with methylene blue injection (in the sensory nerve bundle of the perineal area), sclerotherapy, radiation therapy, and surgical procedures.

PROCTALGIA FUGAX

Proctalgia fugax is a gastrointestinal disorder that causes severe, self-limiting anorectal pain usually lasting 5 seconds to 90 minutes. Patients experience this fleeting and recurring pain over weeks, with no pain between episodes. Although this is a diagnosis of exclusion in the ED, it is important to be aware of the condition. It has several triggers, including sexual activity, stress, constipation, defecation, and menstruation. This disease affects women more than men, most commonly between the ages of 30 and 60 years, with a prevalence of 4–18% in the general population. Proctalgia fugax is thought to be caused by spasm of the internal anal sphincter or compression of the pudendal nerve. Given the fleeting nature of the pain, patients usually do not require medications; however, those with severe symptoms might get relief with topical treatments such as nitroglycerin or diltiazem. Nonpharmacologic agents, such as biofeedback, have been shown to be effective as well.

TABLE 2: Secondary causes of pruritus ani.

Mechanical	Anal fissure, fistula, hemorrhoids, trauma, tight undergarment, unhygienic conditions, vaginal discharge
Dermatitis	Eczema, psoriasis, lichen planus, erythema multiforme
Infections	Pinworm, *Candida*, sexually transmitted disease
Systemic	Diabetes, cholestasis, renal failure, leukemia, HIV, vitamin A, D, and iron deficiency, obesity
Inflammatory	Inflammatory bowel disease
Malignancy	Squamous cell carcinoma, melanoma
Medication	Colchicine, neomycin
Dietary	Tea, coffee, soda, chocolate

SUMMARY

Emergency Physician may get patients of anorectal complaints emergency department. Most of these complaints can be managed conservatively because they are benign and; however, clinicians must be aware that there are a few anorectal emergencies can progress and present as complication. The history and physical examination are important so that critical disorders can be recognized and specific treatment plans can be initiated early. It is important to maintain a broad differential diagnosis of anorectal disease to distinguish benign from serious anorectal disease and its complications. Thorough history and physical can help distinguish between different types of anorectal complaints. Most anorectal complaints can be managed conservatively, but it is imperative to know when to consult surgeons.

MULTIPLE CHOICE QUESTIONS

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105 CHAPTER

Vascular Abdominal Emergencies

Devendra Richhariya

INTRODUCTION

An emergency physician should be ready to consider the uncommon diagnoses while managing abdominal emergencies or a patient with nausea, vomiting, and diarrhea or a patient with abdominal, back, or flank pain. Abdominal vascular emergencies in the differential diagnosis should be considered. Vascular abdominal emergencies are not common and on the basis of clinical findings, they are also difficult to identify and a high index of suspicion is required which when present are often catastrophic. Most of the conditions are time-sensitive, putting perfusion of critical organs (e.g., the bowel) at risk, thus leading to the potential for ischemia, infarction, and translocation of enteric microbes, bacteremia, and sepsis. Aneurysmal dilation of the aorta with rupture leads to rapid hypovolemic shock and death if not diagnosed. Most of the vascular emergencies of abdomen require surgical intervention; diagnostic testing should be performed along with resuscitation, consultation, and involvement of the vascular or general surgeon.

VASCULAR ABDOMINAL ANATOMY

The aorta gives rise to several paired and unpaired vessels within the abdomen. The adrenal, renal, and gonadal arteries are paired arteries and supply blood to respective organs. Most of the digestive tract is supplied by unpaired branches [celiac artery, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA)]. The celiac trunk gives rise to three branches (splenic, left gastric, and common hepatic arteries) which supply the foregut structures from the distal esophagus to the second part of the duodenum, the spleen, the liver, and parts of the pancreas (**Fig. 1**). The SMA typically arises at the approximate level of the first lumbar vertebra about 1 cm below the celiac trunk. The SMA gives rise to several branches that supply the midgut structures extending from the second part of the duodenum to the distal third of the transverse colon (**Fig. 2**). The venous system of the gastrointestinal tract differs from the arterial system in that, rather than draining into the inferior vena cava (IVC), it passes via the portal vein into the liver. Blood passes through the hepatic lobules into the

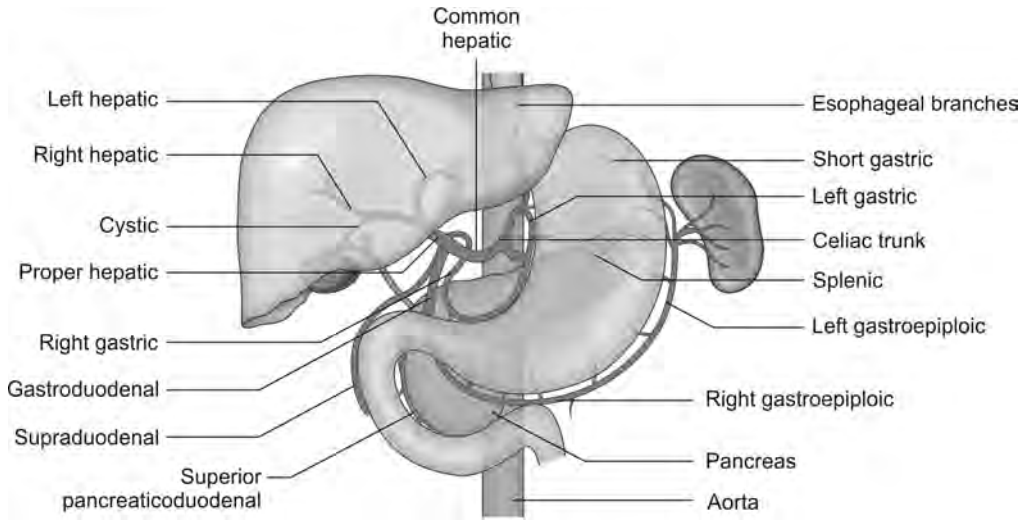


FIG. 1: Celiac trunk and its three major branches: the splenic, left gastric, and common hepatic.

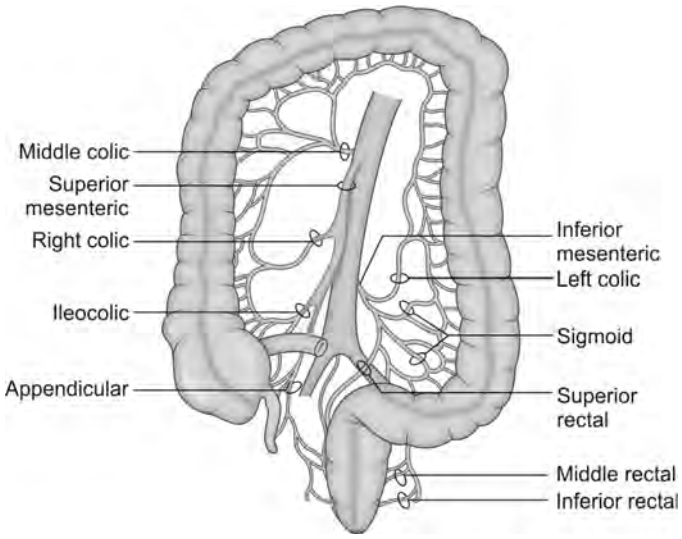


FIG. 2: Superior and inferior mesenteric arteries and their anastomotic connections.

hepatic veins, which pass into the IVC. Pathologic conditions (e.g., cirrhosis, obstruction, thrombosis) that obstruct portal flow cause anastomoses to form between systemic and portal vessels in tissues that are at the watershed junction between the two systems. When anastomoses become very large, they are named varices and locations are at the lower esophagus, the umbilicus, and the rectum.

ABDOMINAL VASCULAR THROMBOSES

Aortic Thrombosis

Acute occlusive aortic thrombosis is a rare condition that is lethal if not diagnosed. Aneurysmal disease, dissection, or severe atherosclerotic disease is associated with nonocclusive aortic thrombosis which is more common. Other conditions associated with aortic thrombotic disease include diabetes, cardiomyopathy, blunt and penetrating abdominal trauma, spinal surgery, polycythemia, thrombocytosis, nephrotic syndrome, exogenous estrogen, the classic hypercoagulable conditions (protein C and S deficiency, factor V Leiden deficiency, antithrombin III deficiency), malignancy, use of some chemotherapeutic agents, antiphospholipid antibody syndrome, and history of aortic grafting. Because of the large diameter of the aorta, emboli (typically from the left ventricle) rarely lead to aortic occlusion. Patients with an acute thrombotic event typically present with symptoms of lower extremity ischemia: bilateral lower extremity, pulselessness, pallor, pain, paresthesia, and possible paralysis. Mesenteric ischemia may also be present. Occlusion of the artery of Adamkiewicz causes spinal cord infarction. Signs of the anterior spinal artery syndrome include paralysis, and both light touch and pinprick sensations are lost but vibratory sensation and proprioception are preserved. The Leriche syndrome results from chronic obstruction of the distal aorta leading to chronic ischemia of the pelvis and lower extremities. This syndrome clinically presents in men, with a triad of symptoms: claudication, absence of lower limb pulses, and erectile dysfunction. Emergent consultation with a vascular surgeon is required in acute ischemia resulting from aortic occlusive disease. Most patients require hospitalization for observation, initiation of anticoagulant, or antiplatelet agents.

Renal Artery Thrombosis

Renal artery thrombosis is also rare and seen in the 30–50-year age group due to development of a clot in situ in existing atherosclerotic lesions. Post renal transplantation thrombosis is a known complication because of the surgical anastomoses and immunosuppressive drugs. Intra-aortic catheter or balloon pump placement, intravenous (IV) cocaine use, and renal angiography are also risk factors. Clinical features of acute renal artery occlusion consist of flank pain, which may be associated with hypertension. The patient may present with nausea, vomiting, and upper abdominal pain on the affected side and hematuria may occur in some patients. An untreated occlusion of the renal artery leads to renal infarction; the serum lactate dehydrogenase (LDH) is typically increased in renal infarction. When renal colic is suspected, unenhanced computed tomography (CT) is helpful in differentiating features of renal artery thrombosis from those of renal colic. Duplex ultrasound is the preferred initial test in the renal transplant recipient. Trauma may also be the cause of renal artery occlusion. Blunt trauma to the abdomen can lead to compression of the artery as well as dissection and thrombosis. Patients typically require surgical revascularization, and the timeliness of this intervention is linked with improved outcomes. Nontraumatic thrombosis is treated with surgical revascularization or sometimes thrombolysis.

Renal Vein Thrombosis

Renal vein thrombosis may be either an acute or a chronic process. Diagnosis depends on a high level of clinical suspicion, because the clinical findings mimic those of renal colic, renal artery occlusion, and pyelonephritis. Acute thrombosis clinically presents as flank pain along with nausea and vomiting. Hematuria and proteinuria may also be noted. Chronic thrombosis may not be clinically evident until the development of complications such as impaired renal function or pulmonary embolism. The left renal vein is affected more often than the right, but up to two thirds of patients have bilateral thrombosis. In contrast to occlusive arterial disease, renal vein thrombosis is also a disease of children and neonates. In the setting of severe volume depletion, dehydration, or sustained hypotension, blood flow is shunted from the renal vein, leading to sluggish flow that may eventually lead to the formation of a clot. In children, a palpable mass in the flank may be present because of the enlargement of the kidney on the affected side. The problem in children, clinically present as a triad of symptoms, includes a palpable mass, gross hematuria, and thrombocytopenia. The risk factors for thrombosis of the renal vein are hypercoagulable, post-transplant, and postoperative states. Blunt trauma and infection may also play a role in the development of thrombosis. The most common disease associated with the development of renal vein thrombosis is the nephrotic syndrome. Patients have direct loss of protein S and antithrombin III in their urine. With excessive proteinuria, the liver is stimulated to produce new proteins, many of which are prothrombotic.

Color Doppler sonography should be used to evaluate the flow in the graft in post-transplant patients. In the rest of the patients, the CT scan is the diagnostic study of choice. IV contrast

should be administered to visualize the vascular structures. In addition to visualizing the thrombus, the kidney on the affected side is typically engorged because of impaired venous drainage. Delayed images show a persistent enhancement from the contrast on CT scan because of the limited venous outflow. Medical management with systemic anticoagulation is the usual treatment for renal vein thrombosis. Patients with, or at risk for, a severe disease (e.g., extensive clot progressing to the IVC, renal failure, bilateral disease, renal transplant) may be candidates for systemic or catheter-directed thrombolytic therapy.

Portal Vein Thrombosis

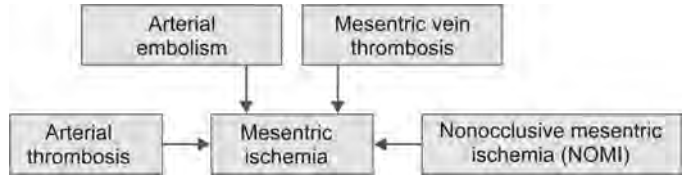
The risk of developing portal vein thrombosis in the general population is very low (<1%). Mostly, it is seen with cirrhotic patients; other risk factors associated with portal vein thrombosis are adjacent inflammatory conditions (e.g., pancreatitis, cholecystitis, diverticulitis, inflammatory bowel disease, appendicitis), malignancies (local or systemic), or hypercoagulable conditions (especially sepsis). Mortality caused by portal vein thrombosis itself is low; however, these patients frequently have other significant comorbidities that combine to give them poor outcomes with this condition. The mechanism by which cirrhosis leads to portal vein thrombosis is not clear. It is believed that decreased portal blood flow, periportal inflammation and fibrosis, and impaired production of anticoagulation factors lead to thrombosis. Portal vein thrombosis in children and neonates is associated with an intra-abdominal infection, including umbilical infections. In the acute phase, several compensatory mechanisms occur, including dilation of the hepatic artery to increase blood supply, development of variceal collaterals between the portal and systemic venous systems, and collateral cavernoma formation.

Acute portal vein thrombosis may present with abdominal pain (which may be localized in the right upper quadrant but is frequently diffuse), nausea, and fever. Signs of intestinal ischemia, which is a secondary effect of acute portal vein thrombosis, may also be present. With chronic thrombosis, patients may remain clinically silent until the secondary effects of the thrombosis occur. These effects include worsening hepatic function, worsening portal hypertension, and hematemesis from esophageal varices. Ultrasound with Doppler is the diagnostic modality of choice for portal vein thrombosis. The absence of flow within the lumen and, in some cases, the presence of a cavernoma identify the disease. If a suspicion exists for extension of the clot into the mesenteric venous system, CT with IV contrast is indicated to evaluate the vasculature and intestines.

Patients with portal vein thrombosis without complications of bleeding or intestinal ischemia are managed with systemic anticoagulation. Empiric thrombolytic therapy in cases of acute thrombosis may be indicated in severely ill patients in consultation with a gastroenterologist, although there may be significant complication rates. Thrombolytics are also considered when standard anticoagulation does not lead to recanalization. A transjugular intrahepatic portosystemic shunt (TIPS) procedure may be considered in patients having liver transplants or as an alternative to thrombolytic therapy.

ISCHEMIC BOWEL

Ischemic bowel can be caused by any one of the four mechanisms (**Flowchart 1**): (1) Arterial thrombosis, (2) Arterial embolism, (3) Venous thrombosis, or (4) Nonocclusive mesenteric ischemia (NOMI). Survival rates vary depending on the mechanism. The overall mortality is as high as 60–80%, especially with delays in diagnosis or in presentation of >24 hours and worse survival rates in older patients, in those who are not candidates for bowel resection, and in those whose cause is NOMI.



FLOWCHART 1: Mechanism of developing the mesenteric ischemia (ischemic bowel).

Mesenteric ischemia is categorized as occlusive or nonocclusive in origin. Occlusive mesenteric ischemia involves either the SMA or the superior mesenteric vein (SMV). Arterial occlusion may be embolic or thrombotic in origin. Mesenteric ischemia and ischemic colitis are different clinical entities. Patients with mesenteric ischemia typically present with abdominal pain. Patients with ischemic colitis present with lower gastrointestinal bleeding and are less likely to report abdominal pain as the primary complaint. Angiography is not indicated in cases of ischemic colitis. Predisposing cardiac conditions include arrhythmia (most commonly atrial fibrillation), myocardial infarction, cardiomyopathy, recent angiography, valvular disorder (e.g., rheumatic valve disease), or ventricular aneurysm. Following surgical embolectomy, the mortality from analyzed results from four decades is 54%.

Thrombotic Occlusion of the Mesenteric Artery

Atherosclerosis is the major cause of arterial thrombosis leading to ischemia of the SMA and is the cause of mesenteric ischemia in 25% of patients. The onset of pain is usually more insidious and may be initially intermittent and eventually become constant. Other causative factors are hypercoagulability, estrogen therapy, and prolonged hypotension. Patients with chronic ischemia may present with intestinal angina (typically epigastric pain precipitated by eating) and describe fear of food and ensuing weight loss. Chronic mesenteric ischemia is usually caused by atherosclerosis and is more common in women and smokers. It is also associated with radiation.

Thrombotic Occlusion of the Mesenteric Vein

About 10–15% of mesenteric ischemia cases are associated with mesenteric venous thrombosis. The risk factors for mesenteric venous thrombosis include oral contraceptives or estrogen therapy, malignancy, hypercoagulability, portal hypertension, portal vein thrombosis or other deep vein thrombosis, sickle cell disease, clotting disorders, hepatitis, pancreatitis, coagulopathic states, sepsis, cigarette smoking, prior abdominal surgery, and alcohol use. Mesenteric venous thrombosis cases (20%) are found to be idiopathic also. Patients may present in a subacute fashion with abdominal pain and diarrhea. Clinical findings are likely to be more severe, with frank peritonitis and bleeding in patients with extensive transmural ischemia. With chronic mesenteric

vein thrombosis, the collateral circulation usually allows for adequate venous drainage, limiting symptoms, and consequent secondary effects of portal hypertension and varix formation. Mesenteric venous thrombosis is usually diagnosed by CT with IV contrast. Most mesenteric venous ischemia is treated nonoperatively with anticoagulation. Thrombolytic therapy for portal vein thrombosis should be considered in relation to risk–benefit profile and in consultation with a gastroenterologist.

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia is defined as ischemia in the absence of identifiable occlusive lesions in the splanchnic arteries or veins. Risk factors associated with NOMI are hypotension, hypovolemia, heart failure, or sepsis, leading to hypoperfusion vasoconstriction, hypotension, and hypoperfusion. Medications associated with NOMI include cocaine, digitalis (splanchnic vasoconstriction), ergot alkaloids and vasopressors, a constricting agent, and β-blockers.

Clinical Findings

Abdominal pain is the chief complaint in most patients with mesenteric ischemia, followed by associated nausea, vomiting, and diarrhea. Pain caused by embolic disease is often acute in onset and the patient may have associated nausea, vomiting, or diarrhea (both may be either bloody or without blood). Bleeding per rectum is reported in 14–16% of cases. Mild abdominal tenderness may be found on examination. As ischemia progress, patients may become hypotensive.

Laboratory Evaluation

There is no single specific test for the diagnosis of mesenteric ischemia. Mesenteric ischemia is commonly associated with anion gap acidosis, leukocytosis, and hemoconcentration. Increased lactate is associated with poor prognosis.

Diagnostic Imaging

Deciding on the most appropriate diagnostic imaging test for mesenteric ischemia is challenging. Plain abdominal radiographs, CT, ultrasound, magnetic resonance imaging (MRI), multislice CT angiography, and angiography are all radiographic modalities that can be considered. Plain radiographs may show pathognomonic findings of mesenteric ischemia (e.g., thumb-printing or bowel loop thickening). Often, these are useful as a first test to evaluate for obstruction or free air though findings are nonspecific. Abdominal radiographs have low sensitivity for the detection of air in the splanchnic vascular system. If portal gas is identified, mesenteric ischemia is the most likely diagnosis and emergent surgical intervention is indicated.

Doppler ultrasound has limited usefulness in the acute and emergent evaluation of mesenteric ischemia. MRI is a time-consuming and costly measure whose accuracy is unconfirmed; CT with IV contrast may show vascular opacification in the vessel lumen as with SMA thrombosis. Dilated loops of bowel, air-fluid levels, and changes in bowel wall enhancement or a combination of these, are nonspecific findings but may indicate more advanced stages of mesenteric ischemia. In the late stage of ischemia, a CT scan shows thickened bowel and air in the bowel wall or pneumatosis intestinalis (**Fig. 3**).

Angiography is still the gold standard in the diagnosis of mesenteric ischemia, but multidetector CT angiography may emerge as a preferred imaging modality because of its ability to assess the bowel wall. When angiography is performed, a catheter is left in the SMA for the administration of vasodilators or papaverine, which is particularly useful in embolic mesenteric ischemia.

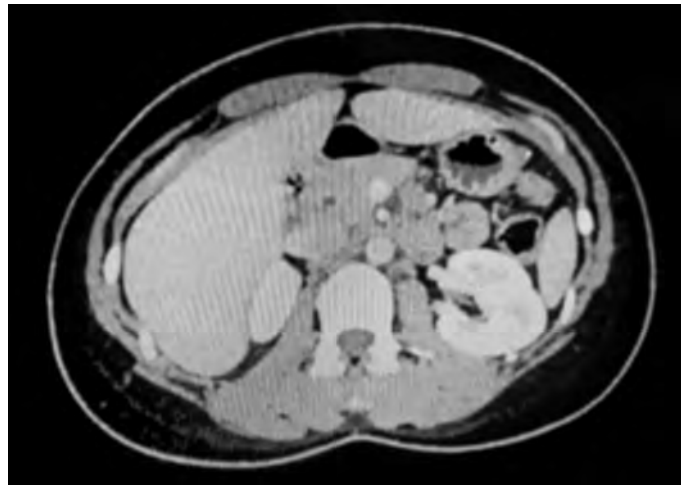


FIG. 3: CT angiogram showing dilated bowel loops and air fluid levels in mesenteric ischemia.

Courtesy: Dr Ashok Puranik.

Treatment

All patients require hemodynamic monitoring, resuscitation, IV fluid, broad-spectrum antibiotic administration, and pain management. Emergent surgical consultation and emergent laparotomy are required if peritoneal signs in acute ischemia are present, and the patient should not be given anything to eat or drink by mouth. Heparin therapy should be initiated if there is no contraindication, and vasopressors should be avoided. A patient with mesenteric ischemia caused by embolic phenomena would require surgical intervention for embolectomy, excision of the infarcted bowel, and consideration of intra-arterial papaverine. The patient with an arterial thrombus is a candidate for similar interventions: thrombectomy and revascularization. Similarly, if the patient has mesenteric venous thrombosis, thrombectomy and excision of the gangrenous bowel may be indicated, and heparin therapy should be initiated. Patients with NOMI should have the underlying cause treated as well as resection of the affected segment of bowel (**Fig. 4**). Prognosis of mesentric ischemia is depends on various factors which are shown in **Figure 5**.

ANEURYSM

A vascular aneurysm is defined by the focal dilatation of an artery to at least 1.5 times its normal diameter. All the three layers of the vessel wall—intima, media, and adventitia—are involved in a true aneurysm; otherwise the dilated segment is referred to as a pseudoaneurysm. There is a broad spectrum of disease severity associated with arterial aneurysms in the abdominal cavity. The patient may remain asymptomatic lifelong or may present with incidental findings during routine health check-ups or may present as catastrophic abdominal emergencies, though a earlier diagnosis of these lesions is common with the increased use of abdominal imaging modalities nowadays.

FIG. 4: Surgical resection of gangrenous ischemic bowel.
(For color version, see plate 12)
Courtesy: Dr Ashok Puranik.

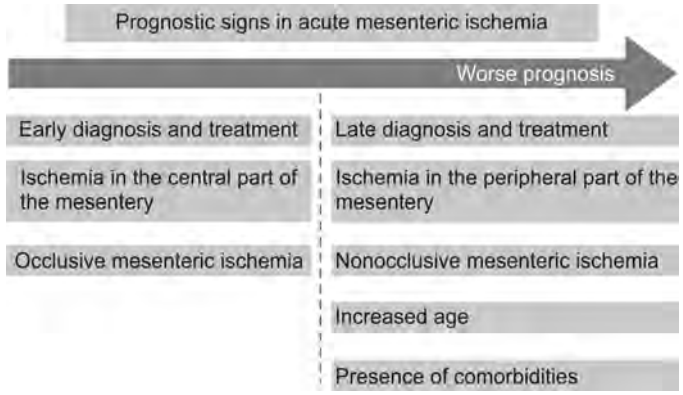

Prognostic signs in acute mesenteric ischemia
Worse prognosis
Early diagnosis and treatment
Late diagnosis and treatment
Ischemia in the central part of the mesentery
Ischemia in the peripheral part of the mesentery
Occlusive mesenteric ischemia
Nonocclusive mesenteric ischemia
Increased age
Presence of comorbidities

FIG. 5: Factors affecting prognosis of acute mesenteric ischemia.

Emergency physicians should be aware of the natural history of a vascular aneurysm as well as its management if it ruptures.

Abdominal Aortic Aneurysm

The aorta is the most common site of an aneurysm in the abdominal cavity and anteroposterior diameter of >3.0 cm is classified as an aneurysm. Most abdominal aortic aneurysms (AAAs) occur in the infrarenal region. Most aneurysms are fusiform (not saccular), entire circumference, and all layers of the vessel are involved. The mean diameter of the infrarenal aorta is 1.66–2.16 cm in older women and 1.99–2.39 cm in older men. The most important complication of AAA is rupture, which occurs almost exclusively in aneurysms larger than 4 cm. The most important risk factors are smoking, family history of AAA, increasing age, and history of atherosclerotic disease for clinically significant aneurysms (>3.9 cm). The pathophysiology of AAA development and subsequent rupture is incompletely understood at this time. The aortic wall is made up of three layers: (1) Intima, (2) Media, and (3) Adventitia. Within the media and adventitia, elastin and collagen are the most important components for maintaining the mechanical integrity of the vessel wall. Elastin is highly concentrated in the medial layer, whereas collagen is concentrated in the adventitia. Damage to and loss of elastin fibers and an associated reduction in the density of smooth muscle cells seem to be integral to the early development of AAA, whereas collagen degradation in the adventitia might be the most important factor in rupture.

Any older patient presenting to the emergency department (ED) with the clinical findings, of abdominal pain, back pain, shock, ruptured or leaking AAA should be suspected, but the presentation of these symptoms and signs is variable. Abdominal pain or back pain are prominent features in patients with a ruptured AAA. AAA mostly ruptured into the retroperitoneal space, remaining ruptured into intraperitoneal, IVC, or duodenum. Most patients presenting to the ED are unaware of this vascular emergency. The early management of patients with suspected unstable AAA, either leaking or ruptured, should focus on rapid diagnosis and early definitive treatment. The presence of known risk factors for the disease (such as male gender, advanced age, and a history of smoking) in association with acute abdominal or back pain should raise the suspicion for an unstable AAA. Pulsatile mass on abdominal palpation has sensitivity ranging from 44 to 97%.

The most useful tool in the diagnostic evaluation of AAA in the ED is bedside ultrasonography. Ultrasound is a highly accurate test, with a sensitivity and specificity approaching 100% in detecting AAA for emergency physicians. Ultrasound can also detect free fluid in the abdomen, associated with a free intraperitoneal rupture. Sonography does not reliably differentiate between ruptured and asymptomatic aneurysms, because hemorrhage most frequently occurs in the retroperitoneal tissues, where ultrasound assessment is limited. CT is a useful imaging modality for newly diagnosed AAA asymptomatic patients to define the anatomic details of the aneurysm; it should not be considered as the initial test of choice for patients with suspected ruptured AAA and unstable patients. CT is helpful where an ultrasound is technically limited or cannot distinguish between a symptomatic and an incidental AAA. For those with a suspected ruptured AAA, aggressive resuscitation is priority, along with diagnostic measures, and consultation with a vascular surgeon should be done simultaneously. Judicious fluid and blood replacement should begin for patients in shock, with large-bore, IV lines in place; once the underlying disorder is an arterial rupture and hemorrhage is confirmed, the vascular surgeon should be involved for surgical repair. For patients with an aneurysm greater than 5.4 cm, a referral should be made to vascular surgery. For those between 4.0 and 5.4 cm, surveillance with ultrasound is recommended every 6–12 months and for those <4.0 cm, every 2–3 years is probably sufficient.

Iliac Artery Aneurysm

Iliac artery aneurysms are defined by a focal dilatation in the vessel greater than 1.5 cm. Symptoms and rupture only occur in aneurysm greater than 4 cm. The risk factors and pathophysiology associated with aneurysms at this site are similar to those for AAA. Patients with AAA also have an iliac artery aneurysm in 10–20% of cases. Isolated iliac artery aneurysms are rare but, when present, the common iliac artery is the most commonly affected site. The emergency physician should be aware that compared with AAA, iliac artery aneurysms are more likely to present with urologic symptoms consistent with renal colic and difficult to visualize with sonography. Because of increased technical difficulties associated with an operation at this site, a ruptured iliac artery aneurysm is associated with high mortality (about 60%) higher than for AAA. However, elective surgery is indicated

when the aneurysm size is greater than 3.5 cm and is strongly recommended when greater than 5 cm.

VISCERAL ARTERY ANEURYSMS

Visceral artery aneurysms, which consist of lesions in renal and splanchnic arteries, are rare and usually asymptomatic and most of the visceral artery aneurysms are detected during routine investigation into unrelated abdominal symptoms. Of those detected, splenic and hepatic artery aneurysms are by far the most common, comprising 80% of visceral artery aneurysms. The natural history is poorly understood and poorly defined clinical presentation. Multiple aneurysms are present in about one third of patients. Most patients are diagnosed or present with symptoms in the sixth decade of life. Aneurysms typically greater than 2 cm are vulnerable for rupture, so this size is often considered for surgical repair in patients with an asymptomatic disease.

Splenic Artery Aneurysm

Splenic artery aneurysm is common in all visceral artery aneurysms, about 60%, and mostly are true aneurysms. Arteriosclerosis, portal hypertension, pancreatitis, and trauma are common risk factors. There is an increased prevalence of the disease in multiparous women and with the increased use of high-resolution ultrasonography in pregnancy, these aneurysms are being detected in otherwise healthy pregnant women. Pregnancy and aneurysm size greater than 2 cm increase the risk of rupture. Ruptured aneurysms are most commonly present with abdominal pain. Shock can be delayed if the initial aneurysm rupture is contained within the lesser peritoneal sac, leading to a double-rupture phenomenon. The treatment of rupture is both resuscitative and operative, including a splenectomy. Endovascular techniques, specifically transarterial embolization, are also useful. There is no consensus on the management of asymptomatic aneurysms.

Hepatic Artery Aneurysm

The second most common visceral artery aneurysm is aneurysms of the hepatic artery comprising 20%. More than half (77%) occur in the common hepatic artery and most of the rest in the extrahepatic segment of the proper hepatic artery. These aneurysms are more common in men in contrast with splenic aneurysms (common in multiparous women). Although abdominal pain and shock suggest rupture, even unruptured hepatic artery aneurysms can be symptomatic secondary to compression on the biliary tree. About 50% of aneurysms rupture into the biliary tract and can present with the classic triad of biliary colic, hematemesis (caused by hemobilia), and jaundice. The mortality of 40% associated with rupture seems to be consistent across case series data. As with splenic artery aneurysm rupture, the treatment has historically been surgical repair; however, transarterial embolization is an increasingly used technique.

Renal Artery Aneurysm

Like other visceral artery aneurysms, renal artery aneurysms are the most common incidental findings during abdominal imaging or investigations into renovascular hypertension. This is also associated with multiparous women and is similar to splenic aneurysms. Arterial fibrodysplasia is the most common vascular disorder associated with these aneurysms. Based on case series data, about 20% are bilateral. Rupture seems to be extremely rare.

SUMMARY

When patients present with abdominal complaints in the ED, the emergency physician should consider the possibility of vascular disorders as clinical situations tend to be dangerous and time specific. In maintaining an appropriate level of suspicion and assessing a patient's risk, the factors associated with the various diseases need to be considered. If a vascular emergency is strongly suspected, the appropriate diagnostic tests should be performed promptly and a vascular surgeon should be engaged as soon as possible. Bedside ultrasonography is an invaluable tool for an emergency physician, especially in suspected ruptured or leaking AAA. CT angiography is becoming the initial imaging test of choice for abdominal vascular diseases caused by occlusive thrombosis. Many of these vascular emergencies are correctable with rapid diagnosis and appropriate resuscitation.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Imaging Modalities in Genitourinary Disease

Aman Gupta

INTRODUCTION

Recent technical advances and discoveries in field of radiology have made imaging of genitourinary (GU) system exciting but challenging. The best choice for imaging the GU system is debatable but must be selected on the basis of patient's symptomatology and clinical context. There are many factors to be considered when deciding which imaging modality should be used first and include radiation exposure, patient age, patient cooperation status, sensitivity, specificity and accuracy, availability of modality, cost, and timeliness of completion. Plain film radiology is perhaps one of the quickest and most inexpensive modalities readily available with considerably less radiation exposure; however, its role is limited to urolithiasis and urinary tract calcification. Ultrasound (US) has the benefits of portability, low cost, availability, and no radiation exposure to the patient. Point-of-care ultrasound (POCUS) is one of the quickest imaging modalities available and is becoming increasingly prevalent in the emergency department, but its sensitivity and specificity depend on operator expertise. Computed tomography (CT) scans have a significant radiation exposure and is much more expensive, but allows evaluation of multiple different systems simultaneously with high degree of accuracy. Magnetic resonance imaging (MRI) has a limited role in the diagnosis of GU pathologic condition because of the fact that it is expensive, is not readily available, and longer study time. However, because of its inherent multiplanner imaging, better soft-tissue resolution and delineation capabilities plays a key role in equivocal CT or US evaluations.

CONVENTIONAL PLAIN FILM RADIOGRAPHY

Plain abdomen-supine-anterior-posterior radiography or more commonly known as kidney, ureter, and bladder (KUB) plain radiography has a low cost, ready availability, and appearance with which referring physicians are familiar but unfortunately compares unfavorably with CT. The full-length abdominal film is taken with the patient supine using a low voltage technique (60–65 kV) to maximize soft-tissue contrast in inspiration using a 14 × 17 inch cassette (for adults) positioned with the lower border at the symphysis pubis to ensure the urinary bladder and urethra are included on the film. Various outlines of anatomical structures can be detected on the KUB, including outlines of renal, psoas, and bladder, much of the axial skeleton, the bowel gas pattern, and the lung bases. A range of pathology may be occasionally detected in these structures, but overall KUB radiography is a relatively unreliable diagnostic tool and its principal use is in the assessment of urinary tract calculi. However, the reported sensitivity and specificity of plain film in detection of renal and ureteric calculus (>5 mm) is only 45–58% and 60–77%, respectively. Various factors, such as stone composition, location, and size, as well as patient body habitus and overlying bowel contents also, determine the sensitivity of the KUB for ureterolithiasis. The detection rate for stones <5 mm is low, with a sensitivity of 12% or less. Presence and/or extent of urinary tract obstruction cannot be determined by KUB. The combination of KUB and US has been proposed to improve sensitivity and specificity of stone detection, especially mid ureteric calculi. The KUB is mostly performed to follow-up a previously proven calculus or as part of an intravenous urography (IVU). There are numerous causes of calcification visible on the plain radiograph, with considerable overlap in their appearances, and a specific diagnosis is often not possible (**Table 1**).

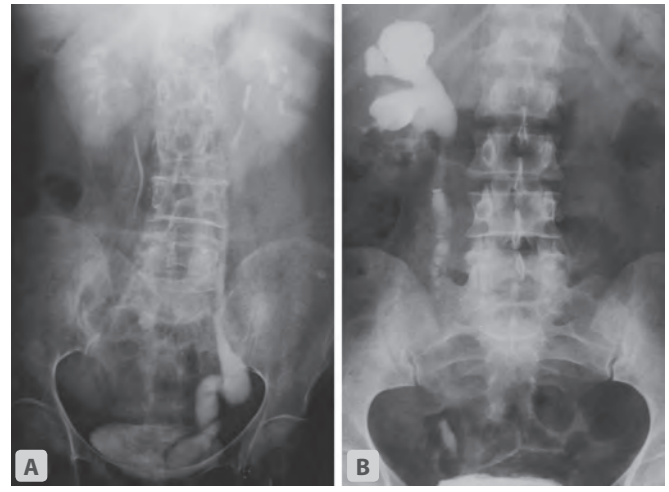
INTRAVENOUS UROGRAPHY

The IVU, or better known as excretory urography (EU), is the classic routine investigation of uroradiology. With the advent of US and multidetector computed radiography (MDCT) its role is now much less, however, it is still widely used and accepted indications for EU are:

- To evaluate the presence or continuing presence of suspected or known ureteral obstruction.
- To assess the integrity of the urinary tract status post-trauma (including iatrogenic interventions), particularly in situations in which cross-sectional imaging is unavailable or inappropriate.
- To assess the urinary tract for suspected congenital anomalies, particularly in situations in which cross-sectional imaging is unavailable or inappropriate.
- To assess the urinary tract for lesions that may explain hematuria or infection. Evaluation of underlying

TABLE 1: Common causes of calcification on the plain radiograph.

Urinary tract	• *Renal*: Calculi, renal cell carcinoma, tuberculosis, and arterial (atheroma or aneurysm) • *Ureter*: Calculi, tuberculosis, and schistosomiasis • *Bladder*: Calculi, schistosomiasis, and transitional cell carcinoma
Outside the urinary tract	• *Musculoskeletal*: Costal cartilage calcification • *Hepatobiliary*: Gallstones and hepatic granuloma • *Pancreas*: Chronic pancreatitis • *Adrenal*: Tuberculosis and Addison's disease • *Spleen*: Granuloma • *Aorta*: Atheroma and aneurysm • *Venous*: Phlebolith • *Lymphatic*: Calcified lymph nodes • *Uterine*: Fibroid



FIGS. 1A AND B: (A) Full length, binder released film of an intravenous urography (IVU) series with left ureterocele; and (B) Retrograde urography (RU) film in postlithotripsy patient showing residual calculi in mid ureter with proximal dilatation.

parenchymal mass or lesion of the urothelial tract can be done by EU where cross-sectional imaging is unavailable or inappropriate.

The IVU consists of a series of plain films taken after administration of an intravenous injection of a water-soluble iodinated contrast media. Traditionally the patient for IVU is prepared with laxatives, 2–4 hours fasting, and fluid restriction prior to the procedure in order to improve opacification of the collecting system. However, it is well accepted now that dehydration is associated with an increased risk of nephrotoxicity and is thus not recommended. Also, modern nonionic contrast agents do not provoke an osmotic diuresis and the degree of opacification is unlikely to be significantly altered by dehydration.

Intravenous urography is performed with some variations in different departments. A standard procedure involves a preliminary post-micturition plain abdomen film (KUB), this should he examined to check exposure factors, centering and presence of radiopaque calculus/calcification. Intravenous water-soluble iodinated contrast is then given as bolus. The standard dose for adult is 300 mg of I_2/kg body weight. A cross-kidney film is taken 5 minutes after injection of contrast (nephrogram). Abdominal compression is then applied to inhibit ureteric drainage and promote distension of the pelvicalyceal systems, optimizing their visualization. A further cross-kidney film is taken at 12–15 minutes to demonstrate pelvicalyceal system (the pyelogram). If the 15 minutes film is satisfactory the compression is removed and a full-length film is taken immediately to demonstrate the ureters (**Fig. 1A**), followed by coned images of the bladder before and after voiding (full-bladder and post-void films). This classical series can he modified based upon findings as each radiograph is reviewed to deal with particular circumstances, to attempt to increase the sensitivity of the procedure, or to reduce the radiation dose to the patient. Some of the most frequently employed modifications are: (1) Delayed images, if there is delay in opacification of the collecting system due to significant acute obstruction. Minimum number of additional films is also necessary to perform. Traditionally concept of doubling time is applied with films taken at 0.5, 1, 2, 4, 16, and 24 hours, as necessary so that the degree of obstruction may be assessed. (2) Prone film, placing the patient prone after the 10-minute image or having the patient mobilize may assist lower ureteric filling and visualization of ureters.

Although, newer low-osmolar contrast medium is relatively safe, there is a small risk of serious anaphylactic-type hypersensitivity reactions. All radiology departments thus necessarily be equipped with emergency drugs, oxygen, resuscitation equipment, and a fulltime radiologist. Knowledge of potential adverse reactions and their treatment is essential for all technical staff in radiology department.

Intravenous urography is used as traditional modality for investigating ureteric calculi. This demonstrates the relationship of a suspected calculus on the plain film to the urinary tract, confirming its location in the collecting system. In most patients with ureteric colic, there is some degree of obstruction, manifested by increasingly dense nephrogram, delayed pyelogram, dilated pelvicalyceal system down to the calculus, with a standing column of contrast in the ureter above the calculus. During last decade, use of IVU is declining for urinary imaging. Reported sensitivity of CT for urinary stone assessment, is 100% as compared with 52–69% for IVU. CT is superior to IVU for urinary tract tumor detection, with sensitivity and specificity of 96% and 99%, respectively. Sensitivity of IVU for detection of renal masses is also much less as compared to US and CT, with reported sensitivities of only 21, 52, and 85% for masses <2, 2–3, and >3 cm, respectively. In addition, masses detected by IVU inevitably require further imaging for lesion confirmation and characterization by either US, CT or MRI.

RETROGRADE UROGRAPHY

Retrograde urography (RU) is a special radiological procedure performed by instillation of contrast medium devoid of air bubbles into a ureteric catheter placed by cystoscopy with aim to optimally opacify the pelvicalyceal system and ureter for delineation of pathologies. The role for RU has been diminished due to advancement in sonography equipment and read availability of MDCT. RU can still be useful as a problem-solving tool when filling defects are detected in the upper urinary tracts on imaging particularly if there is hematuria and/or suspicious

cytology. RU is also performed for assessment of stone disease after renal and ureteric lithotripsy and occasionally used to demonstrate lower end of an obstructed ureter (**Fig. 1B)**.

The urologist positions catheter in ureter cystoscopically and the patient is transferred to the X-ray department. Under screening control 5–20 mL of a water-soluble iodinated contrast agent is injected via catheter and spot films taken of the opacified pelvicalyceal system and ureter. After adequate images have been obtained, the ureteric catheter can be withdrawn to allow contrast injection at a site of concern. Superiority of CT over RU is not fully established by scientific evidence. Few studies available comparing CT urography (CTU) with RU have shown increased sensitivity and specificity for CT detection of urothelial tumors.

CYSTOGRAPHY

Cystography procedure is performed to assess the integrity of the bladder following trauma or surgery or to investigate suspected fistulas involving the bladder. A spot film is taken before administration of contrast followed by infusion of water-soluble iodinated contrast via suprapubic or urethral catheter under screening control. When the bladder has been filled or when extravasation is identified spot films are taken in the supine, oblique, and lateral position. In patients with a suspected vesical fistula, 250 mL of contrast can be used to maximize the chance of demonstrating the fistula. In modern trauma units, conventional contrast cystography is getting replaced by a delayed CT sequence for urinary bladder, 20 minutes after contrast in trauma patients and is reported as accurate in demonstrating extravasation.

RETROGRADE URETHROGRAPHY AND VOIDING CYSTOURETHROGRAM

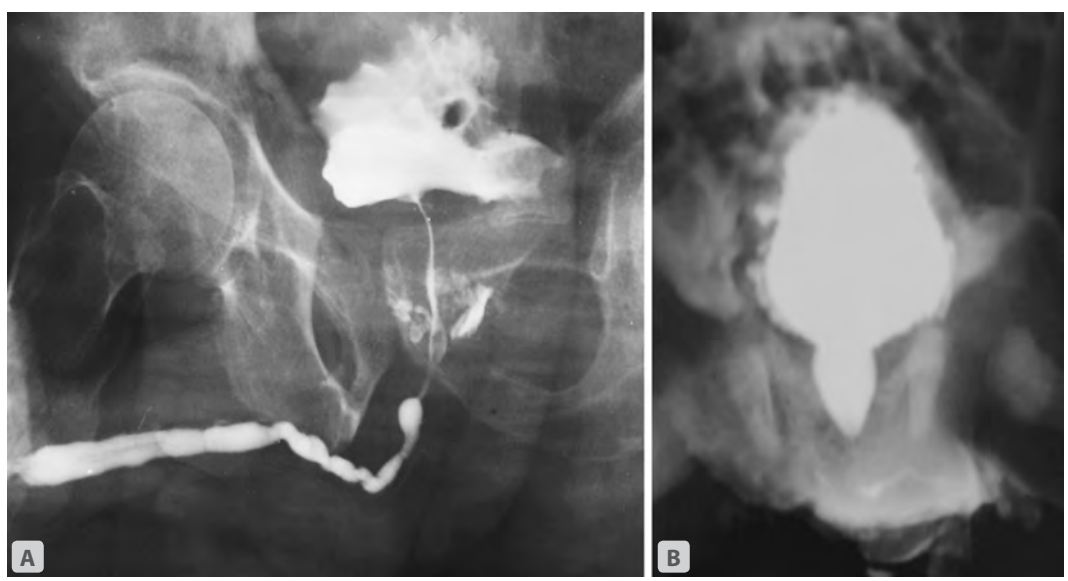
Retrograde urethrography (RUG) or ascending urethrography is used to image male anterior urethra in cases of blunt perineal trauma to assess for urethral disruption, suspected urethral stricture, and fistulas. The patient is positioned in a 45° oblique position and water-soluble iodinated contrast media is gently instilled into a stretched penis through a 12–16 gauge Foley catheter positioned with its balloon in the fossa navicularis and spot films are taken (**Fig. 2A**).

Voiding cystourethrogram (VCUG) or descending urethrography is used to image posterior urethra and demonstrate vesicoureteric reflux, particularly in pediatric patients. The bladder is initially drained of urine and later filled with water-soluble iodinated contrast medium using a Foley or suprapubic catheter. Anteroposterior and oblique bladder imaging is performed using intermittent fluoroscopy with spot images of abnormal findings. Once the bladder is filled to capacity, the urethra is imaged in profile using an oblique projection after catheter removal and during micturition in supine or while standing (**Fig. 2B**).

These procedures are less required now with advances in urethroscopy. Echo-enhanced voiding cystosonography and MR voiding cystography are also now being used for screening or follow-up in patients with known or suspected vesicoureteric reflux.

PERCUTANEOUS NEPHROSTOMY AND ANTEGRADE PYELOGRAPHY

Percutaneous nephrostomy (PCN) is mainly indicated for therapeutic purposes to drain an obstructed collecting system. Some time it is used to divert the urine flow in unobstructed systems and allow ureteric or vesical fistulas to heal. PCN tube mounted on a cannula is positioned percutaneously within the dilated collecting system under US or fluoroscopy guidance. A diagnostic nephrostogram and antegrade pyelogram (**Fig. 3**) can be performed by injecting water-soluble iodinated contrast media through nephrostomy catheter and spot films taken of the collecting system and ureter down to the level of the obstruction to assess cause, especially in patients with



FIGS. 2A AND B: (A) Retrograde urethrography in a 60-year-old male demonstrating beaded penile urethra with stricture posterior urethra; and (B) Voiding cystourethrogram in a 4-year-old male with posterior urethral valve demonstrating dilated posterior urethra with trabeculated urinary bladder wall.

FIG. 3: Antegrade pyelography showing irregular filling defect in right posterior-lateral wall of urinary bladder involving right vesicoureteric junction (VUJ) with dilated right collecting system.

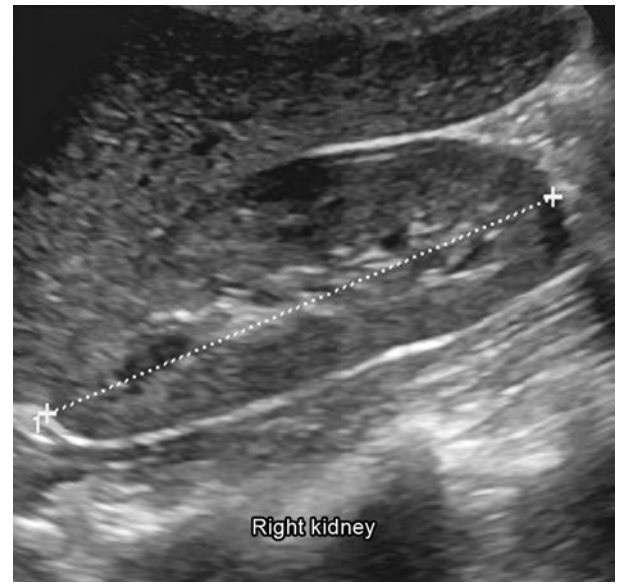


FIG. 4: Sonographic appearance of a normal adult kidney. Note renal parenchymal echotexture slightly less or equal to that of liver and dense central renal sinus echoes.

nonexcretory kidney. The most common complication of these procedures is infection and hemorrhage and appropriate precautions should be taken.

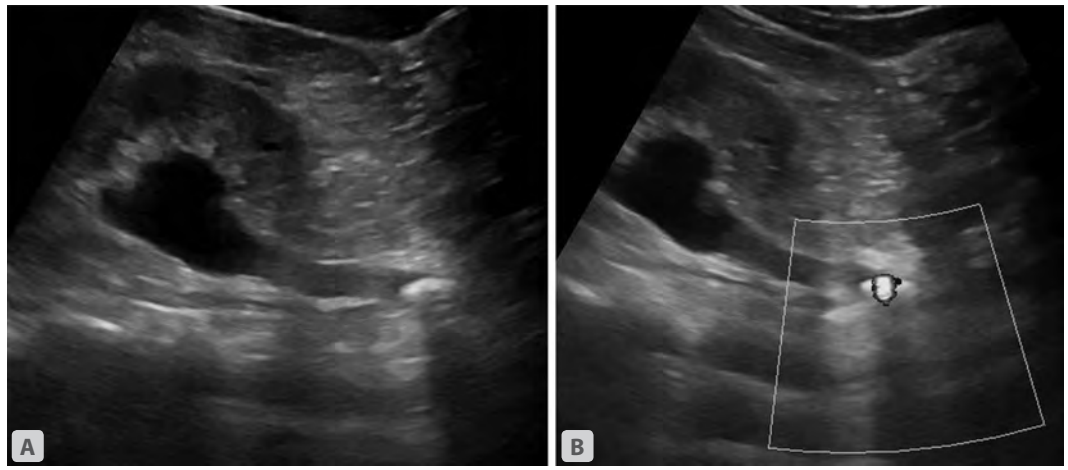
ULTRASOUND

The ready availability, portability, cost effectiveness, and absence of exposure to radiation have made US first imaging modality in the assessment and follow-up of renal diseases. US is valuable in assessment of congenital abnormalities, loin pain, hematuria, infection, tumors, and renal failure. US is very useful in determining the internal architecture of renal lesions detected on other modalities such as hyperattenuating lesions detected on MDCT, to determine whether they represent hyperdense cysts or solid lesions. US is considered safe without need for intravenous contrast or ionizing radiation, valuable in the evaluation of the postrenal transplant patient and able to safely image the structure of the graft, and its perfusion with Doppler imaging. POCUS is very popular and an increasingly growing field complementary to bedside medical examination performed by emergency physicians, unclear findings can be investigated quickly.

On US the normal adult kidneys measures in range of 9–13.5 cm. A difference in size of >1.5 cm between the two raises the possibility of unilateral disease. Renal cortex appears slightly hypoechoic in comparison to the liver and spleen. Renal cortex seen as a peripheral rim with normally inward projecting invaginations (columns of Bertin) between the medullary pyramids. In young healthy adults, cortical thickness is of the order of 2.0–3.0 cm. The renal pyramids are markedly hypoechoic as compared to the cortex in neonates and infants, becoming less hypoechoic with age and in renal parenchymal diseases with loss of corticomedullary differentiation. The central renal sinus echoes contains fat, the calyces, infundibula, part or all of the renal pelvis, blood vessels, lymphatics, and fibrous tissue (**Fig. 4**). The normal undilated ureters are not visualized on sonography, but when obstructed are seen as dilated tubular channels and mural and intraluminal pathologies can be easily picked. Urinary bladder is examined in moderately full stage; the normal wall thickness is 2–3 mm and contents anechoic. In males, the prostate and seminal vesicles are seen posterior to the bladder. In females, uterus and ovaries are evaluated either transabdominally using a sector transducer or transvaginally using an endocavitary transducer.

Ultrasound in the setting of acute flank pain may be very useful because of its inherent advantages of no ionizing radiation, availability, and portability, especially in children and pregnant patients. Urinary tract obstruction secondary to calculi is the most common cause. US usually demonstrates direct signs of obstruction of urinary tract such as hydronephrosis and hydroureter with a reasonable degree of sensitivity (95%), but at the cost of a low specificity of around 67%. Calculi on US are seen as highly echogenic foci with dense distal acoustic shadowing on grey scale and twinkling artifact on color Doppler (**Figs. 5A** and **B**).

Ultrasound is often first imaging investigation in Indian setups for suspected acute pyelonephritis (APN), although as discussed US has a low sensitivity and limited diagnostic accuracy. Features of APN on US include renal enlargement caused by generalized renal edema, renal parenchymal hypoechogenicity, loss of corticomedullary differentiation, and on dynamic scanning restricted renal movements with respiratory excursions. Hydronephrosis, either as a cause for infection or secondary to pyelonephritis, can be seen conspicuously on US. In addition, US can diagnose underlying predisposing conditions such as duplicated system or pelviureteral junction obstruction. Doppler US helpful in differentiating areas of parenchymal hypoperfusion due to arteriolar vasoconstriction and interstitial edema. Contrast-enhanced ultrasonography (CEUS) better demonstrates hypoperfusion and abscess formation.



FIGS. 5A AND B: (A) A proximal ureteric calculus on grey scale ultrasound seen as echogenic foci with posterior acoustic; and (B) Twinkling artifact on color Doppler. Note proximal hydroureteronephrosis.

DOPPLER SONOGRAPHY

Excellent noninvasive tool for evaluating renal artery (RA) hypertension and end-stage renal disease is Doppler sonography. It has high sensitivity and specificity, in the diagnosis of RA stenosis on the basis of Doppler samples obtained from extrarenal arteries combined with intrarenal waveform analysis. Benefit from therapeutic correction of RA stenosis can also be predicted by US. Patients with elevated resistive index (RI) > 0.80 show poor improvement in renal function and hypertension after revascularization.

For evaluation of acute scrotum high-resolution ultrasound (HRUS) in combination with color Doppler has become the imaging modality of choice. On gray-scale sonography, in acute phase of torsion, testis appears enlarged, spermatic cord immediately cranial to the testis and epididymis is twisted, and intrascrotal portion of the cord appears as edematous curled echogenic extratesticular mass causing a characteristic "whirlpool pattern". Color Doppler shows absent or significantly less blood flow in the affected testicle whereas in acute epididymitis/epididymo-orchitis there is thickening and enlargement of the epididymis, the echogenicity of the epididymis and testis is usually decreased with significantly increased blood flow on Doppler.

Transvaginal sonography (TVS) is imaging modality of choice in various gynecologic emergencies particularly, ectopic pregnancies, ruptured or hemorrhagic ovarian cysts, ovarian or adnexal torsions, threatened or inevitable abortions, acute salpingitis, tubo-ovarian abscess, and torsion of a pedunculated subserous myoma. A negative US helpful in excluding most of the significant pathologies. If gynecologic cause of pelvic pain is confirmed on transabdominal or TVS other imaging studies might be unnecessary, in cases where the US examination is equivocal or suboptimal CT or MRI should be considered.

COMPUTED TOMOGRAPHY

Computed tomography has a wide variety of indications, unenhanced CT is used to evaluate urinary tract stones, calcifications, hematoma, and to obtain baseline attenuation of renal masses. CT for renal parenchymal and urothelial tumor detection and characterization requires arterial and nephrographic postintravenous contrast medium acquisitions. Other common indications of CT include assessment of inflammatory and traumatic processes and RA stenosis. CT is also used to direct biopsies and the positioning of percutaneous drains.

Unenhanced CT or stone protocol CT in evaluation of the patients with urinary tract calculi has now emerged as investigation of choice and has replaced IVU in maximum institutes with reported sensitivity as high as 95% and specificity of 98%. Unenhanced CT offers several advantages over conventional IVU: (1) Obviates need of contrast media, (2) is rapid and does not require repeated imaging to determine the site of obstruction, (3) is not only more sensitive in detecting presence of calculi, but also it can detect associated obstruction. Obstruction is suggested by hydronephrosis and hydroureter above the level of the obstructing calculus and also by the presence of secondary signs of obstruction such as perirenal and periureteric fat stranding, and (4) CT has potential advantage of making alternative relevant diagnoses (diverticulitis, appendicitis, cholecystitis, epiploic appendagitis, etc.) in patients with acute abdominal pain. The major disadvantages associated with the use of unenhanced CT are exposure to ionizing radiation, its cost, and availability in peripheral centers. However, in recent years, use of low mAs stone protocol has provide comprehensive evaluation of the urinary tract with effective doses reported in a range comparable to IVU or even lower.

Contrast-enhanced computed tomography (CECT) is considered the imaging technique of choice for diagnosis or follow-up of patients with acute urinary tract infection. The reported sensitivity and specificity of CT for APN is 86.8 and 87.5%, compared with 74.3 and 56.7% for US. Plain CT detects causes of renal obstruction such as stones or soft-tissue masses. Nephrographic-phase imaging is helpful in detecting loss of corticomedullary differentiation with one or more wedge-shaped zones or streaky areas of reduced enhancement extending from the papilla through the medulla to the renal capsule. A striated nephrogram may be observed. Involvement of Gerota's fascia with extrarenal extension may also be noted. The presence of nonenhancing fluid locules within an area of APN suggests fluid liquefaction and abscess formation. APN with diffuse renal involvement causes impaired contrast excretion as per severity of infection. CT findings in patients with emphysematous pyelonephritis include parenchymal

enlargement and focal tissue necrosis, streaks of gas radiating from the papillae, gas-fluid levels, and renal and perirenal abscess.

Computed tomography urography is defined by the European Society of Urogenital Radiology as a CT optimized for renal, ureteric, and bladder examination using thin-slice, excretory-phase imaging after intravenous contrast medium administration. CTU typically consists of three imaging phases. Following unenhanced imaging, thin-section nephrographic phase imaging of the kidneys is acquired using water-soluble iodinated contrast medium. For the detection of renal parenchymal, masses nephrographic phase imaging has the highest sensitivity. Correlation with unenhanced images confirms unequivocal enhancement. The excretory or pyelographic phase is imaged 5–15 minutes after injection and covers the upper urinary tract and bladder (**Figs. 6A** and **B**). CTU protocols vary between institutions and are tailored towards the clinical problem to optimize radiation exposure and urothelial imaging. CTU is excellent modality for detection of upper urinary tract urothelial malignancies. CTU is better than IVU in detection and characterization of both intrinsic and extrinsic causes of ureteric obstruction such as mural thickening, benign and malignant strictures, retroperitoneal masses, lymphadenopathy, retroperitoneal fibrosis, and iatrogenic injury.

The radiologic evaluation of the kidneys and urinary tract in the context of trauma is guided primarily by the patient's hemodynamic status and presence or absence of hematuria. Any penetrating trauma in which direct injury to the kidneys and GU tract is suspected should be evaluated by CECT. The triphasic CT protocol in trauma should include an unenhanced phase to identify internal hemorrhage, a postcontrast corticomedullary phase to identify abnormalities in renal parenchyma, vasculature, and perfusion, and a postcontrast delayed phase obtained 5–10 minutes after contrast to identify any breech within the urinary collecting system. In circumstances where imaging is warranted but CT is contraindicated, US and unenhanced MRI should be considered.

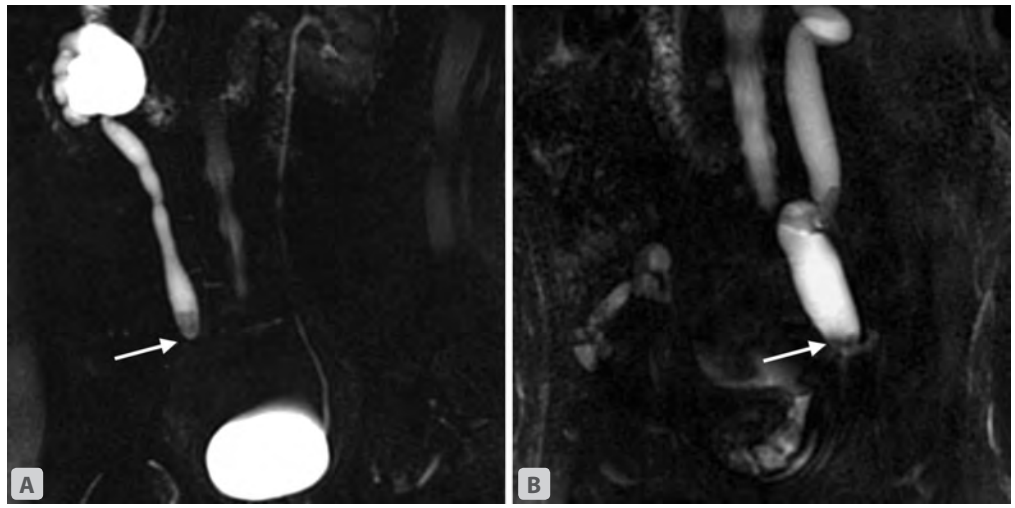
MAGNETIC RESONANCE IMAGING

Computed tomography urography, to date, has emerged as the test of choice for many urologic problems, including urolithiasis, renal masses, urinary tract infection, trauma, and obstructive uropathy. Detailed anatomy of the major portions of the urinary tract-the kidneys, intrarenal collecting systems, ureters, and bladder can be assessed by CTU. Magnetic resonance urography (MRU) may be preferred in a number of clinical scenarios and has the advantage of not using ionizing radiation and the potential to provide more functional information than CT. MRU may be preferable to CTU for performing imaging examinations of pediatric and younger patient populations, pregnant women, patients undergoing repeat assessment of the collecting systems (because of the absence of ionizing radiation), patients with history of allergic to iodinated contrast, and patients with renal dysfunction. There are two types of MR urographic techniques used to display the urinary tract:

1. Static-fluid MRU (also known as static MRU, T2-weighted MR urography, or MR hydrography), and
2. Excretory MRU (also known as T1-weighted MRU)

Static-fluid MRU treats the urinary tract as a static column of fluid and involves imaging of urine (or water) in the urinary tract by using a variety of T2-weighted pulse sequences that exploit the long T2 relaxation time of urine. Breath-hold T2-weighted MR urogram can be obtained with either thick-slab single-shot fast spin-echo (SSFSE) techniques or similar thin-section techniques. To obtain thin-section, three-dimensional (3D) respiratory-triggered sequences can be used that can be postprocessed to create volume rendered (VR) or maximum intensity projection (MIP) images of the entire urinary tract. Coronal heavily T2-weighted static-fluid MR urogram is useful for quickly identifying the level of urinary tract obstruction. Because static-fluid MRU depends on the presence of urine within the collecting systems rather than the excretory function of the kidneys, it is ideally suited for patients with dilated and obstructed collecting systems (**Figs. 7A** and **B**). For detection of periureteral fat stranding (indirect indicator of obstruction

FIGS. 6A AND B: Computed tomography urography images in patient with right staghorn calculus. (A) Thin maximum intensity projection (MIP) coronal image; and (B) Volume rendered image.



FIGS. 7A AND B: Coronal static-fluid magnetic resonance (MR) urogram shows (A) inflammatory stricture, smoothly contoured obstruction of the right ureter; and (B) malignant stricture, abrupt irregular obstruction of left distal ureter.

and tumor infiltration), fat-suppressed T2-weighted images are useful. Excretory MRU is similar to CTU and conventional IVU. Collecting systems images are taken during the excretory phase after administering gadolinium-based contrast agent intravenously. The primary imaging sequence for excretory MRU is the 3D gradient-echo sequence. Fat suppression enhances the compacity of the ureters and is recommended. Excretory T1-weighted sequences can image the kidneys in the corticomedullary, nephrographic, and excretory phases as for CTU. In obstructive uropathy, combined static fluid and excretory MRU can provide valuable information, since T2-weighted sequences demonstrate collecting system dilatation and excretory images demonstrates the ureteric tract above and below the site of obstruction and can provide an estimation of the degree of ureteric stenosis. Spin echo MRI helps differentiate blood clots and stones from tumor by demonstrating contrast enhancement on postcontrast T1-weighted imaging.

NUCLEAR MEDICINE

Nuclear medicine provides data pertaining to renal function, perfusion, and urinary tract dynamics which complements that of IVU, US, CT, and MRI. Renal perfusion and excretory functions of kidney are assessed by radioactive tracers that are excreted by the kidney, while tracers that are retained in the kidney are helpful in assessing renal anatomy. Currently the most satisfactory tracer for imaging renal anatomy is ^{99m}Tc-dimercaptosuccinic acid (DMSA); for investigating renal perfusion and excretion ^{99m}Tc-mercaptoacetyltriglycine (MAG3) is now preferred over earlier tracer excreted solely by glomerular filtration [^{99m}Tc-diethylenetriaminepentaacetate (DTPA)] or by tubular secretion (^{123}I-orthoiodohippurate).

The DMSA scintigraphy is used to locate the functioning renal tissue in renal ectopia and other congenital renal anomalies, differentiate pseudo masses, e.g., prominent columns of Bertini from true lesions such as tumors, cysts, or abscesses which appear as photon-deficient areas and to find scars or nonfunctioning areas of renal parenchyma in renal infections.

Dynamic renal studies are particularly important for the investigation of urinary tract dilatation. MAG3 and Hippuran are extracted and cleared by the renal tubules faster than the glomerular agent DTPA and so preferred for collecting system imaging in pediatric patients. DTPA is less costly and also quicker and easier to prepare than MAG3, and so it may be used in emergent situations where a rapid result is needed, particularly in respect of perfusion, e.g., renal transplant recipient with acute oliguria. A bolus injection of radiopharmaceutical is given into a peripheral vein. Rapid image acquisition is required to demonstrate the perfusion phase and for the excretion phase, sequential images are acquired for 20–30 minutes. The sensitivity of dynamic renal imaging for detecting urinary tract obstruction is maximized by increasing flow rate by giving diuretics. Analysis of the images and renogram curves obtained during the first pass of the tracer illustrate renal perfusion. Size, shape, and location of the kidneys can be assessed by taking the images obtained 3–5 minutes after injection. During the excretion phase serial images can be obtained to assess relative renal function, rate of transit of activity through the renal pelvis, drainage from the pelvis in the sitting position, and the residual bladder volume after micturition. For infants and children with suspected vesicoureteric reflux disease, indirect radionuclide cystography can be performed. After diuresis renography, the patient is placed in a sitting or standing position and the camera repositioned to include both kidneys and the bladder within the field of view. Image frames are collected during micturition and time-activity curves are derived from the region of the bladder, each kidney and along the line of each ureter. Vesicoureteric reflux is confirmed if there is an increase in kidney or ureter counts during micturition. Bladder catheterization is not required for indirect radionuclide cystography is major advantage. The disadvantage is its lack of anatomical details.

SUMMARY

The current and emerging state-of-the-art imaging modalities for evaluation of the GU system are discussed in this chapter. Numerous factors need to be taken into consideration when deciding which imaging modality should be used rather than in a single algorithm to evaluate the entire GU tract. In addition to sensitivity and specificity, availability, cost-effectiveness, and potential limitation of imaging modality are to be considered.

MULTIPLE CHOICE QUESTIONS

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107 CHAPTER

Hematuria

Puneet Ahluwalia

INTRODUCTION

"Hematuria" in simple term means "blood in urine". In normal urine <3 red blood cells/high-power field (RBCs/HPF) can be present. Any hematuria with >3 RBC/HPF is marked as significant and needs further investigation and management. Isolated hematuria can sometimes be observed without any associated obvious underlying condition (e.g., cystitis and ureteral stone) or may the presenting symptoms of a serious condition like underlying malignancy in urinary tract. The causes for hematuria (and the tests needed for evaluation) vary with the age of presentation. Therefore, it is important to know the basic "workup" of the patient presenting with this symptom.

CLASSIFICATION OF HEMATURIA

Hematuria may be classified as *gross* (macroscopic hematuria or which is visible to naked eyes) or *microscopic hematuria* (detected only on urine examination).

Gross Hematuria

Gross hematuria is suspected in patients with history of passing red or brown colored urine. Patients with gross hematuria are usually frightened by the sudden onset of blood in the urine and frequently present to the emergency department for evaluation, fearing that they may be bleeding excessively. Therefore, a detailed history of consumption of any coloring agent or medications should be taken. Gross hematuria, however, with passage of clots almost always indicates a lower urinary tract source.

Microscopic Hematuria

Microscopic hematuria when blood (either RBCs or hemoglobin) is found on a laboratory urine examination or dipstick test. Repeated episodes of microscopic hematuria need evaluation. The level of investigation depends upon the risk profile of patient and the level of suspicion regarding the presence of urinary tract abnormality. Although the presence of three or more RBCs per HPF in a spun urine sediment is considered abnormal, there is no "safe" lower limit below which significant disease can be excluded.

ETIOLOGY

Hematuria can be caused by various underlying pathological conditions or the disease. Age and location of pathology in urinary tract are the main determinant for the causes of hematuria (**Table 1**). Broad range of etiological factors of hematuria needs careful evaluation when presented to emergency department. Smoking leads to urothelial malignancy and age >50 years related to bladder carcinoma.

HISTORY AND INITIAL EVALUATION

History

During the history taking of the patient with hematuria, the clinician should ask for the following clues:

- Family history of renal disease, sickle cell disease, polycystic kidney disease, and diabetes.
- Recent upper respiratory tract infection (can lead to a possible postinfectious glomerulonephritis, vasculitis, and antiglomerular basement membrane disease).
- Recent fever with pyuria and/or dysuria [indicates urinary tract infection (UTI)].
- Any recent flank pain radiating groin (suggestive of ureteral obstruction due to blood clot, calculus, and malignancy).
- History of hesitancy and dribbling in older men (suggestive of prostatic obstruction).
- Bleeding due to excessive anticoagulation. Studies suggest that chronic anticoagulation is not a cause of hematuria and patients on anticoagulants should be evaluated thoroughly to find the underlying cause of hematuria, as one will evaluate in other patients.
- Recent episode of strenuous exercise or trauma.
- Travel history to places endemic for tuberculosis or *Schistosoma haematobium*.
- Is there a history of smoking or any drug abuse?
- Hematuria in suspected analgesic abusers, diabetics, and in Afro-Americans is caused by papillary necrosis.

Initial Evaluation

In the initial evaluation of hematuria, several questions should always be asked. The answers to the following questions

TABLE 1: Etiology of hematuria.

Etiology of hematuria-related to age of patient	*Etiology of hematuria-related to pathological location*	
	Upper collecting system	***Lower collecting system***
• *Young adults and children:* Glomerulonephritis • *Over 20 years:* Nephrolithiasis • *Over 40 years:* BPH (in males) • *Over 50 years:* Malignancy • *All ages:* Urinary tract infections	• Papillary necrosis (sickle cell disease) • Renal vein thrombosis • Renal artery embolism • Benign/malignant renal mass • Glomerular bleeding (Alport's syndrome and IgA nephropathy) • Pyelonephritis • Malignant hypertension • Hydronephrosis • Polycystic kidney disease • Arteriovenous malformation • Renal or ureteric calculi • Ureteric stricture • Postsurgical complications • Trauma • Anticoagulation	• Radiation • Cystitis • Traumatic catheterization • Urethritis • Malignancy (squamous cell carcinoma and transitional cell carcinoma) • Urethral diverticulum • Trauma • Anticoagulation • Transurethral resection of the prostate

(BPH: benign prostate hypertrophy; IgA: immunoglobulin A)

will enable the urologist to target the subsequent diagnostic evaluation efficiently:

- *Gross or microscopic hematuria?* This helps the clinician to identifying any significant pathology. Patient with gross hematuria generally have significant and definitive pathology while negative evaluation in microscopic hematuria.
- *Hematuria occur in beginning or end of stream or during entire stream?* By knowing the timing of hematuria during urination one can figure out the site of origin of hematuria. Initial hematuria due to urethral inflammation, terminal hematuria due to bladder neck or prostatic urethra inflammation, and total hematuria mainly due to bladder and upper urinary tract.
- *Pain with hematuria?* Signify inflammation (cystitis) or obstruction (clots and calculi). Painful hematuria is linked with upper urinary tract hematuria with obstruction of the ureters with clots. During the passage of these clots, the patient experiences colicky flank pain similar to ureteric colic. Another painful cause of hematuria is cystitis. Gross painless hematuria is seen in patients with bladder cancer.
- *Any clots with hematuria?* If present, it is significant hematuria. Presence of any blood clots in the urine sample increases the chances of identifying any significant pathology in the patient. In case of hematuria originating from upper urinary tract, one can see the presence of vermiform (worm-shaped) blood clots. On the other hand, hematuria originating from the bladder and the prosthetic urethra the clots will be amorphous.
- *Transient or persistent hematuria?* Transient microscopic hematuria is a common problem in adults. In most patients with transient hematuria, no obvious etiology is identified. Fever, infection, trauma, and exercise are potential causes of transient hematuria. Transient hematuria can also occur with UTI (e.g., cystitis or prostatitis). In this setting, hematuria is typically accompanied by pyuria and bacteriuria and patients often complain of dysuria. Typically, benign nature of transient hematuria occurs in older patients (40 years of age) in whom even transient hematuria carries an increased risk of malignancy.

  It cannot be overemphasized that hematuria should be considered as symptom of malignancy until proved otherwise, particularly in the adults. Presence of hematuria in adults mandates immediate urologic examination. Bladder cancer is the most common cause of gross hematuria in a patient older than age 50 years.
- *Glomerular or nonglomerular hematuria?* Red or pink urine with clots with normal RBCs morphology is suggestive of extraglomerular source whereas dark red, smoky brown, or coca cola color urine with some dysmorphic RBCs suggests glomerular origin of hematuria. Also, hematuria of glomerular origin is differentiated from nonglomerular based on related significant proteinuria (>500 mg/day) and presence of cast.

Some Other Clues

- *IgA nephropathy (Berger disease)*: Children and young adult (male) having low grade fever. Hereditary nephritis, polycystic kidney disease, or sickle cell disease—family history.
- Ureteral obstruction, flank pain radiating to the groin due to a calculus or blood clot
- Prostatic obstruction, present as hesitancy and dribbling may be present in older men.
- Urinary tract infection, pyuria and dysuria may also be present in bladder malignancy.
- Recent vigorous exercise or trauma in the absence of another possible cause.
- Endometriosis of urinary tract should be suspected in women with cyclic hematuria that is most prominent during and shortly after menstruation. Contamination with menstrual blood should be ruled out by a repeat sample when menstruation has ceased.

Food and Medication

Food habits and medication history should be taken in details as they give rise to brown/red coloration of the urine (**Table 2**). Anticoagulation and drug causing nephritis cause hematuria.

TABLE 2: Food and medication which give rise to brown/red color of the urine.

Food	*Medications*	*Endogenous*
• Berries • Beets • Rhubarb • Fava beans • Paprika • Artificial food color	• Phenytoin • Nonsteroidal anti-inflammatory drugs (NSAIDs) • Rifampin • Quinine chloroquine • Phenothiazines • Nitrofurantoin • Metronidazole • Levodopa and methyldopa • Prochlorperazine • Sulfonamides	• Myoglobin • Free hemoglobin and porphyrins • Bilirubin • Melanin • Amorphous urates • *Serratia marcescens* infection

STEPWISE APPROACH FOR EVALUATION

Step I: Confirmation of Hematuria: Urine Examination

Hematuria may be due to variety of causes. Urolithiasis, UTI, neoplasms of the urinary tract (including both renal cell carcinoma and urothelial tumors), urinary tract trauma, and medical renal disease are among the more common causes.

First step in any patient presenting with suspected hematuria is to confirm the finding with urine examination. A simple and easily available *"dipstick test"* is the first step. A positive dipstick for blood in the urine most commonly indicates *any of the three conditions; hematuria, hemoglobinuria, or myoglobinuria*. Peroxidase-like activity of hemoglobin detects the presence of blood in urine and leads to change in color as per the degree and amount of oxidation.

Hemoglobinuria and myoglobinuria can be distinguished from hematuria by the microscopic examination of centrifuged urine. The diagnosis of hematuria is established by the presence of a large number of erythrocytes. Examination of the serum, in the absence of erythrocytes in urine, distinguishes hemoglobinuria from myoglobinuria. In centrifuged specimen, pink supernatant indicates hemoglobinuria. This is due to affinity of free hemoglobin in the serum to bind haptoglobin. The complex has a high molecular weight, is water insoluble and remains in the serum, causing a pink color. Once all the haptoglobin-binding sites are saturated, free hemoglobin appears in the urine. Myoglobin on the other hand is of low molecular weight and is water soluble.

Hematuria, defined as >3 RBCs/HPF, can be identified with urinary dipsticks with sensitivity of >90%. Conversely, dipstick method has a high false-positive rate for hematuria leading to lower *specificity as compared with microscopy*. Contamination of the urine specimen with menstrual blood is the most common cause of false-positive dipstick results. Increased concentration of erythrocytes and hemoglobin in dehydration with resultant high specific gravity urine is another cause of false-positive result. First morning voided specimen is also more likely to yield false-positive result due to high specific gravity. Vigorous exercise can sometimes increase the number of erythrocytes in the urine leading to false-positive results. Efficacy of dipstick in hematuria screening to identify significant urologic disease remains somewhat controversial. Confirmation of dipstick result with microscopic examination of the centrifuged urinary sediment is imperative before proceeding to more complicated studies.

Step II: Rule Out Benign Causes

History, physical examination, and laboratory examination to rule out benign causes such as infection, menstruation, vigorous exercise, medical renal disease, viral illness, trauma, or recent urological procedures. If a "benign" cause for microscopic hematuria is suspected, the patient should undergo repeat urinalysis 48 hours after cessation of the activity. In patients with bacteriuria or pyuria, a urine culture should be ordered to confirm UTI.

Step III: Baseline Renal Function: Evaluation for Primary Renal Disease

Estimate of renal function including serum creatinine, blood urea nitrogen, and calculated estimated glomerular filtration rate (eGFR) is obtained once benign causes are excluded. Contrast or gadolinium radiologic studies are contraindicated in patients with renal dysfunction. The presence of any of the parameters suggestive of renal parenchymal/glomerular disease warrants concurrent nephrology workup.

Step IV: Urological Evaluation

Urine Cytology

Urinary cytology or cystoscopy may be used. Cystoscopy is required if cytology shows malignant or atypical/suspicious cells.

Imaging

In a patient with otherwise unexplained hematuria, once nephrological or glomerular causes of bleeding are excluded, the diagnostic workup should be directed towards urological evaluation and include a search for lesions in the kidney, collecting system, ureters, bladder, or urethra. The diagnostic yield is directly proportional to age and may be higher for gross hematuria than for microscopic hematuria.

Computed Tomography Urography

It is the investigation of choice for evaluation of hematuria. Computed tomography (CT) with or without contrast is the initial imaging study of choice in hematuria of nonglomerular origin. CT has high sensitivity for detecting stones in identifying renal tumors and other nongenitourinary tract abdominal pathologies that lead to hematuria. The disadvantage of CT scan is the need of intravenous (IV) contrast and radiation exposure to the patient. CT is also not safe for pregnant females.

Magnetic Resonance Urography

For patients with relative or absolute contraindications that preclude use of multiphasic CT (such as renal insufficiency, contrast allergy, and pregnancy), magnetic resonance

urography (MRU) (without/with IV contrast) is an acceptable alternative imaging approach.

Intravenous Pyelography

Intravenous pyelography (IVP) is less sensitive in detecting kidney stones and renal masses (particularly small masses) and has largely been replaced with CT urography (CTU). In case of suspicion of upper tract involvement, a retrograde pyelography is helpful to identify the source of hematuria. Some clinicians believe that IVP is best able to characterize lesions in the urothelium. However, increasing evidence suggests detection rates for urothelial neoplasm with IVP are between 40 and 65%.

Ultrasonography

Renal ultrasound is the next best initial imaging modality in case CT is not available or contraindicated. Ultrasonography is excellent for detection and characterization of renal cysts but is less sensitive in detecting transitional cell carcinoma, small solid lesions (<3 cm), and calculi. However, the combination of ultrasonography and CT may improve the characterization of small-sized renal masses. If initial imaging modalities are inconclusive to identify the source of hematuria then cystoscopy should be planned.

Role of Cystoscopy

In Gross Hematuria

Patients who have gross (macroscopic) hematuria without any evidence of either glomerular disease or infection should undergo cystoscopy since it permits direct visualization of bladder and can detect malignant or other sources of bleeding. Cystoscopy should also be done in patients who have gross hematuria with blood clots even if they have evidence of a glomerular lesion since blood clots are virtually never associated with glomerular bleeding. The presence of blood clots in these patients suggests the concurrent presence of disease in the upper or lower collecting system.

In Microscopic Hematuria

Cystoscopy should also be done in all patients with microscopic hematuria who have no evidence of glomerular disease or other benign causes such as infection or exercise and who are at increased risk for malignancy.

Cystoscopy allows visualizing entire bladder wall for malignancy or any other abnormality. Cystoscopy may also identify the source of the bleeding among patients with gross hematuria. Moreover, cystoscopy is the only modality that permits visualization of the prostate and urethra.

UNEXPLAINED HEMATURIA

In cases of unexplained hematuria, particularly in young and middle-aged patients, glomerular disease or a stone disease is the most likely reason of isolated hematuria. In these patients with persistent isolated hematuria, evaluation with history, cystoscopy, and imaging are often not conclusive and may be normal.

FOLLOW-UP AFTER INITIAL NEGATIVE EVALUATION

Patients who have a negative evaluation for hematuria generally require follow-up with cytology, urinalysis, blood pressure monitoring, and in some cases with repeat imaging and cystoscopy. The necessity for repeat imaging and cystoscopy largely depends upon whether hematuria was transient or persistent, and upon the patient's risk for malignancy.

Follow-up of patients with transient hematuria: Patients who have even one episode of hematuria and are at high risk for malignancy require close follow-up following a negative evaluation.

Follow-up of in cases of persistent hematuria: In a patient with unexplained persistent hematuria, it is imperative to rule out the presence of an underlying malignancy. An undiagnosed carcinoma is potentially the most serious disorder in these patients. The combination of negative imaging, cytology, and cystoscopy most likely rules out the presence of a malignant pathology. However, in few patients, careful follow-up is necessary to reveal the cause of persistent hematuria. Recommended follow-up for patients with asymptomatic microhematuria includes monitoring with annual urinalysis.

1. If two consecutive annual urinalyses are negative in patients with persistent asymptomatic microhematuria, then the follow-up can be concluded.
2. Complete initial urological workup is recommended if microhematuria persists for 3–5 years.

TREATMENT

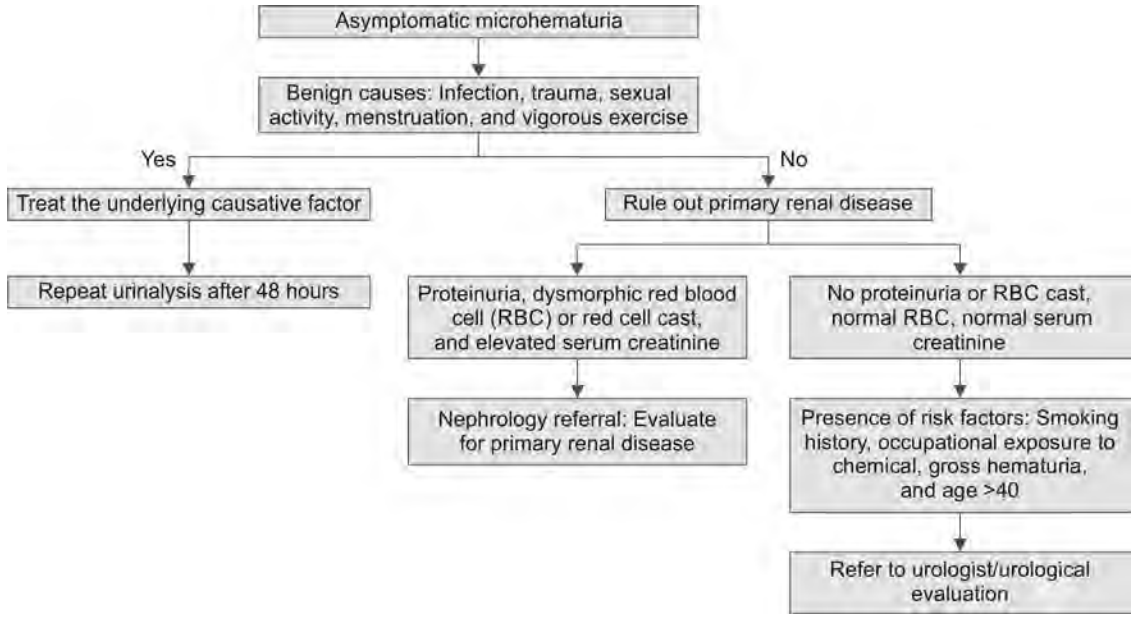
Treatment of hematuria is based on the etiology. In cases presenting to the emergency department, one should assess the hemodynamic stability of the patient first. In hemodynamically stable patients, without any life-threatening cause of hematuria, it is advised to have an outpatient follow-up. As per the recommendations of American Urological Association guideline, patients with microscopic hematuria without any benign cause should be referred to urology service for assessment of urinary tract malignancy.

Patients with gross hematuria may present to the emergency department with acute urinary retention due to bladder outlet obstruction and intravesical clot formation. This condition is treated by Foley's catheterization and may be followed by a bladder wash in consultation with the urologist.

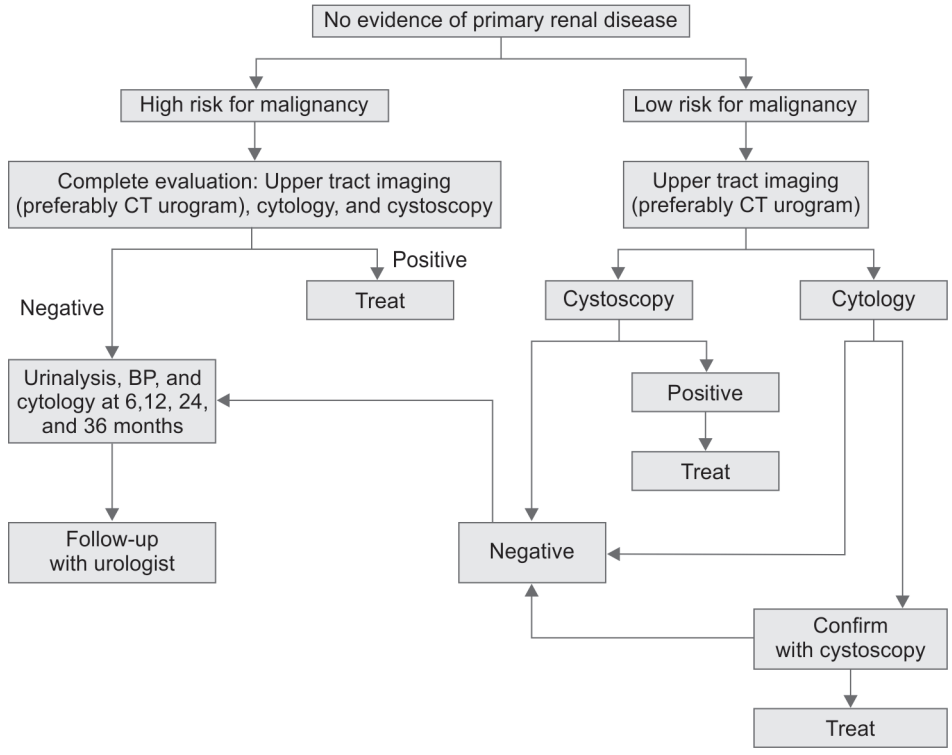
Hemodynamically unstable patients with pain, intolerance to oral medications and fluids, and other comorbid conditions with bladder obstruction or with life-threatening cause of hematuria should be stabilized in the emergency department and are to be admitted under appropriate specialist.

SUMMARY

The presence of RBCs in the urine is hematuria. It can be microscopic (detected by dipstick or microscopic examination) or gross (visible to naked eyes). Evaluation of asymptomatic microscopic hematuria is summarized in **Flowchart 1**. In adults, any unexplained hematuria is


Asymptomatic microhematuria
Benign causes: Infection, trauma, sexual activity, menstruation, and vigorous exercise
Yes
No
Treat the underlying causative factor
Rule out primary renal disease
Repeat urinalysis after 48 hours
Proteinuria, dysmorphic red blood cell (RBC) or red cell cast, and elevated serum creatinine
No proteinuria or RBC cast, normal RBC, normal serum creatinine
Nephrology referral: Evaluate for primary renal disease
Presence of risk factors: Smoking history, occupational exposure to chemical, gross hematuria, and age >40
Refer to urologist/urological evaluation

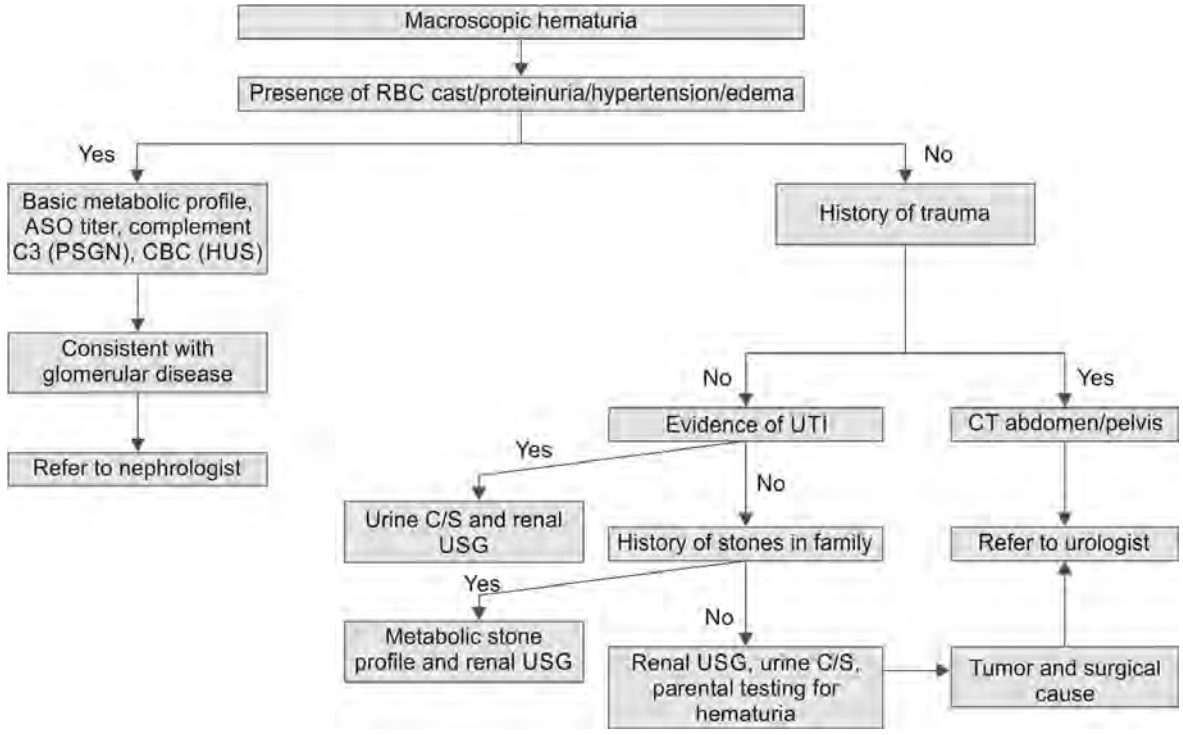
FLOWCHART 1: Evaluation of asymptomatic microscopic hematuria.



(BP: blood pressure; CT: computed tomography)

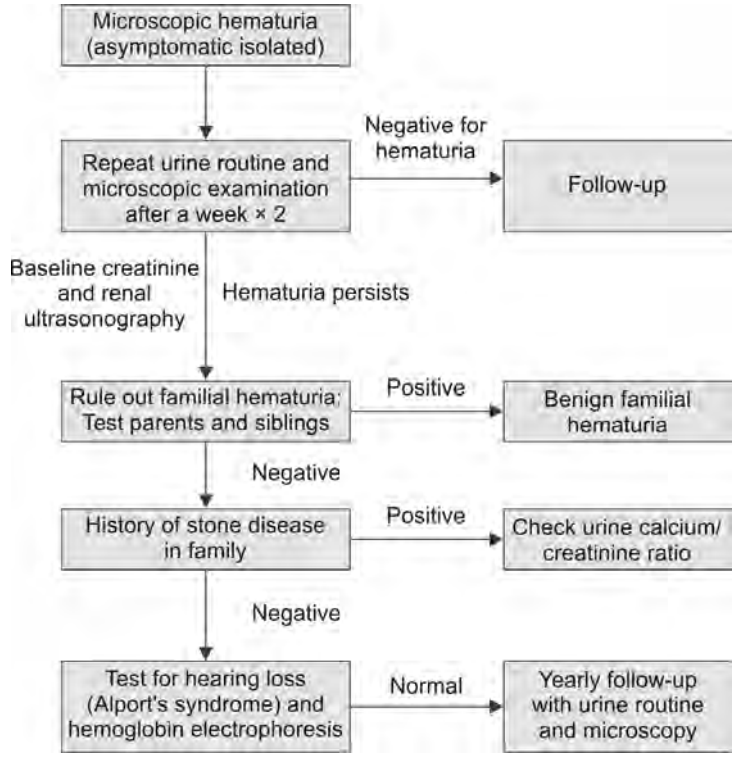
FLOWCHART 2: Urologic evaluation of hematuria.

assumed malignant until proven otherwise. Patients with gross hematuria should undergo a mandatory evaluation of the upper and lower urinary tract whereas patients with asymptomatic microscopic hematuria should have urologic evaluation upon ruling out of benign causes (**Flowchart 2**). The evaluation should include urine analysis, renal functions test, cystoscopy, renal and genitourinary ultrasonography and CT. Treatment of hematuria is based on the etiology. Hemodynamically unstable patients should be stabilized in the emergency department and are admitted for further management. Evaluation of microscopic and macroscopic hematuria is summarized in **Flowcharts 3** and **4**.



(ASO: antistreptolysin O; CBC: complete blood count; C/S: culture and sensitivity; CT: computed tomography; HUS: hemolytic uremic syndrome; PSGN: poststreptococcal glomerulonephritis; RBC: red blood cell; USG: ultrasonography; UTI: urinary tract infection)

FLOWCHART 3: Evaluation of macroscopic hematuria in children.


Microscopic hematuria (asymptomatic isolated)
Repeat urine routine and microscopic examination after a week × 2
Negative for hematuria
Follow-up
Baseline creatinine and renal ultrasonography
Hematuria persists
Rule out familial hematuria; Test parents and siblings
Positive
Benign familial hematuria
Negative
History of stone disease in family
Positive
Check urine calcium/ creatinine ratio
Negative
Test for hearing loss (Alport's syndrome) and hemoglobin electrophoresis
Normal
Yearly follow-up with urine routine and microscopy

FLOWCHART 4: Evaluation of microscopic hematuria (asymptomatic isolated) in a child.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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108 CHAPTER

Acute Urinary Retention

Puneet Ahluwalia

INTRODUCTION

Acute urinary retention (AUR) is the sudden painful inability to void, with relief of pain following drainage of bladder. It is one of the most common emergencies encountered in urology. A combination of reduced or absent urine output with lower abdominal pain is not enough to make a diagnosis of AUR. Sometimes a surgical condition with lower abdominal pain and reduced urine output due to fluid depletion, can give a false impression of AUR. Therefore, central to the diagnosis of AUR is the presence of large volume of urine. What actually defines this large volume has not been strictly described but volumes of 500–800 mL are typical. In men, the most common cause of AUR is benign prostatic hyperplasia (BPH). AUR is rarely encountered in women. It is imperative to know the etiopathogenesis and management of AUR. The present chapter focuses on both aspects.

EPIDEMIOLOGY

Acute urinary retention is common in men. The incidence increases with age, occurring most frequently in men over age 60. The reported incidence is about 0.5–2.5% person years. The risk is cumulative and increases with age. It is estimated that over a 5-year period, approximately 10% of men over the age of 70 and almost one-third of men in their 80s will develop AUR. In contrast, women rarely present with AUR. It is estimated that there are three cases of AUR per 100,000 women per year. The female-to-male incidence rate ratio is 1:13.

ETIOPATHOGENESIS

Various pathophysiologic mechanisms play a role in the development of AUR. There is no specific etiology and usually it is multifactorial. Etiologic factors responsible for AUR are divided into following broad categories.

- *Obstructive causes*: Outflow obstruction with increased urethral resistance
- *Neurogenic*: Neurologic impairment, interruption of sensory or motor innervations of the bladder.
- *Myogenic*: Inefficient detrusor muscle contraction with low bladder pressure
- *Others*: Infections drugs

Outflow Obstruction

Obstruction is the most common cause of AUR. A range of mechanical and dynamic factors are responsible for the outflow obstruction. Mechanical obstruction refers to a physical narrowing at any level in urethral channel from bladder neck to external urethral meatus. Dynamic obstruction refers to increased sphincteric activity with increased muscle tone within and around the urethra.

In men, the most common cause of obstruction is bladder outlet obstruction due to BPH. In a study of 310 men over a 2-year period, urinary retention was caused by BPH in 53% of patients. Other obstructive causes accounted for another 23%. Risk factors for developing AUR in patients with BPH include advanced age, severity of lower urinary tract symptoms (LUTS), enlarged prostate gland, and decreased urinary flow rate. Other causes of outflow obstruction in men include urethral stricture, urolithiasis, cancer prostate, phimosis, or paraphimosis and bladder cancer. Urinary retention from bladder tumors is usually caused by blood clots from intravesicular bleeding and often presents with painless hematuria.

In women, obstruction is generally secondary to anatomic distortion due to various reasons as pelvic organ prolapsed, pelvic masses, or rarely urethral diverticulum. Fecal impaction and gastrointestinal or retroperitoneal masses are large enough to cause extrinsic bladder. Neck compression can also sometimes present with retention of urine. Obstructive causes of AUR in men and women are summarized in **Table 1**.

Age

Several well-controlled studies provided considerable insights into the risk factors for AUR. Perhaps the most significant of these risk factors is age. Studies demonstrate a nearly linear increase in the age-specific incidence of AUR for men ranging in age from 40 to older than 80 years.

Lower Urinary Tract Symptoms

Increased symptom severity is associated with increased risk of AUR in several large population-based or cohort studies. The Olmsted County study focused on age, symptom severity, maximum flow rate, and prostate volume. Incidence rates per 1,000 patient-years increased from 2.6 to 9.3 for men in their

TABLE 1: Obstructive causes of acute urinary retention (AUR).

Males	*Females*	*Both*
• Benign prostatic hyperplasia • Meatal stenosis • Urethral stricture • Phimosis • Paraphimosis	• Pelvic organ prolapse (cystocele, rectocele, and uterine prolapse) • Pelvic mass (gynecologic malignancy, uterine fibroid, and ovarian cyst) • Retroverted impacted gravid uterus	• Urolithiasis (bladder stone) • Bladder tumor • Constipation with fecal impaction • Retroperitoneal mass • Gastrointestinal malignancy • Foreign body

40s to their 70s if they had mild symptoms and from 3.0 to 34.7 if they had more than mild symptoms.

Urodynamic Parameters

The relative risk increased for older men, men with moderate-to-severe symptoms (3.2 times), those with a flow rate under 12 mL/s (3.9 times) and those with a prostate volume >30 mL by transrectal ultrasound (TRUS) (3.0 times), all compared with a baseline risk of 1.0 time for the corresponding groups.

Prostate Volume and Serum Prostate-specific Antigen Levels

In the Proscar Long-Term Efficacy and Safety Study (PLESS) and Medical Therapy of Prostatic Symptoms (MTOPS) study, a linear relationship between risk of AUR and prostate volume and serum prostate-specific antigen (PSA) has been demonstrated. An analysis revealed a combination of factors such as serum PSA, frequency, symptom severity index, maximum urinary flow rate, and hesitancy as being only slightly superior to PSA alone in predicting AUR.

Neurologic Impairment

Normal functioning of the bladder and lower urinary tract depends on a complex interaction between the brain, autonomic nervous system, and somatic nerves supplying the bladder and urethra. Interruption along these pathways can result in unsustainable detrusor muscle contraction or incomplete relaxation of sphincter leading to urinary retention.

Neurogenic or neuropathic bladder is defined as any defective functioning of the bladder muscle due to impaired innervation. Urinary retention from neurologic causes occurs equally in both sexes. Although most patients with neurogenic bladder experience incontinence, a significant number might also have urinary retention. Various causes of neurogenic bladder related to spinal cord brain and autonomic nervous system are summarized in **Table 2**.

Up to 56% of patients who have suffered a stroke experience urinary retention, primarily because of detrusor hyporeflexia. In a prospective study, 23 of 80 patients with ischemic stroke developed. AUR can occur with spinal cord injuries from trauma, infarct or demyelination, epidural abscess and epidural metastasis, Guillain–Barré syndrome, diabetic neuropathy, and stroke.

TABLE 2: Causes of neurologic bladder associated with acute urinary retention (AUR).

Autonomic nervous system	*Brain*	*Spinal cord*
• Autonomic neuropathy • Diabetes mellitus • Guillain–Barré syndrome • Herpes zoster virus • Lyme disease • Pernicious anemia • Poliomyelitis • Radical pelvic surgery • Sacral agenesis • Spinal cord trauma • Tabes dorsalis	• Cerebrovascular episode • Multiple sclerosis • Brain tumor • Hydrocephalus • Parkinson's disease • Shy–Drager syndrome	• Intervertebral disk disease • Dysraphic lesions • Spina bifida occulta • Meningomyelocele • Multiple sclerosis • Spinal cord hematoma or abscess • Spinal cord trauma • Spinal stenosis • Transverse myelitis • Conus medullaris or cauda equine tumors or masses

Up to 45% of patients with diabetes mellitus and 75–100% of patients with diabetic peripheral neuropathy experience bladder dysfunction and include urinary retention. Voiding dysfunction tends to correlate with the severity of multiple sclerosis and occurs in up to 80% of patients, with urinary retention being present in approximately 20%. AUR is typically accompanied by back pain and/or other neurologic deficits.

Inefficient Detrusor Muscle

Inefficient detrusor contraction leading to AUR can be due to multiple factors including neurologic disease as above affecting the detrusor contraction or long-standing untreated obstruction leading to detrusor failure. Sometimes a precipitating event results in an acute distended bladder (e.g., with a fluid challenge, during general or epidural analgesia without an indwelling catheter). This most often occurs in patients with some unrecognized obstructive urinary symptoms at baseline.

Other Causes

Acute urinary retention is most often secondary to mechanical outflow obstruction. Other etiologies include medication, infection, trauma, and postoperative and pregnancy-related urine retention.

Medications

Multiple medications are implicated as a cause of urinary retention; most common among these are the anticholinergic and sympathomimetic drugs. These medications lead to AUR through a variety of mechanisms. Patients taking opioids and anticholinergic medications are at higher risk for AUR due to decreased bladder sensation. Anticholinergic medications also reduce detrusor contractility. Nasal decongestants that contain sympathomimetic agents increase smooth muscle tone in the region of the bladder neck. Nonsteroid inflammatory drugs are sometimes responsible for AUR. Nonsteroidal anti-inflammatory drug (NSAID)-induced urinary retention is thought to occur by inhibition of prostaglandin-mediated detrusor muscle contraction.

Infection

Infections may lead to AUR in the setting of inflammation that causes obstruction. The most common cause of infectious AUR is acute prostatitis. Acute prostatitis is usually caused by gram-negative organisms, such as *Escherichia coli* and *Proteus* species, and results in swelling of the acutely inflamed gland.

For example, an acutely-inflamed prostate gland from acute prostatitis can cause AUR, particularly in men who already have BPH. Urethritis from urinary tract infection or urethritis can cause urethral edema and can result in AUR. Genital herpes may cause AUR both from local inflammation as well as sacral nerve involvement. Other infections that have been associated with AUR include varicella zoster and vulvovaginitis, summarized in **Table 3**.

Trauma

Patients with trauma to the pelvis, urethra, or penis may develop AUR from mechanical disruption. AUR may also occur in postoperative period.

Postoperative Urinary Retention

Multiple factors as pain, traumatic instrumentation, bladder over distension, and pharmacologic agents (particularly opioid narcotics and prazosin) thought to play a role. After rectal surgery, patients will experience urinary retention up to 70% of the time. As many as 78% of patients who have had total hip arthroplasty and up to 25% of patients who have had outpatient gynecologic surgery will develop urinary retention. During hemorrhoidectomy, the use of selective pudendal nerve block rather than spinal anesthesia may decrease urinary retention.

Pregnancy-associated Urinary Retention

Urinary retention during pregnancy is usually the result of an impacted retroverted uterus obstructing the internal urethral meatus and is most often encountered at 16 weeks of gestation. In postpartum period, the incidence of AUR is reported to be 1.7–17.9%. Risk factors include nulliparity, prolonged labor, instrumental delivery, epidural anesthesia, and cesarean section. Other causes of AUR are summarized in **Table 4**.

CATEGORIES OF URINARY RETENTION

From a clinical and prognostic point of view AUR has been divided into two broad categories as spontaneous and precipitated. Precipitated AUR refers to inability to urinate after a triggering event such as nonprostate-related surgery, e.g., hemorrhoidectomy, catheterization, anesthesia, ingestion of drugs as sympathomimetic or anticholinergics or antihistaminic, and excessive fluid intake. All other episodes of AUR are classified as spontaneous AUR. The clinical significance of differentiating the two types of AUR lies in the final outcomes of these patients. In a study by Roehborn et al., after an episode of spontaneous AUR, 15% of patients had another episode of spontaneous AUR and a total of 75% underwent surgery, whereas after precipitated AUR only 9% had an episode of spontaneous AUR, and 26% underwent surgery.

TABLE 3: Infections associated with acute urinary retention (AUR).

Sex		
Males	***Females***	***Both***
• Prostatitis • Prostatic abscess • Periurethral abscess • Balanitis	• Acute vulvovaginitis • Vaginal lichen planus • Vaginal lichen sclerosis • Vaginal pemphigus • Bilharziasis • Echinococcosis	• Urethritis • Bacterial cystitis • Tubercular cystitis • Guillain–Barré syndrome • Herpes simplex virus encephalitis • Varicella-zoster virus • Lyme disease • Transverse myelitis

TABLE 4: Other causes of acute urinary retention (AUR).

Males	***Females***	***Both***
Penile trauma	• Pregnancy associated • Postpartum complication • External urethral sphincter dysfunction	• Disruption of posterior urethra and or bladder neck in pelvic fracture • Postoperative complication • Psychogenic cause

CLINICAL PRESENTATION

Acute urinary retention generally presents as an inability to pass urine. It is typically associated with lower abdominal and/or suprapubic discomfort. Affected patients are often restless and may appear in considerable distress. These manifestations may be less pronounced when AUR is superimposed upon chronic urinary retention. Chronic urinary retention is often painless. Acute-on-chronic urinary retention may present with overflow incontinence. The patients may complain of incontinence rather than the inability to pass urine. Patients with AUR are likely to present initially to an emergency department or the office of a primary care clinician. Most common emergency scenarios encountered by an emergency physician are the bladder outlet obstruction caused by BPH or neurogenic bladder. Hospitalized patients may develop AUR, often related to medications or after surgical procedures.

EVALUATION

Detailed history, physical examination, and diagnostic testing can help determine the etiology of urinary retention.

History

The patient history should focus on age of presentation, sex, previous history of retention or LUTS, prostate disease (hyperplasia or cancer), pelvic or prostate surgery, radiation, or pelvic trauma. Patients will generally give history of multiple lower urinary tract voiding or storage symptoms, including frequency, urgency, nocturia, straining to void, poor urinary stream, hesitancy, sensation of incomplete bladder emptying, and intermittent urinary stream. The patient should also be asked about the presence of incontinence, hematuria, dysuria, fever, low back pain, neurologic symptoms, or rash. The physician should inquire about precipitating factors, including alcohol consumption, recent surgery, urinary tract infection, genitourinary instrumentation, constipation, large

fluid intake, cold exposure, and prolonged travel. Finally, a complete list of medications, including over the counter medications should be obtained. Younger patient age, a history of cancer or intravenous drug abuse, and the presence of back pain or neurologic symptoms suggest the possibility of spinal cord injury or compression. Therefore, a history of neurologic disease, spinal trauma or tumor, and any change in baseline neurologic status is important and should be carefully noted. However, patients with spinal pathology generally do not present primarily with AUR. These patients will most often have other signs and symptoms of spinal cord pathology with AUR being one part of clinical picture. Patients can also present with overflow incontinence and have a history of recurrent urinary tract infection (UTI). History of long-standing diabetes mellitus is also important, but most patients present with painless retention because of diabetic cystopathy. History of presence of pain in any form as restlessness or suprapubic discomfort is important as it may point towards etiology of retention. Acute urine retention of obstructive etiology is usually painful.

Physical Examination

In patients with AUR of unknown etiology, the physical examination should include the following: General physical examination including vitals, general well-being, and systemic examination. Systemic examination should focus on lower abdominal palpation. The urinary bladder may be palpable or percussible. Usually urinary bladder is percussible or palpable if it contains 150–200 mL of urine. In obese patient this may not be appreciable but deep suprapubic palpation will provoke discomfort. A digital rectal examination (DRE) should always be done in both sexes. This is important for detailed evaluation of prostate, masses, fecal impaction, perianal sensation, and rectal sphincter tone. In men, a normal prostate examination does not preclude BPH as a cause of obstruction as size of the dose not correlates the presentation. Prostatic abscess should be looked for in DRE as a hot boggy tender prostate. In women with urinary retention, it is imperative to do per vaginal examination.

In addition to the above, neurologic examination should be done in patients with suspected neurogenic bladder to test the integrity of sacral nerve roots that subserve the bladder function. This includes a general neurologic examination, as well as specific examinations related to bladder function. These include the cremasteric reflex, bulbocavernosus reflex (BCR), voluntary contractions of the pelvic floor, anal sphincter tone, and perianal sensation in the S2 to S4 dermatomes. BCR is done by squeezing the glans penis while performing a DRE. Contraction of anus felt by the examining finder indicates that afferent and efferent sacral nerves and sacral cord are intact. In females, after catheterization same reflex can be elicited by gently tugging the catheter onto the bladder neck while doing DRE, when the contraction of anus indicates integrity of afferent and efferent sacral nerves and sacral cord.

Laboratory Studies

A urine sample should be obtained and sent for urinalysis and urine culture. The urine sample is collected with standard sterile precautions after catheter insertion. The need for other laboratory testing should be determined based upon findings from the patient's history and physical examination. Most patients who present to the emergency room with concern for urinary retention have serum electrolytes and creatinine checked. These should be checked in any patient whose history suggests acute-on-chronic urinary retention, to evaluate for renal failure. Other laboratory study that may be helpful includes a complete blood count (CBC) for suspected infection. Blood gas analysis sample should be sent in patients presenting with sepsis with or without renal failure to look for metabolic acidosis. Serum PSA testing is not recommended in the setting of AUR as it is expected to be elevated during the episode.

Radiological Investigation

This includes an ultrasound kidney, ureter, bladder with prostate, and urine retention volume. Upper tracts are to be looked for hydroureteronephrosis. All these basic investigations help tailoring the emergency management of a patient presenting with AUR.

INITIAL MANAGEMENT OF ACUTE URINARY RETENTION

Urethral catheterization is the mainstay of initial management of AUR. This is for immediate decompression with relief of pain due to overdistended bladder. Standard transurethral catheters are readily available and can usually be easily inserted. If urethral catheterization is unsuccessful or contraindicated, the patient should be referred immediately to a physician trained in advanced catheterization techniques, such as placement of a firm, angulated Coude catheter or a suprapubic catheter. Record the volume drained which will confirm the diagnosis, determines the subsequent management, and provide prognostic information with regard to outcome.

Acute or Acute-on-chronic Retention

A group of elderly people are not aware of, but they actually have urine retention. This has been particularly defined as chronic retention. This has been further subdivided into low-pressure chronic retention or high-pressure chronic retention (*HPCR*). In 1984, Mitchell defined *HPCR of urine* as maintenance of voiding, with a bladder volume of >800 mL and intravesical pressure of >30 cmH_2O, often accompanied by hydronephrosis. This over the time may lead to renal failure. To the contrary low-pressure chronic retention is maintenance of voiding with a bladder volume of >800 mL, but with low normal intravesical pressure and without upper tract changes. The patient continues to void spontaneously without sensation of incomplete voiding. Often the first symptom is bed wetting and inspection of the abdomen reveals a grossly distended bladder confirmed by palpation and/or percussion. Sometimes a patient with HPCR is suddenly unable to pass urine, called as acute-on-chronic retention. Patient presents with palpable bladder, raised serum creatinine, and bilateral hydroureteronephrosis on ultrasound. On catheterization a large volume of urine is drained, often amounting to 1–2 L. As mentioned above recording of volume of urine is important as it holds differentiating two groups of patients, those with acute retention of urine with retention volume of <800 mL and those with acute-on-chronic retention with retention volume of >800 mL. All these patients may develop postobstructive diuresis and it is imperative to keep regular watch on vitals, urine output, and electrolytes.

What to do Next?

Further plan depends on the type of retention whether precipitated or spontaneous and etiology of AUR. Precipitated

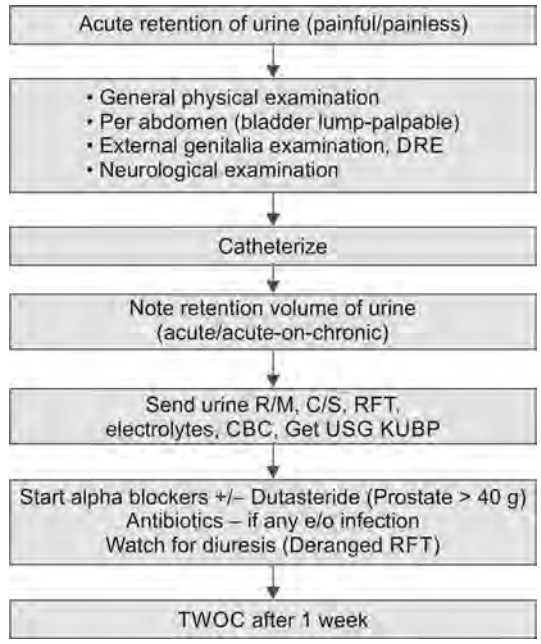
urine retention often does not recur and should be managed with a trial without catheter (TWOC) after exclusion of the precipitating factor. Spontaneous retention often recurs. In case of BPH, usually it is advisable give a TWOC and not to proceed straight to transurethral resection of the prostate (TURP).

The American Urological Association (AUA) guidelines recommend at least one attempted trial of voiding after catheter removal before considering surgical intervention. In these patients the optimal amount of time to leave a catheter in place is unknown. Up to three-fourths of men will have recurrent urinary retention within 1 week if the bladder is simply drained. One-fourth of men will void successfully after a TWOC.

Of those with successful *TWOC* about 50%, 60%, and 70% develop AUR within 1 week, 1 month, and after a year, respectively. Factors affecting the failure of TWOC are maximal flow rate of <5 mL/s, average voided volume of <150 mL.

An alpha blocker started 24–72 hours before TWOC increase the likelihood of successful voiding. The duration of alpha blockers after successful TWOC has not been determined yet. Also, it is not known whether continued use prevents further risk of AUR. Usually alpha blockers are continued after successful TWOC and finasteride or dutasteride is combined with them in case of prostate >40 g. A TWOC is clearly not indicated in patients with back pressure changes on the kidneys.

In patients with chronic urinary retention with inefficient detrusor contraction, especially those with neurogenic bladder can be managed with clean and intermittent self-catheterization. This technique is considered first-line treatment for managing urinary retention caused by neurogenic bladder and can reduce complications, such as renal failure, upper urinary tract deterioration, and urosepsis. Further definitive management of urinary retention depends upon the underlying etiology and may involve surgical and medical treatment. A basic algorithm of managing a male patient presenting with AUR is provided in **Flowchart 1**.


Acute retention of urine (painful/painless)
• General physical examination
• Per abdomen (bladder lump-palpable)
• External genitalia examination, DRE
• Neurological examination
Catheterize
Note retention volume of urine (acute/acute-on-chronic)
Send urine R/M, C/S, RFT, electrolytes, CBC, Get USG KUBP
Start alpha blockers +/– Dutasteride (Prostate > 40 g)
Antibiotics – if any e/o infection
Watch for diuresis (Deranged RFT)
TWOC after 1 week

(CBC: complete blood count; C/S: culture and sensitivity; DRE: digital rectal examination; RFT: renal function test; R/M: routine microscopy; TWOC: trial without catheter; USG KUBP: ultrasound kidney, ureter, bladder and prostate)

FLOWCHART 1: Algorithm for emergency management in case of AUR in a male patient.

SUMMARY

Benign prostatic hypertrophy (BPH) is the most common cause of AUR in men. Patient with acute retention of urine presents to ED with pain while passing the urine and usually gets relief with bladder catheterization. Lower abdominal pain and inability to pass the urine are not enough for diagnosis, nowadays better modalities are available for evaluation of causes and their management. The risk for patients diagnosed with BPH is naturally higher. In addition to serum PSA, prostate volume, maximum flow rate, and symptom severity should be considered while adopting the conservative and medical therapy. Efforts toward primary prevention of AUR are important because surgical treatment carries a higher rate of morbidity in those who are older and have more severe symptoms, larger glands, and higher PSA values.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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109 CHAPTER

Acute Kidney Injury and Rhabdomyolysis

Ankit Purohit, Devendra Richhariya

INTRODUCTION

Large number of patient present to emergency department (ED) with clinical features of renal failure. Emergency physicians (EPs) role become important in the evaluation and management of renal disease. Patients with renal dysfunction, either acute or chronic, are frequently encountered in the ED. Patients may have complaints directly related to their kidney dysfunction, or they may have subtle clinical signs, and some may have no signs or symptoms of renal disease. EP must be aware about early recognition, diagnosis, prevention of further iatrogenic injury, and management of renal disease. Basic renal physiology, differential diagnosis and approach to therapy, and strategies to prevent renal injury, will be discussed in this chapter for adult patients who present to the ED with renal injury or failure. General understanding about terminology related to renal failure are *acute kidney injury (AKI):* Rapid decline in renal functions (earlier termed as "acute renal failure") *chronic kidney disease (CKD)*: Progressive persistent decline in renal function over months or years [earlier termed as "chronic renal failure" (CRF)] *end-stage renal disease (ESRD):* Minimal/absent renal function, requiring renal replacement therapy with hemodialysis or peritoneal dialysis. But, various functional and structural criteria are used to define various terminology of renal failure (**Table 1**).

PATHOPHYSIOLOGY

Four important steps in the renal function are: (1) Glomeruli receive blood flow delivered through circulation, (2) An ultrafiltrate is formed in the glomeruli and then delivered to the renal tubules, (3) Renal tubules reabsorbed the solutes and/or water, and (4) Tubular fluid (now urine) exits the tubules, draining to the renal pelvis, the ureters, and the bladder, and urine is then expelled via the urethra. Any process that interferes with any of the above four structures or steps involved in this process causes renal disease. Rapid decline in renal function give rise to AKI, and progressive decline/insult of renal function during months or years resulting CKD.

Each kidney contributes to the total glomerular filtration rate (GFR) through its approximately 1 million nephrons. The volume of fluid filtered per unit time is termed as GFR and can be calculated by measuring any steady state concentration of chemical in the blood plasma and is freely filtered by the kidney but is neither secreted nor absorbed in the kidney [GFR—(urine concentration flow)/plasma concentration].

TABLE 1: Criteria for defining AKI, AKD, CKD, and NKD.

	Duration	*Functional criteria*	*Structural criteria*
AKI	≤7 days	Increase in SCr by ≥50% within 7 days or increase in SCr by ≥0.3 mg/dL (26.5 µmol/L) within 2 days or oliguria for ≥6 h	Not defined
AKD	<3 month	AKI or GFR < 60 mL/min/1.73 m^2 or decrease in GFR by ≥35% over baseline or increase in SCr > 50% over baseline	Elevated marker of kidney damage (albuminuria, hematuria, or pyuria are most common)
CKD	>3 month	GFR < 60 mL/min/1.73 m^2	Elevated marker of kidney damage (albuminuria is most common)
NKD	NA	GFR ≥ 60 mL/min/1.73 m^2, stable GFR (no decrease by 35% within 3 months), stable SCr (no increase by 50% within 3 months or increase by 0.3 mg/dL within 2 days), no oliguria for ≥6 h	No marker of kidney damage

* NKD implies no functional or structural criteria according to the definitions for AKI, AKD, or CKD.

(AKD: acute kidney disease; AKI: acute kidney injury; CKD: chronic kidney disease; GFR: glomerular filtration rate; NKD: no kidney disease; SCr: serum creatinine)

Structural and functional changes within the kidney occur with progressive damage to nephrons. Initially, the kidney tries to maintain GFR with the remaining healthy nephrons through hyperfiltration and compensatory hypertrophy of nephron and normal clearance of plasma solutes is maintained by the kidney. If risk factors cannot be removed or physiologic insult to nephron persists and damaged nephrons cannot recover, renal reserve may be exhausted permanently. Decline in GFR, leading ultimately to oliguria, decreased urine output (UOP), or anuria, the absence of urine formation and finally renal injury and/or renal failure occurs.

Metabolism of creatine phosphate in muscle tissue and is freely filtered by the glomerulus and give rise to serum creatinine (SCr). Most laboratories, and clinical setting, use SCr as an easy and attractive index for measurement in GFR, but several drawbacks to the use of SCr as a surrogate marker for GFR. Various factors such as body mass, body composition, race, sex, total body volume, muscle metabolism, and diet influence the SCr. Apart from these nonrenal factors, significant day-to-day variations in creatinine excretion also occurs, making any single measurement SCr an imperfect measure of a patient's true renal function.

In some settings creatinine clearance (CrCl) is also used as a marker of overall renal function and an estimate of GFR. Most calculations of CrCl depend on measurement of SCr as well as a measurement of urinary creatinine concentrations (UCr) and the measured volume from a 24-hour collection of urine. In addition, certain medications (such as cimetidine and trimethoprim) may inhibit creatinine secretion. Modification of Diet in Renal Disease (MDRD) equation or the Cockcroft-Gault formula is often used in clinical research for estimations of GFR or CrCl. Both make corrections for patient variables such as age and sex. Medical calculators both online and handheld electronic devices can be used by clinicians for these formulas, values can be estimated easily, useful in ED settings.

ACUTE KIDNEY INJURY

Acute kidney injury is a common presenting problem encountered in ED associated with increased risk of mortality and often progression to CKD. AKI is more troublesome particularly in the elderly population. Derangement such as metabolic acidosis and body fluid volume disturbances are associated with AKI. The epidemiology of AKI in hospitalized or critically ill populations is well known, but in the general ED population is not well studied. The patient seen in the emergency or acute setting is often diverse with complex medical histories and without effective primary care follow-up so evidence-based approach for the management of AKI in the emergency setting is required. Most of the time, ED is the place where community-acquired AKI is identified for the first time. Thus, EP should identify, manage AKI appropriately in ED.

DEFINITION

A variety of definitions for AKI proposed in literature. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) group defined AKI based on the UOP and the SCr concentration. This definition is an increase in SCr of ≥0.3 mg/dL within 48 hours or an increase in SCr >1.5 times baseline within 7 days or decreased UOP for 6 hours (**Table 2**). Other classification systems of AKI, such as Risk, Injury, Failure, Loss, and End-stage (RIFLE) and Acute Kidney Injury Network (AKIN), can also be used, but as per studies all three criteria are effective tools for predicting mortality without significant differences among them but advantage of KDIGO is that it covers parameters in AKIN and RIFLE.

TABLE 2: Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for acute kidney injuries (AKIs).

AKI stage	*Serum creatinine (SCr)*	*Urine output*
1	1.5–1.9 × baseline OR ≥0.3 mg/dL increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 × baseline	<0.5 mL/kg/h for >12 h
3	3.0 × baseline OR initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h
Risk, Injury, Failure, Loss, and End-stage (RIFLE) Criteria		
1	Increase in SCr ≥150% mg/dL	<0.5 mL/kg/h for 6–12 h
2	Increase in SCr ≥200–300% mg/dL	<0.5 mL/kg/h for ≥12 h
3	Increase in Cr 300% OR creatinine >4 mg/mL with acute increase 0.5 mg/dL or initiationofrenalreplacement therapy	<0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h

Source: Data from Moore PK, Hsu RK, Liu KD. Management of acute kidney injury: core curriculum 2018. Am J Kidney Dis. 2018;72(1):136-48.

Acute kidney injury is defined as a sudden reduction in kidney function that is characterized by a diminished GFR as manifested by an increased SCr or reduced UOP. AKI is further divided into three categories: (1) *Prerenal,* a kidney blood flow decrease; (2) *Intrarenal,* or kidney parenchymal injury; and (3) *Postrenal,* or urine flow obstruction. Intrarenal AKI is subdivided again on the basis of part of the kidney is involved: glomeruli, vasculature, or interstitium. Treatment of AKI depends on the causes and type of insult, so finding the source of AKI is important. As earlier discussed, SCr concentration is not accurate, for assessment of patients with AKI. CrCl is better tool for assessing AKI as it measures effectiveness of the glomeruli to filter creatinine from the plasma and is a close approximation of the GFR. Dilution, volume overload states, and reductions of creatinine production during the acute phases of an illness are confounding factors during estimation of SCr values. In critical and acute care settings, patient's body muscle mass is also fluctuate which alters the relative SCr levels. For these reasons, and to apply steady-state kinetics more accurately, other biomarkers (**Table 3**) are being studied as potential surrogates for acute kidney function such as serum cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1). However, in the acute setting, SCr remains the most validated estimation of GFR to determine kidney function.

RISK FACTORS AND CAUSES FOR ACUTE KIDNEY INJURY

Emergency physician should assess risk factors in all patients of AKI, but particularly those in critical condition. Risk factors

TABLE 3: Several novel biomarkers for AKI.

Biomarker	*Function affected/ evaluated*	*Use*
Cystatin C (serum)	Marker of glomerular filtration	• Shows good accuracy for early diagnosis of AKI • Seems to be particularly useful in patients with sepsis
NGAL (serum)	Marker of renal tubular inflammation	Correlates well with acute changes in SCr
IL-18 (urine)	Marker of renal tubular inflammation	• Facilitates the diagnosis of AKI • Marked increased in patients with acute tubular necrosis • Predicts mortality
KIM-1 (urine)	Marker of injury to the proximal tubule, especially following ischemic insult	May be highly effective at distinguishing acute tubular necrosis from other types of renal injury

(AKI: acute kidney injury; IL-18: interleukin-18; KIM-1: kidney injury molecule-1; NGAL: neutrophil gelatinase-associated lipocalin; SCr: serum creatinine)

for developing AKI are multiple, well-studied, and well-defined. In comparison to younger patients, elderly patients (65 years or older) are more prone to AKI and have a poorer prognosis, despite advances in treatments, such as dialysis. Chronic underlying diseases, such as hypertension, diabetes, congestive heart failure, atherosclerosis, CKD, and obstructive (postrenal) uropathy, volume depletion, surgical procedures, sepsis or acute infections, and nephrotoxic agents are notable medical conditions that place patients at higher risk for developing AKI.

In patients with these risk factors who go on to develop AKI, there have been significant differences in further complications, such as delay discharging from hospital, ventilator use, and concomitant diseases.

Prerenal azotemia or acute tubular necrosis (ATN) is the main cause of AKI in >75% of patients. Body fluid losses, fluid sequestration, decreased cardiac output, or renal artery narrowing are causes for *prerenal failure*. ATN, interstitial, glomerular, and small vessel disease *are the causes for intrarenal failure*. *Postrenal causes* are those secondary to obstruction. Ultrasound can assess for masses, hydronephrosis, ureteral dilatation, and the absence of ureteral jets entering the bladder. Causes of AKI are given in **Table 4**.

TABLE 4: Causes of acute kidney injury.

Prerenal	• Low systemic volume (*congestive heart failure and liver failure)* • Hypovolemia • Low cardiac output • Dysfunctional kidney autoregulation • ACE inhibitors • Angiotensin receptor blockers • Nonsteroidal anti-inflammatory drugs • *Causes of poor renal perfusion leading to prerenal acute kidney injury:* ○ Volume depletion (diuretics, diarrhea, blood loss anemia, osmotic diuresis, diuretic overuse, burns, and vomiting) • *Decreased arterial pressure:* ○ *Medication*: NSAIDs, cyclosporine, tacrolimus, and angiotensin receptor blocker ○ Cardiorenal syndrome and hepatorenal syndrome ○ Intra-abdominal hypertension and systemic vasodilation: Sepsis
Intrarenal	• *Glomerular:* ○ Postinfections ○ Glomerulonephritis • *Tubular:* ○ Ischemia • *Nephrotoxins:* Endogenous toxins such as calcium, uric acid, hemolysis, rhabdomyolysis, contrast media, and chemotoxic agents • *Interstitial:* ○ *Medications*: Aminoglycosides, cephalosporin, penicillin ○ *Infection*: *Streptococcus* and Epstein–Barr virus ○ *Systemic disease*: Lupus and sarcoidosis • *Vascular:* ○ Renal thrombosis ○ Malignant hypertension
Postrenal	• Bladder obstruction • Prostate enlargement • Urinary retention • Malignancy • Bilateral obstructive nephrolithiasis • Obstruction of single functioning kidney

(ACE: angiotensin-converting enzyme; NSAIDs: nonsteroidal anti-inflammatory drugs)

Acute Glomerulonephritis

Glomerulonephritis, caused by autoimmune damage to the kidneys themselves, one of the intrinsic causes of AKI and progress to inflammatory changes leading to renal failure due to subsequent fibrosis of the glomerular apparatus. Nephrotic and nephritic syndromes are the presentations of this disease. Clinical features of nephritic syndrome include hematuria, proteinuria, decreased renal function, and high blood pressure. Hematuria/proteinuria is the common presentation of intrinsic renal disease and is often overlooked by EP and critical consideration in managing patients appropriately. Even mild rise in kidney function laboratory values, high blood pressure, or urinary issues can give rise to rapid deterioration of renal function if not identified or managed quickly. Progression to chronic renal failure from acute glomerulonephritis syndromes can be prevented with prompt and early management.

In poststreptococcal glomerulonephritis, antibodies formed against streptococcal antigen adhere to glomeruli at the time of infection. Complement and coagulation cascades initiated by inflammatory pathways, which leads to cell lysis, fibrin deposition, and ultimately damage to the native

structure of the glomeruli. In the long term, permanent scarring and damage of glomeruli occurs due to intraglomerular hypertension and destruction of the normal anatomy. The description of other various types of acute glomerulonephritis, e.g., postinfectious glomerulonephritis, immunoglobulin A (IgA) nephropathy, microscopic polyangiitis, and lupus nephritis are out of the scope of this chapter. The laboratory studies such as complement levels are not very important in the emergency setting. Meanwhile EP should focus on clinical presentations, especially in patients who present with nephrotic syndrome: hypertension, periorbital swelling, or lower leg edema, and AKI. Several types of acute glomerulonephritis or nephrotic syndrome manifest more in pediatric patients so consider appropriate age groups also in the ED. Young children between 2 and 12 years old, more often in boys than girls, are most commonly have postinfectious glomerulonephritis. Postinfection glomerulonephritis is suspected in a patient complained of a sore throat or skin infection, typically 1–12 weeks before presentation. Wegener granulomatosis or microscopic polyangiitis may presents with respiratory infections, purpura, and arthritis with signs of nephritic syndrome.

There are two main modalities of treatment for acute glomerulonephritis, supportive care (blood pressure control and dialysis) and immunosuppressive therapies to counteract the autoimmune cascade causing intrinsic renal damage. Blood pressure control is important in slowing down the decline of GFR or proteinuria. Angiotensin-converting enzyme (ACE) inhibitors have antiproteinuric and antifibrotic effects and are typically used in the chronic phase (i.e., CKD). Use of diuretics and management of hyperkalemia, acidosis, uremia, and fluid overload are the other supportive measures though these supportive measures do not reverse the underlying pathophysiology. Immunosuppressive treatments include steroids, mycophenolate mofetil, cyclophosphamide, pulse steroids, or intravenous (IV) immunoglobulins. These therapies are often complex and require management with specialists.

Sepsis

The sepsis is the leading cause of death among patients with AKI and is responsible for >40% of mortality. A study done by Levy and colleagues demonstrated 45% of patients with AKI who died had developed sepsis. Similar findings demonstrated by Mehta and colleagues through the Program to Improve Care in Acute Renal Disease database which showed 40% of patients with AKI went on to develop sepsis. Conclusion of these studies and analyses are that patients with AKI should be closely monitored for the development of infection. It is now thought that inflammatory responses represent the dominant abnormality in sepsis-associated AKI. Currently, supportive care with fluid resuscitation remains the focus of treatment in patient with sepsis. Recently, studies comparing early goal-directed therapy have not been able to demonstrate a benefit to protocolized resuscitation with early goal-directed therapy in septic shock compared with usual care. Waechter and colleagues demonstrated that the focus of resuscitation in the first 1 hour with aggressive fluid administration and initiation of vasoactive agents within the first 6 hours have produced the best patient outcomes. Isotonic solutions should be used because there is no evidence to support the use of colloids in sepsis. Finally, vasopressin or norepinephrine (NE) either can be used as the initial vasopressor for septic shock, VANISH trial showed no difference in AKI or mortality on comparison study. There is no benefit of dopamine and its agonist for the prevention of AKI as per various studies. To reduce mortality in patients with AKI, close monitoring is required for development of infection and prompt treatment is indicated.

Drug-induced Acute Kidney Injury

Drug-induced kidney disease is frequently seen in clinical practice as a cause of renal dysfunction. Acute episodes of acute renal failure due to drugs account for nearly 20%. Drug-induced nephrotoxicity is high among older adults about 66%. Therapeutic drug-induced AKI may be classified into tubular injury, glomerular injury, interstitial injury, and crystal-induced injury. Age, diabetes, or underlying renal insufficiency coupled with drug interactions are the important risk factors and understanding about these can help prevent AKI secondary to medications. There are too many drugs to list, and many drugs work together through multiple injury pathways to cause. For example, if patients are on calcium channel blockers for their hypertension, started on a macrolide for an acute respiratory process is associated with a higher risk for hospitalization with AKI. Surveillance and real-time analysis for nephrotoxic medication in the ED by pharmacists can be done for reductions in AKI.

Normal GFR is 120 mL/min in healthy young adults, and the kidney autoregulates GFR to preserve GFR and UOP. Certain drugs can interfere with the kidney's autoregulation ability to maintain glomerular pressure and decrease GFR. Renal tubular cells play important role in reabsorbing glomerular filtrate which exposes them to high levels of circulating toxins and drugs. Aminoglycosides, contrast, and vancomycin drugs associated with AKI by impairing mitochondrial function. Urinary presence of "muddy brown casts" of epithelial cells is pathognomonic for ATN. If the cause is identified and corrected early, the overall prognosis for ATN is good.

Acute interstitial nephritis, an inflammatory injury that is often nondose related which can result from a hypersensitivity reaction. Many drugs can cause acute interstitial nephritis, including allopurinol; β-lactams, quinolones, sulfonamides, and acyclovir; diuretics (loops and thiazides); nonsteroidal anti-inflammatory drugs; proton pump inhibitors (PPIs); and ranitidine.

Proton pump inhibitors have been associated with worsening SCr, two main electrolyte abnormalities (hyponatremia and hypomagnesemia) and an increased risk for AKI. Certain medications not soluble in human urine, they precipitate in the renal tubules in the presence of risk factors such as volume depletion, underlying kidney disease, and metabolic disturbances that promote changes in urinary pH favoring AKI. Ampicillin, ciprofloxacin, sulfa drugs, indinavir, and methotrexate are the commonly prescribed drugs associated with production of crystals.

There are many drugs that can present as nephritic syndrome due to glomerular injury and inflammatory disease. Some important drugs such as bisphosphonates and hydralazine typically cause ATN. Thus, monitoring of SCr is recommended before treatment and in the setting of renal insufficiency holding therapy is required. It is very important to know that illicit drugs, specifically synthetic cannabinoids, may lead to AKI in addition to myocardial

infarction, psychosis, seizures, and hyperemesis. Interestingly, in methamphetamine- or cocaine-induced rhabdomyolysis creatinine kinase (CK) does not raise much. Acute tubular injury is the most common injury in these patients and treatment is supportive and rarely requires steroids.

Contrast-induced Acute Kidney Injury

A type of AKI that results within a few days of exposure to iodinated contrast for imaging studies is termed as contrast-induced nephropathy. After hypoperfusion and nephrotoxic drugs this is the third most common cause of new AKI in hospitalized patients. The contrast-induced nephropathy/AKI is self-limited, but associated with increased mortality and even progression to CKD. Patients with an estimated GFR < 60 mL/min/1.73 m^2 are higher risk for contrast-induced AKIs. In clinical practice, radiologists take detail relevant history about comorbidities, other nephrotoxic medications before administering potentially harmful contrast. In high-risk patient, use the lowest possible radiocontrast concentrations, administer IV hydration pre-exposure and postexposure, minimize nephrotoxic agents, and renal replacement therapy (RRT) in critical cases should be considered. It is important to screen patients for reliable follow-up.

Tepel et al. reported that oral N-acetylcysteine (600 mg twice daily) along with hydration before and after the exposure to contrast medium provide significant protection against contrast induced nephropathy as compared with hydration alone.

CLINICAL EVALUATION

Acute kidney injury induce life-threatening complications include severe metabolic acidosis; hyperkalemia; and volume overload states, such as pulmonary edema or pericardial tamponade. Targeted history and physical examination can help in identifying these complications. In the acute setting it is difficult but important to know if kidney function abnormalities are at baseline or truly represent an acute injury; a baseline kidney function is ascertained via record or sometime the patient knows his or her baseline kidney function. Ascertain the source of the injury once AKI is identified. Before considering intrarenal sources, it is important to first rule out prerenal and postrenal sources. Recent volume losses, such as hemorrhage, gastrointestinal or urinary fluid losses, and recent postoperative courses during which the patient was either hypotensive or exposed to iodinated contrast for imaging (although this is controversial) for responsible for prerenal injury. Consider obstructive postrenal sources in patients with signs of nocturia, or urinary frequency, which may be suggestive of prostatic or other obstruction and retention. In patients with reduced GFR, search for exposure to nephrotoxic agents include antibiotics, such as vancomycin; aminoglycosides; nonsteroidal anti-inflammatory drugs; and ACE inhibitors/angiotensin receptor blockers. Once iodinated radiocontrast thought to be nephrotoxic; but recent studies have shown that this association is not as strong as previously believed.

Further evaluate patients in terms of hemodynamic and volume status on physical examination. Check for dry mouth, reduced skin turgor, cool peripheral extremities, and delayed capillary refill times. Examine vital signs for evidence of shock, if present invasive hemodynamic monitoring with arterial lines, central venous pressure monitoring is required. Point of care ultrasonography of the inferior vena cava at end expiration and the internal diameter of the right ventricle at end diastole helpful in assessing hypovolemia and underfilling, respectively. These patients may require a wide range of therapies from IV fluids to diuretics or, in most critical situations, RRT.

DIAGNOSTIC TESTING

Acute kidney injury is diagnosed by evaluating laboratory values, urinalysis, urine sediment, and urine chemistries. Prerenal azotemia is considered when high ratio of blood urea nitrogen (BUN) to creatinine is observed. In this setting, urine sodium concentration of <20 mEq/L as sodium is inappropriately retained and is also indicative of prerenal cause. Ultrasound of the kidneys with postvoid bladder volumes should be performed if obstruction is suspected. Further investigation of intrarenal causes includes urine electrolytes and urine osmoles. Kidney biopsy should be performed only with the direction of the nephrologist and typically reserved for patients suspected of intrarenal cause. Kidney biopsy can be performed if etiologies include systemic lupus erythematosus, glomerulonephritis, and ATN.

Presence of renal disease can be identified by estimation of several novel biomarkers; clinical trials are currently underway to evaluate the efficacy of these markers. Several biomarkers are currently being evaluated in trials with the goal to identify a biomarker, or a panel of biomarkers, that would be helpful in the early diagnosis of AKI, and also able to differentiate between different types of renal injury, and could provide an accurate prognosis, all with a high degree of specificity and sensitivity. To that end including serum measurements of cystatin C and NGAL and urine measurements of interleukin (IL)-18 and KIM-1 are the few examples of novel biomarkers though their use is not so widespread in clinical practice. However, they may represent the future for identification and assessment of the severity of renal disease. In spite of the well-known limitations described earlier, clinicians more frequently rely on BUN and SCr at the time of presentation and compare them with baseline values (when known) to help guide diagnosis and treatment.

MANAGEMENT OF ACUTE KIDNEY INJURY IN THE EMERGENCY DEPARTMENT

Volume Status

Body is able to autoregulate blood flow to the kidneys during normal physiologic stress despite acute changes in blood pressure, but this mechanism is disrupted in AKI. Patients may present with hypervolemia, such as peripheral edema, pulmonary edema, respiratory distress, heart failure, pericardial effusion, or cardiac tamponade. To manage the complication of these conditions diuretics, fluid restriction, RRT, or appropriate procedures to alleviate the volume are used.

Conversely fluid resuscitation should be used in patients with hypovolemia because it is essential to maintain organ perfusion. Patients receiving IV fluids are a delicate issue, as they may become acutely volume overloaded. The use of vasopressors can further reduce blood flow to the kidneys. Early goal-directed therapy in patients with sepsis who received crystalloid fluids had no effect on mortality or the need for RRT as per several large trials. Several retrospective studies have

demonstrated that volume overload states associated with high mortality in critically ill patients. For this reason, volume status of the patient should be frequently monitored. Administer of IV fluid therapy is recommended if clinical history reveals large volume losses, such as vomiting and severe diarrhea, and physical examination supported hypovolemia. Patients who do not respond to fluid resuscitation consider using vasopressors. Crystalloids equilibrate solutes across cell membranes, e.g., lactated Ringer or normal saline. Colloid fluids depend on oncotic gradients to increase volume in an intravascular space, e.g., albumin, gelatine, or starches.

Several studies like Crystalloid versus Hydroxyethyl Starch Trial (CHEST) have examined crystalloids versus colloids in AKI where critical care unit patients were randomly assigned saline solution versus colloids. In the colloid group there was an increased risk of RRT. Crystalloid group overall had more incidences of AKI by RIFLE criteria driven by UOP, the colloid arm of the study had more severe AKI and therefore a trend toward RRT. Recent literature demonstrates mixed reviews on balanced fluid resuscitation versus normal saline depending on acuity of the patient. The *SMART trial* (0.9% normal saline versus balanced crystalloids lactated Ringer solution) demonstrated a marginal superiority in secondary outcomes of balanced crystalloids, particularly patients who received large volumes of resuscitation in adverse kidney events, time to discharge, and mortality in critically ill adult. Another recent study, the *SALT-ED trial*, which was essentially a negative trial in adult ED patient who received a minimal of 500 mL of IV isotonic crystalloids, showed no difference in the number of hospital-free days in both treatment groups, although the secondary outcome (incidence of major adverse kidney events at 0 day) was in favor of balanced crystalloids. There is no outstanding difference in balanced crystalloids versus normal saline; considering weaknesses of both studies from the practical point of view, one should consider balanced crystalloids in critically ill and high volume resuscitated patients. Colloids are beneficial in some specific subgroup of AKI like large volume depletion, e.g., paracentesis or end-stage liver disease. In the emergent setting, overall goal of assessing the volume status is to improve cardiac output and therefore improve tissue oxygenation. Close monitoring of urinary output and mean arterial pressure is required. In emergency department frequent clinical evaluation for pulmonary congestion and urinary output 75–100 mL/h (1-3 L total) is considered appropriate.

Hemodynamic Optimization with Vasopressor Therapy

Vasopressor administration becomes necessary to achieve adequate renal perfusion in patients who continue to have hemodynamic instability with a low MAP despite fluid resuscitation. Target an initial MAP of ≥65 mm Hg, with vasopressor administration. No specific vasopressor recommendation for the treatment and/or prevention of AKI in patients with shock but NE has been found to improve CrCl in patients with distributive shock. Renal-dose dopamine infusion to achieve renal vasodilation has not been found to reduce the incidence of AKI, need for RRT, or patient mortality. In fact, dopamine may worsen both renal perfusion and GFR. As a result, KDIGO has provided a 1A recommendation against using low-dose dopamine in patients with AKI.

Metabolic Derangements

Kidneys maintain the body's electrolyte balance and in AKI, because of reduced filtration, patients often develop hyperkalemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, or symptoms of uremia and associated complications such as bleeding, pericarditis, or altered mental status. Clinical manifestations of hyperkalemia which occurs at potassium levels > 7.0 mEq/L include muscle weakness/paralysis and cardiac arrhythmias secondary to conduction abnormalities. Hyperkalemia causing conduction abnormalities is detected on electrocardiograms (ECGs). The most common ECG changes of hyperkalemia findings are tall, peaked T waves with shortened QT interval, lengthening of PR interval and QRS duration, absence of P waves, and ultimately sine wave pattern as the QRS progresses in duration. In patients with hyperkalemia and ECG changes, administration of calcium gluconate or calcium carbonate (1 g IV over minutes, repeat as needed) recommended to stabilize the cardiac membrane. Then use drugs which promote potassium ions to shift intracellularly are regular insulin (10 U IV or weight-based and administered with glucose), β-2 adrenergic agonists (nebulized albuterol), or sodium bicarbonate (50 mEq/50 mL IV). After this if the patient's volume status has been assessed and determined to be hypervolemic or euvolemic with appropriate supportive fluids one can use loop diuretics (furosemide, 40–60 mg IV) or cation resins (sodium polystyrene sulfonate, 15 g orally) to eliminate potassium in the urine and stool (**Table 5**). There is limited evidence regarding use of cation resins, such as sodium polystyrene sulfonate (Kayexalate), there are some potential untoward effects and that may outweigh benefits. Newer binding agents, such as patiromer and sodium zirconium cyclosilicate (ZS-9) are studied recently. Patiromer is a synthetic polymer of nonabsorbable beads that exchanges calcium for potassium excretion in the stool in the distal colon. A recent meta-analysis investigating patiromer and ZS-9 found that these agents were more efficacious compared with Kayexalate, although further studies are warranted to test side effects, use in specific patient populations, and medication interactions.

Sodium Bicarbonate Therapy

Administration of sodium bicarbonate in patients with AKI has been controversial. Acidemia and serum pH improved after administration of sodium bicarbonate without reversing the cause of acid production. Patients with severe metabolic acidosis may require sodium bicarbonate therapy as a temporizing measure while the clinician attempts to reverse the underlying cause. Bicarbonate therapy may be helpful in stabilizing the hemodynamic and improve vasopressor sensitivity in patients with a pH <7.1. The recently published BICAR-ICU trial (Sodium Bicarbonate Therapy for Patients with Severe Metabolic Acidemia in the Intensive Care Unit) found no difference between 28-day mortality or organ failure at 7 days between treatment and control groups. However, patients with severe AKI did show a trend toward decreased need for RRT who received bicarbonate therapy. Clinicians should be aware of some clinically significant side effects of sodium bicarbonate therapy. A transient increase in arterial partial pressure of carbon dioxide (pCO_2) can occur, as sodium bicarbonate ultimately gets metabolized to CO_2, which may be detrimental for patients with an already extreme minute ventilation.

TABLE 5: Drugs to treat hyperkalemia—dose onset duration.				
Effect	***Treatment***	***Dose***	***Onset***	***Duration***
Stabilize membrane	Calcium gluconate and calcium carbonate	10 mL intravenous (IV) over 10 min	Immediate	30–60 min
Shifters	Albuterol	10–20 mg nebulization	30 min	2 h
	Insulin	10 units IV with dextrose 25–50 g	20 min	4–6 h
	Sodium bicarbonate	150 mmol IV	Hours	Hours
Excretors	Furosemide	40–80 mg IV	15 min	2–3 h
	Sodium polystyrene	15–30 g in 15–30 mL	Hours	4–6 h
Definitive	Hemodialysis		Immediate	3 h

Blood Pressure Management

Patients with kidney disease typically present with hypertension and associated organ ischemia, patients are likely habituated to higher blood pressures. The pathophysiology of hypertension depends on the duration of disease, acute versus chronic, and type of kidney disease (i.e., vasculitis vs. intrinsic kidney disease). Adrenergic-blocking agents should be considered to control the blood pressure. Labetalol given in 20-mg IV bolus initially, followed by 20–80 mg every 10 minutes to a total dose of 300 mg. As an alternative, hydralazine, a direct arteriolar vasodilator, can be given in doses of 10-mg IV boluses. MAP should be reduced slowly, by no >20% in the 1st hour and gradually by no >15% over the subsequent 24 hours.

Volume overload is the common manifestations of acute glomerulonephritis. Volume overload is caused by sodium retention from increased reabsorption in the collecting tubules. Volume expansion suppresses the renin–angiotensin–aldosterone system and enhances release of atrial natriuretic peptide. Hypertension in acute glomerulonephritis is primarily because of volume overload so the preferred initial therapy is diuretics. Loop diuretics, such as furosemide, are particularly effective in patients with reduced GFR. Second-line therapy is ACE inhibitors because these drugs activate the otherwise pathologically suppressed renin–angiotensin–aldosterone system mechanism. *Antihypertensive medications* for AKI-induced hypertension are furosemide, lisinopril, labetalol, and hydralazine.

Diuretics

In hypervolemic states, loop diuretics are recommended because these medications not only prevent volume overload, but also minimize ischemic tubular injury by decreasing metabolic demand from the activation of the sodium-potassium-chloride cotransporter in the renal medulla. However, multiple studies did not support the benefits of diuretics in AKI. The current KDIGO recommendation is to use diuretics in only two situations, frank hypervolemia or in early AKI to promote UOP.

Glycemic Control

The kidneys play an important role in glucose excretion and insulin metabolism so patients with AKI are higher risk for severe hypoglycemia. Blood sugar concentrations should be between 110 and 149 mg/dL as per KDIGO group recommendation. These guidelines are based on Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study.

Organ Damage

Other vital organs, particularly the heart, liver, and lungs are also affected in AKI. Metabolic acidosis is known to reduce the myocardial contractility. Myocardial stunning occurs due to hypoperfusion of the heart. Complex pathophysiologic mechanism between the kidneys and liver leads to development of hepatorenal syndrome, form of kidney injury, unresponsive to fluids, in chronic liver disease that causes systemic and splanchnic vasodilation, and kidney vasoconstriction. Noncardiogenic pulmonary edema (acute respiratory distress syndrome) occurs due to renal failure. These patients often require mechanical ventilation as these conditions do not respond to fluid diuresis.

ACID-BASE DERANGEMENT IN THE CRITICALLY ILL ACUTE KIDNEY INJURY

Knowledge about patient's acid-base derangement is important before treatment initiation.

Acid-base Homeostasis

Normally kidney excrete acid load, through the Na^+/H^+ transporter, which excretes approximately 1 mEq of H^+ ions per kg per day in the urine. Any pathophysiological process which gives rise to excessive acid production, inability to reabsorb a bicarbonate buffer, or decreased H+ excretion causes metabolic acidosis occurs. Patients with AKI may present with a metabolic acidosis, often classified as either an anion gap or nonanion gap metabolic acidosis (NAGMA).

Acute kidney injury-associated NAGMA occurs due to a loss of bicarbonate without concomitant increase in exogenous acid production. Conditions associated with NAGMA are severe hypovolemia secondary to diarrhea where the large bowel has impaired ability to reabsorb bicarbonate deteriorating chronic renal dysfunction as well as renal tubular acidosis (RTA). Patients with an acute RTA have impaired bicarbonate reabsorption secondary to ion transporter dysfunction. *Anion gap metabolic acidosis (AGMA)* often precipitate because of an increased acid production and because of an acute decrease in GFR the kidneys are unable to excrete. In the critically ill most common causes of AGMA include lactic acidosis and ketoacidosis. More causes of AGMA are listed in **Table 6**.

TABLE 6: Common causes of anion gap metabolic acidosis (AGMA).

AGMA mnemonic	*Causes*
M	Methanol
U	Uremia
D	Diabetic, alcohol, and starvation ketoacidosis
P	Paracetamol/acetaminophen
I	Isoniazid, iron ingestion, and inborn error of metabolism
L	Lactic acidosis
E	Ethanol and ethylene glycol
S	Salicylates

Lactic acidosis is the most common AGMA encountered in critically ill patient. Poor tissue perfusion and inadequate oxygen delivery causes lactate production. Lactate generation precipitate metabolic acidosis that can cause myocardial depression, catecholamine resistance, and progressive vasodilatory shock. Despite a maximum level of plasma catecholamines (released in response to hypoperfusion) and inappropriate activation of other vasodilatory mechanisms, vascular wall smooth muscle is unable to constrict, *vasodilatory shock* occurs. Sodium bicarbonate or dialysis may be helpful in correction of the acidic environment and improve patient's vasodilatory shock, transiently but effective treatment should be focused on reversing the inciting event.

RENAL REPLACEMENT THERAPY

Renal replacement therapy or dialysis is the ultimate treatment for severe AKI leading to critical life-threatening derangements, such as volume overload, acidosis, hyperkalemia, and toxin accumulation. In dialysis, either diffusion (i.e., hemodialysis) or convection (hemofiltration), or a combination of the two techniques is used for removal of solutes and fluids from the body. The decision to start RRT exceeds the scope of core emergency medicine and initiate nephrologist consultation to consider for emergent dialysis. *Indications for emergent dialysis* (**Table 7**) are: (1) Acidosis (pH 6.5 refractory to treatment); (2) Ingestions of dialyzable drugs (salicylates, lithium, and toxic alcohols); (3) Overload (especially with hypertension and increasing oxygen requirements); (4) Uremia (bleeding, pericarditis, and encephalopathy).

Initiation of Renal Replacement Therapy

Temporary vascular access is required for initiation of RRT in critically ill patients. To facilitate emergent RRT use of a 10-French or 12-French, double-lumen, central venous dialysis catheter is placed. Emergently placed temporary nontunneled hemodialysis catheters can be placed preferentially in the right internal jugular vein under ultrasonography guidance. If the right internal jugular vein is not accessible, femoral vein access is preferred over left internal jugular vein cannulation. Temporary hemodialysis catheters in subclavian vein should be avoided because associated with higher rates of central vein stenosis, which may prevent the use of the ipsilateral arm as a site for long-term hemodialysis access (arteriovenous graft or fistula) in the future.

TABLE 7: Mnemonic for emergent hemodialysis indications.

A	*Acidemia*: Severe metabolic acidosis despite adequate medical optimization (pH < 7.1)
E	*Electrolytes*: Particularly hyperkalemia refractory to medical therapy
I	*Ingestion*: Poisoning by drugs that are able to be eliminated with RRT
O	*Overload*: Volume overload resulting in hypoxic respiratory failure necessitating mechanical ventilation
U	*Uremia*: Complications secondary to increased BUN (bleeding, pericarditis, and encephalopathy)

(BUN: blood urea nitrogen; RRT: renal replacement therapy)

Source: Data from Nee P, Bailey D, Todd V, Lewington AJ, Wootten AE, Sim KJ. Critical care in the emergency department: acute kidney injury. Emerg Med J. 2016;33:361-5.

Temporary hemodialysis catheter's distal tip must be located within a large central vessel in order to optimize catheter blood flow. Catheter length is an important consideration, and in general should be 12–15 cm for right internal jugular, 15–20 cm for left internal jugular, and 19–24 cm for femoral vein access. Optimal catheter placement is important for establishing an effective venovenous hemodialysis circuit to provide adequate extracorporeal blood flow for fluid and/or solute removal.

Mode of Renal Replacement Therapy

Renal replacement therapy via intermittent or continuous hemodialysis should be decided once appropriate vascular access has been obtained and confirmed in the right location. A comprehensive understanding is required about indication of hemodialysis, hemodynamic, as well as the logistics needed to initiate either mode (**Table 8**). Preferred mode of RRT for rapid removal of toxins (poisoning), electrolytes (hyperkalemia), and intravascular fluid volume is intermittent hemodialysis (iHD) which can provide external blood filtration at blood flow rates of 300–500 mL/min. A single hemodialysis session can often be completed in 2–4 hours. Before initiation of iHD hemodynamic stability is generally required. In critically ill patients with hypotension or vasopressor dependence, continuous RRT (CRRT) is preferred. CRRT is run at a much slower blood flow rate (usually 20–40 mL/kg/h) to achieve the same effects of iHD, but over a 24-hour period. It is the preferred mode of RRT in patients who have unstable hemodynamic or requires vasoactive support.

The drawbacks of CRRT are its inability to clear toxins rapidly due to its low blood flow rate, the need for anticoagulation to prevent circuit clot formation, and prolonged limitations to patient mobility, increased nursing resource burden, which includes frequently changing the CRRT machine's dialysate bath and laboratory draws.

RHABDOMYOLYSIS

Rhabdomyolysis is a syndrome characterized by skeletal muscle injury which is measured with myoglobin, CK, and lactate dehydrogenase. Muscle injury can cause significant life-threatening electrolyte disorders, acute renal injury and

muscle injury secondary to trauma, myositis, medications, and muscle dystrophies. Common conditions associated with rhabdomyolysis are shown in **Figure 1**. Hypovolemia patient are more prone for developing the renal injury. Subsequently to maintain perfusion leads to renal vasoconstriction, and muscle breakdown products filtered through renal tubules.

TABLE 8: Comparison of two common modes of dialysis.

	Intermittent hemodialysis	***Continuous RRT(CRRT)***
Indications	Ambulatory, hemodynamically stable, electrolyte, and poison clearance	Critically ill, nonambulatory
Solute transport	Diffusion	Convection
Blood flow (mL/min)	300–400	150–200
Dialysate	30	1
Efficiency	High	Low
Hemodynamic stability	Poor	Good
Duration	Average 3 h	Continuous for 24 h
Anticoagulation	Not required, secondary to high blood flow rate	Required (within CRRT filter)
Logistic	Need tap water supply, technically difficult to initiate	High workload, immobility, and costly

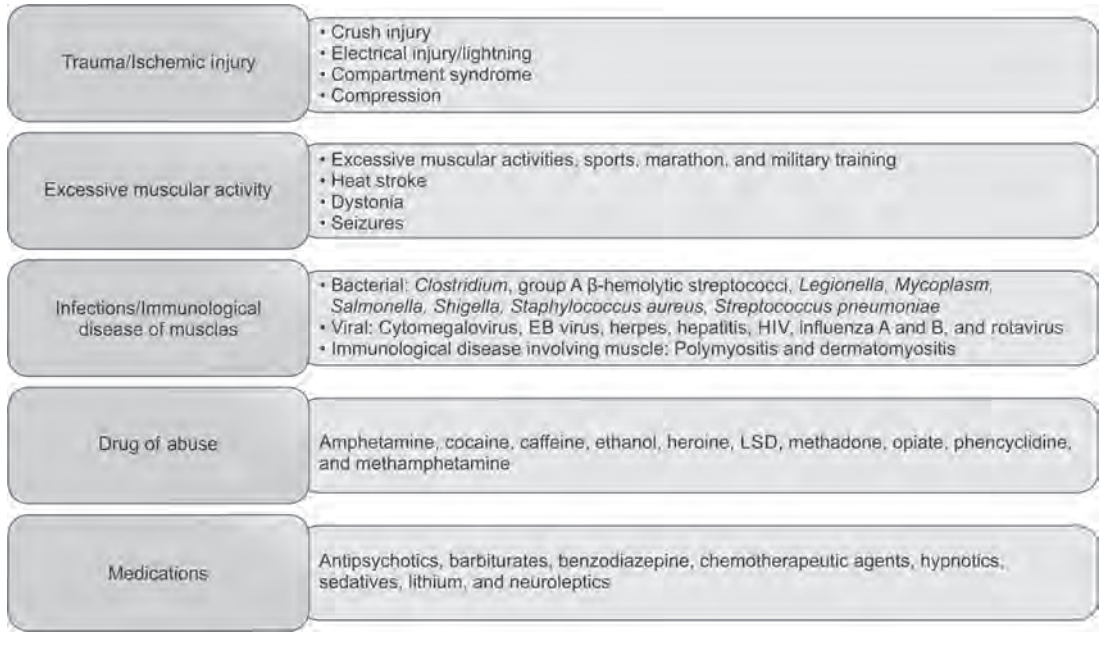
(CRRT: continuous renal replacement therapy)

Source: Data from Alvarez G, Chrusch C, Hulme T, Posadas-Calleja JG. Renal replacement therapy: a practical update. Can J Anesth. 2019;66:593-604.

Clinically, patients present with a history of myalgias, muscle weakness, and dark colored urine; occasionally nausea, vomiting, or fever may manifest. Sometime history may not be accurate and patients may present after a seizure, unknown use of medication, or variety of activity level from prolonged immobilization to running a marathon. In diagnosis, a five-time or greater increase of CK levels from upper limit of normal (1,000 IU/L) and detection of myoglobin in the urine should be taken into consideration. Myoglobin is released from damaged muscle and hem-containing protein. CK levels start rising 2–12 hours after muscle injury and peak at 24–72 hours. Studies have shown 50% chance of progression to AKI if CK levels >5,000 IU/L. The management of rhabdomyolysis in the early phase includes aggressive fluid resuscitation and electrolyte correction to improve renal perfusion and promote adequate UOP. This is important to prevent the azotemia. Consider sodium bicarbonate, 50 mmol for each 2–3 L of IV fluid therapy, although it is controversial. Balanced crystalloids or normal saline, either IV fluids may be used, as no clear benefit noted over each other. Patient should be monitored very closely because damaged muscle cells release potassium and phosphorus and RRT may be considered based on electrolyte derangements, such as hyperkalemia, hypercalcemia, anuria, hyperazotemia, or kidney injury not responding to volume resuscitation. Treatment goals include urinary output goal of 200 mL/h, urine pH > 6.5, and plasma pH 7.5. Summary of managing the rhabdomyolysis patient is as follows: Elevated CK → IV hydration with normal saline or 5% dextrose in normal saline → Goal UOP 200 mL/h, plasma pH < 7.5 → Serial evaluations for worsening AKI, electrolyte disturbances, and compartment syndrome → Consider admission for CK > 5,000 IU/L or patients at high risk for AKI.

DISPOSITION

In the acute setting, the disposition of patients with AKI is varied. These patients are at increased risk for progression


Trauma/Ischemic injury
• Crush injury
• Electrical injury/lightning
• Compartment syndrome
• Compression
Excessive muscular activity
• Excessive muscular activities, sports, marathon, and military training
• Heat stroke
• Dystonia
• Seizures
Infections/Immunological disease of muscles
• Bacterial: Clostridium, group A β-hemolytic streptococci, Legionella, Mycoplasm, Salmonella, Shigella, Staphylococcus aureus, Streptococcus pneumoniae
• Viral: Cytomegalovirus, EB virus, herpes, hepatitis, HIV, influenza A and B, and rotavirus
• Immunological disease involving muscle: Polymyositis and dermatomyositis
Drug of abuse
Amphetamine, cocaine, caffeine, ethanol, heroine, LSD, methadone, opiate, phencyclidine, and methamphetamine
Medications
Antipsychotics, barbiturates, benzodiazepine, chemotherapeutic agents, hypnotics, sedatives, lithium, and neuroleptics

(EB: Epstein–Barr; HIV: human immunodeficiency virus; LSD: lysergic acid diethylamide)

FIG. 1: Common conditions associated with rhabdomyolysis.

to CKD and increased mortality, so hospitalization of these patients is recommended to ascertain the source of insult and observe for correction of kidney function. Mostly an AKI is indicative of kidney insult either from prerenal, intrarenal, or postrenal sources. If the patient has reliable follow-up and can check their kidney function in 3 months or who have an isolated AKI and are otherwise appropriate for discharge, arrange solid follow-up. In the emergent setting, consultation to nephrology or urology services may be indicated. For life-threatening acidosis, medically unresponsive electrolyte derangements, toxic ingestion, volume overload, or uremia consultation for emergent dialysis is appropriate. Typically AKIs suspected secondary to intrinsic kidney disease, such as acute glomerulonephritis, nephrologists should be consulted. For AKI due to postrenal causes, such as obstructive nephrolithiasis consult urologist.

SUMMARY

Comprehensive overview and evidence-based acute management of kidney injuries in the ED setting is required. Prompt urgent interventions should be implemented after taking summary of causes of AKIs and performing clinical evaluations. Management of specific high-risk acute conditions, such as rhabdomyolysis and contrast-induced AKIs, and higher risk populations, such as the elderly should be kept in mind. AKI is a common diagnosis in ED with multiple complications and consequences. Treatment and management rely on early diagnosis and estimation of the cause for AKI. EP should be able to rapidly obtain a detailed history, perform a thorough physical examination, and identify high-risk elements contributing to the patient's decreased renal function. Effective treatment of critically ill patients with AKI depends on these skills. Mostly patients improve with conservative therapy, including normalizing fluid status, hemodynamic support, removal of offending agents, and addressing the patient's underlying disorder. As a temporizing intervention until the underlying disorder can be treated and reversed sodium bicarbonate therapy may be useful in patients with a severe metabolic acidosis (arterial pH < 7.1). A subgroup of patients with AKI requires initiation of emergent RRT despite aggressive medical intervention. RRT or hemodialysis is the treatment modality when conservative management fails. Type of RRT mode, appropriate temporary dialysis catheter equipment, and insertion site are the important points to address before initiation of RRT. Timely interventions that address these needs in critically ill patients with AKI are important to ensure the best long-term chances of recovery.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

End-stage Renal Disease

Devendra Richhariya

INTRODUCTION

Patients with end-stage renal disease (ESRD) present several complex management issues to emergency physicians. Timely interventions may reduce morbidity and mortality in these patients. With early identification and treatment of anemia, renal osteodystrophy, uremic malnutrition, hyperlipidemia, and cardiovascular disease, primary care physicians and nephrologists together can make significant difference toward extending and improving the lives of patients with ESRD. Two modalities of renal replacement therapy *dialytic therapy* (hemodialysis and peritoneal dialysis) and *renal transplant* is currently available for management of ESRD. For most of the patient hemodialysis is the initial therapy.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as persistent or sustained damage lasting longer than 3 months and resulting in a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 (**Table 1**). Discussion and knowledge about CKD and ESRD are important as patients with CKD are more likely to have longer hospital stays and heavy financial burden if preventive measures are not taken or disease process is not managed in early stage. Diabetes mellitus, hypertension, human immunodeficiency virus, and autoimmune and inherited diseases (including polycystic kidney disease and sickle cell disease) are the most frequent causes of CKD. Diabetes and hypertension are the most frequently encountered comorbidities associated with CKD. Incidence of renal failure is continuing to increase with increasing population of diabetes and hypertension. In emergency department, various clinical situations are presented with features of CKD which further complicate the evaluation and treatment of the patient along with emergency physician should take precaution about administration of contrast media, medication dosing, even when patients present with complaints not directly related to their kidney disease. In emergency department, patients with chronic or end-stage kidney disease frequently present with clinical features that are directly related to CKD and their complication, including fluid overload, electrolyte imbalance, or infection. Patients who already suffering from CKD, acute worsening of renal failure can occur due to several acute insults, including nephrotoxic agents, hypovolemia, and decreased renal perfusion. Any of the causes of acute kidney injury (AKI) can be superimposed on chronic renal insufficiency, leading to acute worsening of renal function. So, the role of emergency physician is to recognize the presence of the disease process in their patients and limit further renal insults during diagnosis and treatment of emergency conditions. Emergency physician frequently attending the patients who are chronically receiving renal replacement therapy (RRT) and should be prepared for complications related to CKD/ESRD and related to these procedures. So, it is worthy to discuss about RRT, including peritoneal dialysis (PD) and hemodialysis (HD) in this chapter itself. Infections, bleeding, complications related to volume management, and electrolyte abnormalities are common in patients on RRT. When patients fail to get their RRT as scheduled, complications related to fluid management and electrolyte become more problematic. Among patients with ESRD, infections due to sepsis are the leading cause of mortality. It is also important to note that a percentage of patients with ESRD on RRT proceed to renal transplantation. It is important for the emergency physician to take immediate corrective action in worsening renal function with renal transplant patient that may be caused by any of the insults that can cause AKI and that early identification of the cause and rapid treatment are crucial in the patient with only a single functioning kidney. Furthermore, acute or subacute worsening

TABLE 1: Stages of chronic renal failure.

Stage of chronic renal failure	*GFR mL/min/1.73 m^2*
Stage 1 (kidney damage not evidenced by GFR)	GFR ≥ 90
Stage 2 (mild disease)	GFR 60–89
Stage 3 (mild-to-moderate disease)	GFR 30–59
Stage 4 (moderate-to-severe disease)	GFR 15–29
Stage 5 (requirement of dialysis and kidney transplant)	GFR < 15

(GFR: glomerular filtration rate)

of renal failure in the patient with transplant may also be a sign of transplant rejection, and the patient's transplant surgeon or nephrologist should be consulted early in the course of evaluation and treatment.

END-STAGE RENAL DISEASE

End-stage renal disease is the irreversible loss of renal function, resulting in the accumulation of toxins and the loss of internal homeostasis. Uremia, the clinical syndrome resulting from ESRD, requires RRT for survival. At present, two basic modalities of RRT available: Dialytic therapy, either HD or PD and renal transplant. In the vast majority of new cases of adult ESRD initial therapy is HD, with a few patients starting PD and renal transplants. Cardiac causes account for about half of all deaths followed by infections, cerebrovascular events, and malignancy.

PATHOPHYSIOLOGY

Renal failure leads to inability to excrete about >70 chemicals from the body and accumulation of waste chemicals in uremic plasma, toxins, individually or in combination, cause uremic organ dysfunction and give rise to symptoms of uremia. Cyanate, guanidine, polyamines, and β2-microglobulin are the other potential uremic toxins apart from urea. Dialysis able to reverse not all but most of the untoward effect of the uremia because many toxins are highly protein bound and nondialyzable and many uremia-related organ dysfunctions persist after dialysis. The kidneys secrete erythropoietin and 1α-hydroxylase, which is necessary to produce the active form of vitamin D3. Because 85% of erythropoietin is produced in the kidneys, depressed level of the renal hormones $1,25(OH)_2$-vitamin D3 and erythropoietin occurs in ESRD and manifests as anemia in uremic syndrome. Vitamin D3 deficiency results in decreased gastrointestinal (GI) calcium absorption, inducing secondary hyperparathyroidism and leading to renal bone disease. Normal feedback mechanism in secretion of hormone is also disturbed in uremia leading to oversecretion of hormones. Excess free oxygen radicals are produced in uremic state, which react with carbohydrates, lipids, and amino acids to create advanced glycation end products. Thus, progressive nature of the atherosclerosis and amyloidosis is seen in ESRD patients.

CLINICAL FEATURES OF UREMIA

Uremia is a clinical syndrome consists of a group of symptoms, signs, or laboratory tests (**Table 2**). Correlation can be established between the symptoms of uremia and low GFR (8–10 mL/min/1.73 m^2). Raised blood urea nitrogen (BUN) and serum creatinine levels represent inaccurate picture of the clinical syndrome of uremia. Severity of the patient's symptoms related to uremia such as fluid overload (51%), hyperkalemia (18%), and severe acid-base disturbances are the most common reasons for emergency dialysis.

Cardiovascular Complications

Cardiovascular diseases such as coronary artery disease, left ventricular hypertrophy, and congestive heart failure are common and 10–20 times higher in ESRD and patient on dialysis. Preexisting conditions (e.g., hypertension and diabetes), uremia (e.g., uremic toxins, hyperlipidemias, homocysteine level, and hyperparathyroidism), and dialysis-related conditions (e.g., hypotension, dialysis membrane reactions, and hypoalbuminemia) are the causes responsible for cardiovascular disease in ESRD.

Cardiac Markers

Traditional misconception is markers of myocardial damage (troponins I and T) and is unreliable for diagnosis of ischemic cardiovascular disease in ESRD and dialysis patients. Troponin I and T are commonly elevated in asymptomatic HD patients and probably reflect left ventricular hypertrophy and microvascular disease, and associated with long-term risks of coronary artery disease. 20% or more dynamic rise and with at least one value above the 99th percentile higher baseline

TABLE 2: Clinical features of uremia.

Common uremic features	Pruritus and generalized muscle cramping
GI symptoms	Anorexia, nausea, vomiting, hiccups, altered taste, GI bleeding, ascites, diverticulitis, and diverticulosis
Cardiac	Coronary artery disease • *Hypertension*: Essential hypertension, glomerulonephritis, renal artery stenosis, and fluid overload • *Heart failure*: Fluid overload, uremic cardiomyopathy, high output, and AV fistula • *Pericarditis*: Uremic related to dialysis and pericardial tamponade
Hematologic	Anemia, reduced RBC survival, low erythropoietin level, bleeding diathesis, and humoral and cellular immune deficiency
Neurologic	• *Uremic encephalopathy*: Decrease in alertness, memory and cognition, disturbed sleep, slurred speech, asterixis, seizure, and coma • Dialysis dementia • Subdural hematoma • *Peripheral neuropathy*: Restless leg syndrome, sensorimotor neuropathy, and autonomic neuropathy
Renal bone disease	• Vitamin D deficiency and aluminum intoxication • Hyperparathyroidism • Metastatic calcification

(AV: arteriovenous; GI: gastrointestinal; RBC: red blood cell)

levels of troponin T and I, many define myocardial infarction in ESRD patient.

Hypertension

Hypertension in ESRD patient is primarily due to increased total peripheral resistance increases in blood volume, decreased vascular compliance, the vasopressor effects of native kidneys, the renin-angiotensin system, and the sympathetic nervous system. Most cases of hypertension in ESRD can be controlled with adrenergic blocking agents, angiotensin-converting enzyme inhibitors, or vasodilating agents, such as hydralazine or minoxidil.

Heart Failure

Heart failure in ESRD patients is primarily caused by hypertension, followed by coronary artery disease and valvular defects. Other causes of heart failure in ESRD patient are uremic cardiomyopathy, fluid overload, and arteriovenous fistula-related high-output failure. Natriuretic peptide levels are elevated in HD patients. Concomitant left ventricular hypertrophy and systolic dysfunction in HD patients give rise to elevated levels of natriuretic peptides. When all other causes of congestive heart failure have been excluded, uremic cardiomyopathy is diagnosed as exclusion because left ventricular dysfunction is related to ischemic heart disease, hypertension, and hypoalbuminemia in most uremic patients. Dialysis rarely improves left ventricular function in uremic patients with congestive heart failure.

Pulmonary Edema

Fluid overload is common cause of pulmonary edema in ESRD patient. Supplemental oxygen, bilevel positive airway pressure, nitrates, and angiotensin-converting enzyme inhibitors are the main therapies for pulmonary edema. Loop diuretics, such as furosemide [(60–100 mg intravenous (IV)], may be beneficial due to short-lived vasodilatory actions even in those with minimal urine output. HD is the definitive treatment for fluid overload in ESRD patients.

Cardiac Tamponade

Classic findings of cardiac tamponade such as changes in mental status, hypotension, or shortness of breath may not present in any critically ill ESRD patient. Warning signs suggesting the diagnosis of tamponade increased are interdialytic weight gain, increased edema, and intradialytic hypotension. Point-of-care ultrasound is the best method to detect pericardial effusion and tamponade. Ultrasound (US)-guided bedside pericardiocentesis should be performed in hemodynamically significant and unstable patients' pericardial effusions.

Pericarditis

Pericarditis is common in uremia. Fluid overload, abnormal platelet function, and increased fibrinolysis and inflammation are the common causes of uremic pericarditis. Pericardial contents are sterile unless infected and are abundant with fibrin and inflammatory cells. Pericardial friction rubs can be heard on cardiac auscultation in uremic pericarditis, which are louder than in most other forms of pericarditis. BUN level is nearly always >60 mg/dL. Typical electrocardiogram (ECG) changes of acute pericarditis may not be present as inflammatory cells do not penetrate into the myocardium. Associated abnormalities such as left ventricular hypertrophy, ischemia, and metabolic abnormalities (e.g., hyperkalemia and hypocalcemia) can be present in ECG. Suspect infection when the ECG has features typical of acute pericarditis. Dialysis-related pericarditis is most common during inadequate dialysis or due to missed sessions or vascular access problems. HD is most commonly associated with dialysis-related pericarditis. Improved dialysis techniques have lessened the incident of dialysis-related pericarditis. Management of uremic and dialysis-related pericarditis in patients in hemodynamically stable condition is intensive dialysis. HD is preferred over PD because of the higher clearance rates of HD. HD is effective in most of the cases of dialysis-related pericarditis. Indomethacin, colchicine, and steroids are not useful for ESRD pericarditis. If pericardial effusion is not resolved within 10–14 days of HD, anterior pericardiectomy is required, and total pericardiectomy reserved for constrictive pericarditis.

Hematologic Complications

Anemia

Decreased erythropoietin, blood loss from dialysis, frequent phlebotomy, and decreased red blood cell survival times, all these cause precipitate anemia in ESRD and patient on dialysis. Factitious anemia can also be noticed in dialysis patient due to fluctuations in plasma blood volume. Anemia is treated with regular infusions of human recombinant erythropoietin (erythropoietin replacement therapy) which improves the quality of life for ESRD patients by increasing exercise capacity and tolerance.

Coagulopathy

Risks of GI tract bleeding, subdural hematomas, subcapsular liver hematomas, and intraocular bleeding are increased in ESRD patient. Several mechanisms involved with uremic bleeding are decreased platelet function, abnormal platelet-vessel wall interactions, altered von Willebrand factor, anemia, and abnormal guanidinosuccinic acid-dependent production of nitric oxide and creatine. Best predictor of clinically important defects in hemostasis is skin bleeding test. Patients receiving aspirin or warfarin are at greater risk of major bleeding. Infusions of desmopressin, 0.3 μg/kg IV/subcutaneous (SC) (benefit in 1 hour), or cryoprecipitate, 10 units given over 30 minutes (benefit in 4 hours) used to improve bleeding times. Conjugated estrogen, 25 mg IV or 6 mg/kg/day (benefit in 6 hours) and tranexamic acid are also used as an alternative is another option.

Immune Disorders

Incidence of infectious diseases is common in ESRD patients due to immunological deficiency and the HD filter membrane may exacerbate immunodeficiency by complement activation after exposure and dialysis does not improve the immune function.

Neurologic Complications

Hemodialysis patients are more prone for developing stroke, both hemorrhagic and ischemic. Subdural hematomas occur more frequently (~10 times) in dialysis patients than in the

general population. Nonspecific central neurologic symptoms associated with renal failure known as uremic encephalopathy. Uremic encephalopathy is best diagnosed after eliminating structural, vascular, infectious, toxic, and metabolic causes of neurologic dysfunction. Features of dementia are nonspecific. MRI may show basal ganglia lesions. Neurologic findings of uremic encephalopathy may improve with dialysis. Peripheral neuropathy (lower limb > upper limb) is one of the most frequent neurologic manifestations of ESRD manifest as paresthesia, reduction in deep tendon reflexes, impaired vibration sense, muscle wasting, and weakness. Autonomic dysfunction manifests as impotence, postural dizziness, gastric fullness, bowel dysfunction, and reduced sweating. Treatment with vitamins, amitriptyline, gabapentin, and carbamazepine is only marginally effective. Conventional HD has limited role in improving autonomic dysfunction; however, elevated sympathetic activity may be reduced by daily short HD and long nocturnal HD.

Renal Bone Disease

Phosphate excretion decreases, which results in increased serum phosphate levels as the GFR falls in ESRD. Metastatic calcification can occur when the calcium phosphate product [Ca^{2+} (mg/dL) × PO_4 (mg/dL)] is >70–80. Calcification of synovial membrane causes pseudogout and clinically present as joint pain. Metastatic calcification in small vessels clinically present as skin and finger necrosis, while calcifications in the cardiac and pulmonary systems become life-threatening. Treatment consists of the use of low-calcium dialysate and phosphate-binding gels.

β2-microglobulin Amyloidosis

Patients >50 years of age and on dialysis for >10 years are on high risk of developing dialysis-related amyloidosis (β2-microglobulin amyloidosis). Development of chronic inflammatory condition (deposition of advanced glycation end products) is responsible for amyloidosis. Common sites for amyloid deposits are the GI tract, bones, and joints. Complications include GI perforation, bone cysts with pathologic fractures, and arthropathies, including carpal tunnel syndrome and rotator cuff tears.

HEMODIALYSIS

Hemodialysis—Technical Aspects

Hemodialysis requires extracorporeal filter "dialyzer" substitutes for the glomerulus to produce an ultrafiltrate of plasma (**Fig. 1**). Dialyzer consists of semipermeable membrane and blood is taken and returned through the sterile tubing. Dialysis fluid is used which has electrolyte composition similar to extracellular fluid (**Table 3**). Dialysis fluid is passed in opposite direction across the outside of membrane. Pressure gradient across the hemodialyzer filter is adjusted during HD to control the amount of fluid removal (ultrafiltration). During HD, blood is removed from the vascular access site by large-bore needles (typically 15 gauge), circulated through the dialysis machine at rates of 300–500 mL/min, and returned to the patient. The dialysate usually flows at a rate of 500–800 mL/min through the dialysis filter in the direction opposite to blood flow. To prevent thrombosis at the vascular access site small amounts of IV heparin, 1,000–2,000 units, are used. HD sessions typically take 3–4 hours. Solute removal (clearance) during HD depends on the filter pore size, the amount of ultrafiltration (solute drag), and the concentration gradient across the filter (diffusion).

Vascular Access for Hemodialysis

When urgent dialysis is required, vascular access is achieved by placing the double lumen catheter in Jugular vein (preferably) subclavian vein or femoral vein.

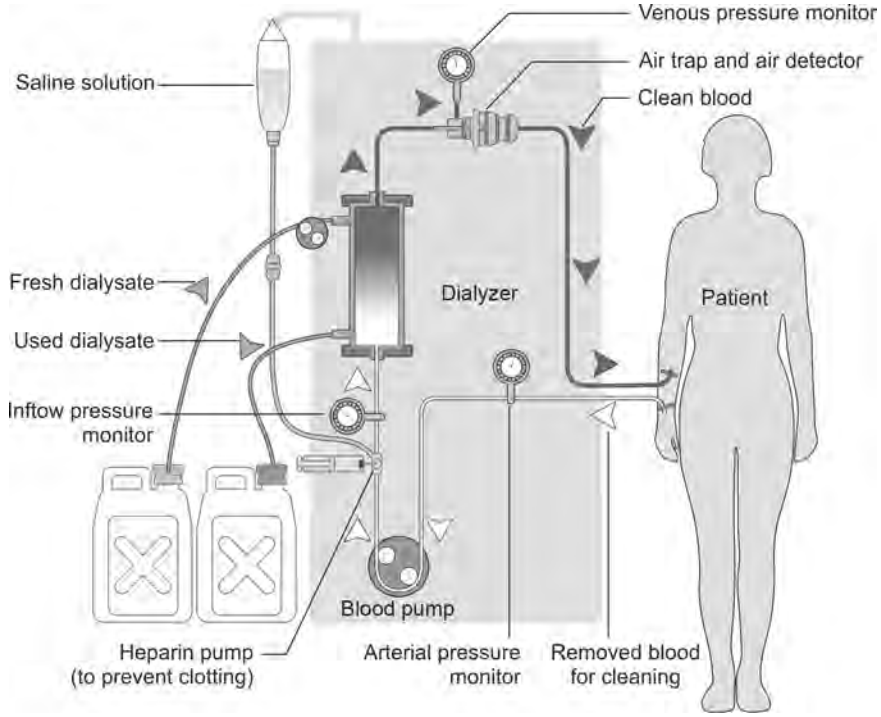

FIG. 1: Schematic diagram of hemodialysis circuit.

TABLE 3: Major electrolyte components of hemodialysate peritoneal dialysate.

Component	*Hemodialysate*	*Peritoneal dialysate*
Na	140	130–135
K	2	0
Ca	1.25	0.75–1.75
Mg	0.25	0.25–0.75
Cl	105	95–102
HCO_3	35	-
Lactate	-	35–40
Glucose	0.20	1.36–3.86

Cimino–Brescia Fistula

Cephalic vein is anastomosed to radial artery or ulnar artery is preferred as 2-year survival rate is >75%.

If arteriovenous fistula creation is not possible due to nonsuitability of native artery or vein, an interposing vascular graft made of an autologous vein, polytetrafluoroethylene (PTFE), must be used for vascular access. In comparison to natural arteriovenous fistulas, these grafts are associated with higher complication rate and shorter functional life expectancies. The third form of tunneled-cuffed catheters is also used for achieving vascular access for HD. The right internal jugular vein is the most common site for tunneled-cuffed catheter placement. Tunneled-cuffed catheters should not be removed by pulling. Vascular access-related complications lead to increased hospital stay and further complicated the HD procedure. The most common vascular access-related complications of HD are failure to provide adequate flow (300 mL/min) and infection. Thrombosis and stenosis of the vascular access are the most common causes of inadequate dialysis flow. Direct injection of alteplase can be used to treat thrombosis of vascular access and vascular surgeon opinion should be taken.

Vascular access infections occur in 2–5% of arteriovenous fistulas and approximately 10% of grafts over their functional lifetimes. Infected arteriovenous fistulas are at increased risk of bleeding. Patients with an infected access often present with fever, hypotension, or an elevated white blood cell (WBC) count. *Staphylococcus aureus* is the most common infecting organism, followed by gram-negative bacteria. Hospitalization is required to treat the vascular access infection, and vancomycin is the drug of choice (15 mg/kg or 1 g IV) because of its effectiveness against methicillin-resistant organisms and long half-life (5–7 days) in dialysis patient. An aminoglycoside (gentamicin 100 mg IV initially and after each dialysis treatment) is added if gram-negative organisms are suspected, but the patient is monitored closely because of toxicity. Other measures include removal and delayed replacement of the catheter, catheter exchange over a guidewire, and the use of antimicrobial/citrate lock solutions, although limited controlled data exist.

Bleeding

Another serious complication related to vascular access is life-threatening hemorrhage. Aneurysms, anastomosis rupture, and overanticoagulation are the possible causes of hemorrhage. Control bleeding immediately with manual pressure applied to the puncture sites for 5–10 minutes, and observe the patient for 1–2 hours if bleeding stopped. When simple methods fail to control hemorrhage or large-volume bleeding occurs, consult a vascular surgeon.

Vascular Insufficiency

In approximately 1% of all patients, vascular insufficiency of the extremity distal to the vascular access occurs. This "steal syndrome" clinically presents as exercise pain, nonhealing ulcers, and cool, pulseless digits as a result of shunting of arterial blood to the venous side of the access. Doppler US or angiography is the best diagnostic approach, consult vascular surgery and treatment is surgical.

Complications during Hemodialysis

Hypotension

The most frequent complication observed during HD is low blood pressure occurring in 50% of patient. During HD, average 1–3 L of fluid is removed over a 4-hour session, but 2 L/h fluid removal is possible. During ultrafiltration, normal blood pressure maintenance is depending on cardiovascular compensatory mechanisms and refilling of the vascular space by fluid shifts from the interstitial and intracellular compartments. Most common cause of intradialytic hypotension is excessive ultrafiltration due to underestimation of the patient's ideal blood volume (dry weight). Optimal dry weight is often clinically defined when hypotension prevents further fluid removal. Differential diagnosis of intradialytic hypotension includes myocardial dysfunction from ischemia, hypoxia, arrhythmias, and early pericardial tamponade. Other causes contribute to hypotension are abnormalities of vascular tone from sepsis or antihypertensive medications. Measures should be taken to prevent intradialytic hypotension are improving nutrition, performing ultrafiltration before dialysis, and increasing the sodium concentration of the dialysate solution. All these measures enhance the vascular refilling. The timing of intradialytic hypotension is often helpful in formulating a differential diagnosis. Causes of hypotension during early phase of dialysis session are preexisting hypovolemia, predialysis fluid losses, GI bleeding, sepsis, vomiting, diarrhea, or decreased intake of salt and water. Blood loss can occur from blood tubing or hemodialyzer filter leaks. If hypotension occurs at the end of dialysis, mostly cause is excessive ultrafiltration, but pericardial or cardiac disease can also precipitate hypotension at the end of dialysis. Orthostatic hypotension, tachycardia, dizziness, and syncope may occur due to hypotension during HD. Measure to be taken to manage intradialytic hypotension includes stopping of HD and placing the patient in the Trendelenburg position. Patient should receive salt by mouth (broth) or normal saline, 100–500 mL IV, if hypotension persists. Further extensive evaluation required if these conservative measures fail. Assessment of volume status, cardiac function, pericardial disease, infection, and GI bleeding is helpful. In an intensive care setting, further volume expansion or the administration of vasopressors to support blood pressure may require under invasive hemodynamic monitoring.

Dialysis Disequilibrium

Dialysis disequilibrium is a clinical syndrome occurring at the end of dialysis when large solute clearances occur during HD and is characterized by nausea, vomiting, and hypertension, which can progress to seizure, coma, and death. Patient's first dialysis session or during hypercatabolic states are the conditions when this clinical syndrome occurs the most. Dialysis disequilibrium may occur due to osmolar imbalance between the brain and the blood resulting in cerebral edema. Limiting solute clearance when initiating HD is the preventive measure. This condition can be managed by stopping dialysis and administering 5 mL of 10–23% sodium chloride or mannitol 0.25 g/kg IV to increase serum osmolality.

Air Embolism

When blood is pumped through an extracorporeal circuit there is always a risk of air embolism. The clinical presentation depends on the patient's body position at the time of the incident increased intracranial pressure and neurologic symptoms if patient sitting, air passes through the internal jugular vein to the cerebral circulation. Pulmonary hypertension and systemic hypotension occur in a recumbent position; air goes into the right ventricle and pulmonary circulation. Air embolism symptoms are acute dyspnea, chest tightness, and loss of consciousness, and sometimes full cardiac arrest. Signs include cyanosis and a churning sound in the heart from air bubbles in the blood. Clamp the venous blood line and place the patient supine, if air embolism is suspected. Start 100% oxygen to aid reabsorption of the air. Percutaneous aspiration of air from the right ventricle, IV administration of steroids, full heparinization, and hyperbaric oxygen treatment are the other measures for vascular air embolism.

Electrolyte Disturbance

Due to errors in mixing the dialysate concentrate with water, electrolyte abnormalities, rapid osmolar shifts may occur and manifests as hemolysis. However, hyperkalemia is the most common electrolyte disturbance that requires intervention. Hypoglycemia occurs in diabetic and nondiabetic ESRD patients. In addition to drugs, malnutrition and sepsis are important causes of hypoglycemia.

PERITONEAL DIALYSIS

Peritoneal Dialysis—Technical Aspects

Peritoneal membrane is the blood–dialysate interface in PD (**Fig. 2**). Osmotic pressure differences between the blood and dialysate determine the amount of ultrafiltration, which can be adjusted by changing the dialysate glucose concentration. Similar to HD, PD relies on the processes of clearance (solute removal) and ultrafiltration (fluid removal) as alternative to functions of the nephron. Solute removal occurs through process of diffusion. Dialysate contains 1.5% and 4.25% glucose formulations, which can be adjusted to increase or decrease ultrafiltration. Standard PD regimens consists of four exchanges daily, with 2 L of dialysate infused and left in place for several hours before draining. During the day, approximately 8 L are infused and about 10 L are drained, for a removal of approximately 2 L/day of fluid. In emergency department setting PD can be performed, over the long-term throughout the day (continuous ambulatory PD), or through multiple exchanges at night while the patient sleeps (continuous cyclic PD).

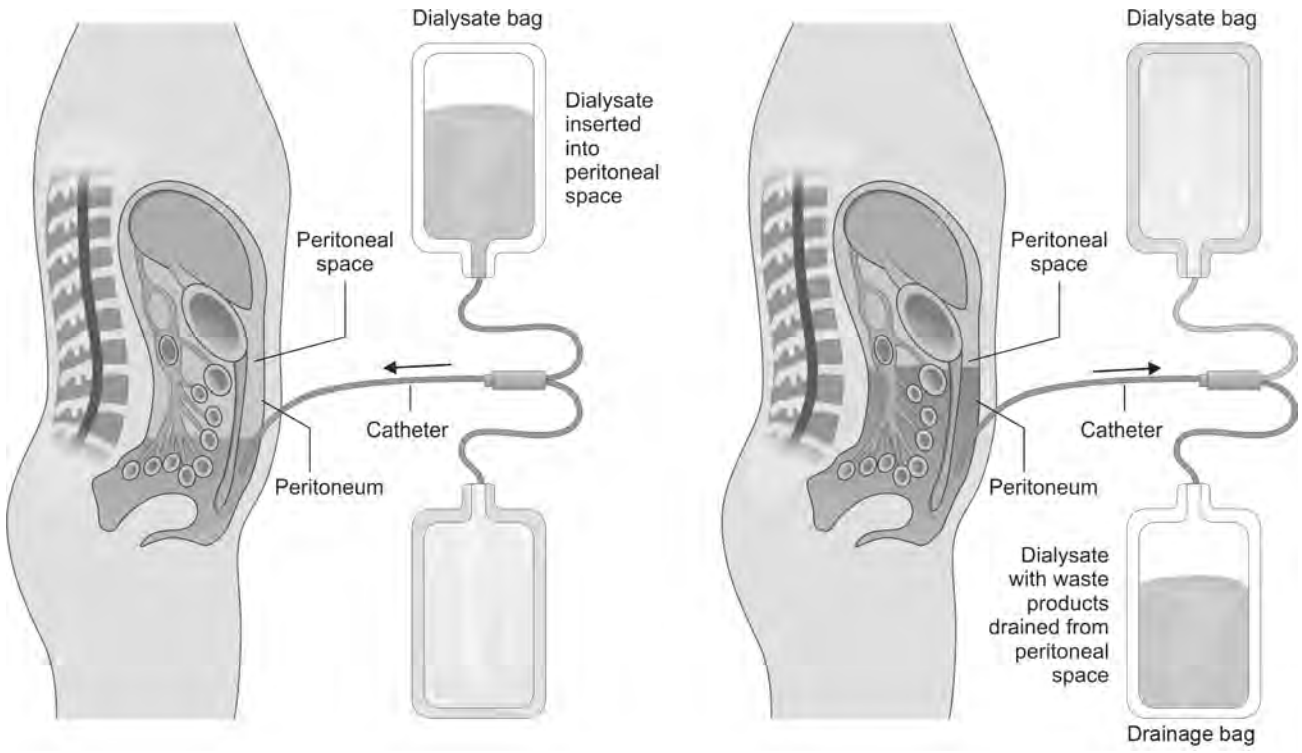

FIG. 2: Schematic diagram of peritoneal dialysis.

Complications of Continuous Ambulatory Peritoneal Dialysis

Peritonitis

Peritonitis is the most common complication of PD. Fever, abdominal pain, and rebound tenderness are the clinical presentations of peritonitis in PD patients. Cloudy effluent observed which suggests peritonitis, confirmed by Gram stain, cell count, and culture. The cell count in PD-related peritonitis is usually >100 leukocytes/mm^3 with >50% neutrophils.

Organisms isolated in PD-related peritonitis are *S. epidermidis*, *S. aureus*, *Streptococcus* species, gram-negative bacteria, anaerobic bacteria, and fungi. Empiric therapy begins with a few rapid exchanges of fluid lavage to decrease the number of inflammatory cells in the peritoneum, with added heparin (500–1,000 units/L dialysate) to decrease fibrin clot formation. A first-generation cephalosporin can be mixed with the dialysate, 500 mg/L with the first exchange and 200 mg/L with subsequent exchanges. In penicillin-allergic patients, use vancomycin 500 mg/L and maintenance doses of 50 mg/L per exchange. If seeking gram-negative coverage, add gentamicin 100 mg/L and maintenance doses of 4–8 mg/L per exchange. Recommendation is to treat for 7 days after the first negative culture results, usually resulting in a total of 10 days of therapy. Hospitalization of patient based on the patient's clinical appearance. Parenteral antibiotics are not needed.

Abdominal Wall Complications

Pain, erythema, swelling, and discharge around the PD catheter exit site suggestive of infection. *S. aureus* and *Pseudomonas aeruginosa* are the most common causative bacteria. Oral first-generation cephalosporin or ciprofloxacin started as empiric therapy as an outpatient therapy. Further follow-up of patients should be done in continuous ambulatory PD centers.

RENAL TRANSPLANT

End-stage renal diseases are increasing around the globe. Renal transplant can improve patient's quality of life and increases the survival as well. Over the past few decades living donor transplants are increasing and reducing the gap between demand and supply. Donors include those who are genetically related to the recipient or emotionally related (such as spouse, partner, or close friend). Living donation has become more acceptable with improvements in surgical nephrectomy techniques (laparoscopic and mini-open donor), reduced postoperative pain, shorter hospital stay, and faster return to work.

Causes of ESRD that can be managed by renal transplant: Diabetes mellitus, chronic glomerulonephritis, polycystic kidney, nephrosclerosis, interstitial nephritis, IgA nephropathy systemic lupus erythematosus, and Alport syndrome.

Relative contraindication for renal transplant: Comorbid conditions, age >65 years, untreated coronary artery disease, obesity, HIV infection, chronic Hepatitis B or C infection, and malignancy.

Procedure: Since the original operation described by Kuss et al. in 1951, procedure for a renal transplant is the same. The most common approach is a pelvic operation with extraperitoneal placement of the kidney. The right side is usually chosen, as the iliac vessels on the right are more superficial than on the left. The renal transplant involves three important anastomoses: the donor renal artery is anastomosed to the recipient external iliac artery (end-to-side); the donor renal vein is anastomosed to the external iliac vein (end-to-side); and the donor ureter is reimplanted to the recipient's bladder forming a ureteroneocystostomy with a JJ ureteric stent left in situ. The JJ-stent is removed 8–12 weeks postoperatively under local anaesthetic via flexible cystoscopy.

Factors affecting the renal transplant outcome: HLA matching and cross match is routine and remains fundamental of renal transplant. Graft survival is >87% when recipient and donor are HLA identical by serological and molecular methods.

Complications following the renal transplantation: Over the time techniques for renal transplant have improved so surgical complications are less. The most common surgical complication after a renal transplant is wound complications; these include wound infections, and fascial dehiscence or incisional hernias. The main medical complications in the first few weeks after transplantation are rejection and infection (**Table 4**).

Long-term follow-up after renal transplant: Depending on the type of graft, the average lifespan of a renal transplant is now 8–15 years. Lifelong regular follow-up of the transplant recipient in the transplant clinic is routine. Patients' general practitioners' role is to monitoring risk factors for cardiovascular disease and maintaining a high level of suspicion for any complication.

TABLE 4: Complications after renal transplant.

Surgical complications	*Early*: Hemorrhage • Renal artery thrombosis • Renal vein thrombosis • Recipient vasculature injury • Urine leak • Lymphocele • Wound complications
	Late: Ureteral obstruction • Transplant renal artery stenosis
Medical complications	*Early*: Acute rejection—acute cellular, antibody mediated • Infection—bacterial, viral (cytomegalovirus), fungal (pneumocystis)
	Late: Immunosuppression related—specific side effect profile, malignancy, chronic alloimmune injury • Allograft related—recurrent disease • Renal disease—anemia, bone disease • Cardiovascular disease • Infections—polyomavirus

SUMMARY

Chronic kidney disease and ESRD are recognized as a major health problem affecting considerably large population. In view of growing elderly population and increasing numbers of patients with diabetes and hypertension, prevalence of CKD patients will continue to rise. Complications associated with CKD: Anemia, hyperlipidemia, nutrition, osteodystrophy, and cardiovascular risk make the management of this medical problem unique and complex. Patients with CKD present several complex management issues to emergency physician. The staging system is significant in stratifying the patients according to disease severity and excellent tool for management of CKD and dialysis patients and recommend treatments according to disease stage. Morbidity and mortality in these patients can be reduced with early identification and treatment of anemia, renal osteodystrophy, uremic malnutrition, hyperlipidemia, and cardiovascular disease. Primary care physicians and nephrologists together are making significant strides toward extending and improving the lives of patients with chronic renal disease and ESRD.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Kidney and Ureteral Stones

Devendra Richhariya

INTRODUCTION

Urinary stone disease (USD) is a generic term that refers to the presence of stones within the urinary tract, commonly known as kidney stones, urolithiasis, or nephrolithiasis. USD is a common disease in the India. Its prevalence has steadily increased in the recent decades. Based on the acute nature of presentation, kidney stones generate a large volume of emergency department (ED) visits and hospital admission. Given the frequent presentation of USD in the ED, it is essential for the emergency practitioner to have the expertise in diagnosis and the management of this disease. Terminologies related to renal stones are summarized in **Box 1**.

RISK FACTORS

The risk factors for USD are influenced by urine composition, which can be affected by many factors including dietary, systemic illness, and environment. Some are modifiable whereas others are not. Risk factors can be categorized into nondietary, dietary, and urinary. **Table 1** presents summary of risk factors.

Nondietary

Incidence of USD is more common in men (three times) than in women. The risk of USD is 2.5 times more likely if there is a family history. Prior history of USD and systemic medical conditions such as diabetes, obesity, gout, hypertension, chronic kidney disease, Crohn's disease, hyperthyroidism, primary hyperparathyroidism, sarcoidosis, and renal tubular acidosis have all been implicated in increasing the risk of USD. Environmental exposures such as living in warmer climates and certain occupations in which the individual works in higher temperature have been proposed as risk factors for development of USD. This is thought to be related to a combination of factors including insensible water loss from heat and increased vitamin D exposure from living in warmer climates and low fluid intake due to certain occupation's lack of access to bathroom leading to lower urine volume and a higher risk of stone formation.

BOX 1: Terminology related to renal stone.

Urolithiasis: Calculi in urinary tract, including kidneys, ureters, bladder, and/or urethra

Nephrolithiasis: Calculi in the kidney

Ureterolithiasis: Calculi in one or both ureters

Kidney stone: Common terminology that refers to calculi in the kidneys, but often includes calculi in the lower urinary tract as well

Dietary

The composition of urine is influenced by dietary intake and environment, and several dietary factors have been implicated in the development of USD. Nutrients that have role in USD are

TABLE 1: Risk factors of urinary stone disease.

Nonmodifiable (nondietary)	• *Family history* (2.5 times increased risk) • *Structural anatomy of urinary system*: Calyceal diverticulum, horseshoe kidney, ureterocele, vesicoureteral reflux—ureteral strictures • *Medical history*: Gastric bypass, hypertension, diabetes, metabolic syndrome, primary hyperparathyroidism, sarcoidosis, Crohn's disease, gout, renal tubular acidosis, hyperthyroidism, and multiple myeloma
Modifiable (dietary)	Low fluid intake, low calcium diet, high animal protein diet, high oxalate intake, high sodium diet, hot weather, obesity, and decreased exercise
Medication	• *Medication stones*: Indinavir, triamterene, and acyclovir • *Promote calcium stones*: Loop diuretics, acetazolamide, theophylline, and glucocorticoids • *Promote uric acid stones*: Thiazides, salicylates probenecid, and allopurinol
Urinary	Low urine volume, urine concentration, urine composition, low urine pH, hypercalciuria, hyperoxaluria, and hypocitraturia

calcium, animal protein, oxalate, sodium, sucrose, magnesium, and potassium. Certain factors such as low fluid intake, low calcium diet, high animal protein diet, and high sodium diet are known to contribute to the risk of USD. In addition, the use of certain stone-forming medications also increases the risk of stone formation. Conditions that enhance enteric oxalate absorption often in the setting of malabsorption such as patients with history of gastric bypass, bariatric surgery, and short bowel syndrome are discussed in the next section.

Urinary

Urinary stone formation is intricately related to urine composition, low urine volume, urine concentration, and urine pH. Conditions such as hypercalciuria, hyperoxaluria, and hypocitraturia all increase urinary concentration of these ions and can cause stone formation when the urine becomes supersaturated. The persistent low pH promotes the precipitation of uric acid and is associated with the formation of uric acid stones.

CAUSE

There are four main types of urinary stones, with the majority (75–90%) composed of *calcium oxalate*, followed by *uric acid* (5–20%), *calcium phosphate* (6–13%), *struvite* (2–15%), and *cystine* (0.5–1%). **Table 2** presents stone types and composition. The exact pathogenesis of stone formation is complex and involves both metabolic and environmental factors. This pathogenesis is not entirely understood, but it is clear that it is affected by urine composition. Stone formation usually starts in the kidney and is due to urinary supersaturation with free ions (e.g., calcium and oxalate in calcium oxalate stones), and this leads to the formation of crystals. It is thought that the process starts with the formation of a nucleus, which is a heterogeneous mixture of substances such as uric acid, and this forms a nidus for nucleation, around which the stone grows. Increased urinary ion excretion and decreased urine volume will favor stone formation. High urine flow rate will reduce supersaturation. However, despite similar degree of urine saturation, stones form in some people whereas not in others, and this may be due to the presence of promoters and inhibitors of crystallization in the urine.

TABLE 2: Stone composition and causes.

Stone composition	*Causes*
Calcium oxalate and calcium phosphate 90%	• Hypercalciuria (high dietary sodium and protein, hypercalcemia) • Hyperuricosuria (high purine and high protein diet) hyperoxaluria (low dietary calcium, high oxalate diet or oxalate absorption, and genetic hyperoxaluria) • Hypocitraturia (chronic metabolic acidosis and inflammatory bowel disease)
Struvite (magnesium ammonium phosphate) 2–15%	Urine infection from urea-splitting bacteria (i.e., *Proteus*, *Klebsiella*, and *Corynebacterium*), staghorn formation, and high urine pH
Uric acid 5–20%	• Hyperuricosuria (gout) • Low urine pH • Radiolucent
Cystine 1%	Cystinuria—autosomal recessive disorder of cystine, ornithine, arginine, and lysine staghorn formation
Others <1%	Medications (raltegravir, indinavir, and triamterene)

CLINICAL PRESENTATION

The classic presentation of kidney stone is an acute onset, severe unilateral flank pain radiating to the ipsilateral groin; classically it starts at night. The pain is usually episodic, lasting 20–60 minutes, and does not completely resolve before the next wave of pain. The typical patient is usually writhing in distress and unable to find a comfortable position. In contrast to the patient with acute abdomen, they do not lie still. As the stone descend into the ureter, the pain may descend to the abdomen corresponding to the location of the stone with associated dysuria, urgency, and frequency. Approximately 30% of patients will report hematuria. Patients will experience nausea and vomiting due to the shared splanchnic innervations of the renal capsule and intestine. Fever is not typically present, unless associated with infection. There are several conditions that may mimic renal colic. **Table 3** lists the most common.

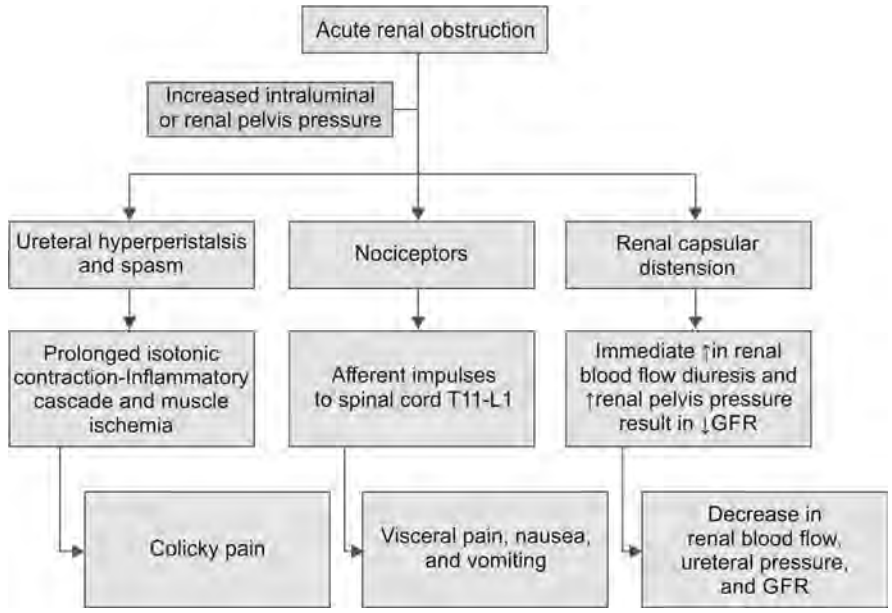
The mechanism of renal colic or the pain cycle related to kidney stones has a complex mechanism as well (**Flowchart 1**). While there is mechanical injury to the ureteral wall from the passage of kidney stones, the pain associated with urolithiasis is attributed to the obstruction of the urinary tract and the resulting increase in renal pelvic pressures leading to renal capsular distention, stimulation of nociceptors, and hyperperistalsis of the ureter.

EMERGENCY DEPARTMENT EVALUATION

The diagnosis of the USD includes a history and physical examination, evaluation of patient's risk factors and comorbid conditions, and the likelihood of an important alternate diagnosis. Typically, laboratory evaluations are done, which include a complete blood count, a metabolic panel to assess renal function, and urinalysis to assess for the presence of hematuria and infection. Confirmatory imaging is not always

TABLE 3: Renal colic mimics.

Gynecologic	Hemorrhagic cyst, dermoid cyst, endometrioma, ovarian neoplasm, ovarian torsion, fibroid, ectopic pregnancy, and pelvic inflammatory disease
Gastrointestinal	Appendicitis, diverticulitis, biliary disorders, pancreatitis, and small bowel obstruction
Urological	Pyelonephritis and urinary tract infection
Vascular	Abdominal aortic aneurysm, aortic dissection, renal artery thrombosis, renal infarction, mesenteric artery dissection or embolism, and intraperitoneal or retroperitoneal hemorrhage
Musculoskeletal	Mechanical low back pain and fractures
Miscellaneous	Herpes zoster infection (shingles)


Acute renal obstruction
Increased intraluminal or renal pelvis pressure
Ureteral hyperperistalsis and spasm
Nociceptors
Renal capsular distension
Prolonged isotonic contraction-Inflammatory cascade and muscle ischemia
Afferent impulses to spinal cord T11-L1
Immediate ↑in renal blood flow diuresis and ↑renal pelvis pressure result in ↓GFR
Colicky pain
Visceral pain, nausea, and vomiting
Decrease in renal blood flow, ureteral pressure, and GFR

(GFR: glomerular filtration rate)

FLOWCHART 1: Mechanisms of pain in renal colic.

necessary. For example, in a patient with known history of kidney stones, with a typical presentation and low likelihood of an important alternate diagnosis or complications, conservative management may be appropriate. However, in patients with no prior history of USD and with high risk for complication and alternate diagnosis, diagnostic imaging should be considered. The development of a clinical prediction rule, the STONE score, aims to evaluate the likelihood of uncomplicated ureteral stones and clinically important alternative diagnosis. This rule uses five objective criteria (gender, duration of pain, race, nausea/vomiting, and erythrocytes on urine dipstick) to categorize patients into low, moderate, and high probability of having a ureteral stone. The total score is 0–13 and is divided into three groups—low-risk: 0–5, moderate risk: 6–9, and high-risk: 10–13. This scoring system attempts to predict the likelihood of uncomplicated ureteral stones and is inversely associated with likelihood of an acutely important alternate diagnosis. This clinical prediction rule has the potential to guide decision-making regarding diagnostic imaging and treatment options. When this prediction rule was attempted to be externally validated, research found that the STONE score can aggregate patients into low-, medium-, and high-risk groups but lacks the sensitivity (53%) to allow clinicians to avoid obtaining a computed tomography (CT) scan. Further validation is required regarding the utility of this prediction rule.

IMAGING MODALITIES

When a patient presents to the ED with suspected renal colic, there is no consensus on which imaging modality should be obtained or even if imaging is necessary in the ED. The imaging is important in patient with suspected renal colic to confirm the diagnosis, obtain information about the stone size and location, diagnose complications related to USD, and rule out any potential disorders that mimic renal colic. Some physicians prefer imaging every patient who presents with suspected renal colic; others image only patients with first-time stones. CT of the abdomen and pelvis without contrast can be performed using low radiating dose scanning protocols or standard dose scanning protocols. Some clinicians reserve CT for patients who do not improve with conservative therapy or if another diagnosis is suspected. CT of the abdomen and pelvis without contrast using low-dose radiation scanning is the preferred examination for most adults. It has the highest diagnostic accuracy for renal and ureteral stones. It provides information on the stone size, location, and site of obstruction. CT scan is also useful in determining alternate diagnosis. CT of the abdomen and pelvis without contrast cannot evaluate kidney function. Ultrasound of the kidney and bladder can help diagnose renal colic indirectly by detecting hydronephrosis and the symmetry of the ureteral jets. Ultrasound can determine if a patient has unilateral or bilateral hydronephrosis and rarely can visualize presence of ureteral stones. This imaging modality is quick, noninvasive, and does not expose the patient to radiation; therefore, it is the preferred imaging modality in the pregnant patient and in recurrent nature of USD. Some clinicians prefer to obtain a CT scan after performing an ultrasound, either when an ultrasound is positive to confirm stone size and location in order to formulate a treatment plan or when an ultrasound is negative to confirm the negative test and to determine an alternate diagnosis.

Performing an ultrasound as the initial imaging test might decrease the need to order an abdominal and pelvic CT scan and thus decrease the radiation exposure to the patient. The abdominal radiography cannot detect hydronephrosis and has a sensitivity of 57% for stone detection and localization. An intravenous pyelography (IVP) involves radiographic imaging of the kidney, ureters, and the bladder before and after intravenous contrast dye is administered. It can diagnose hydronephrosis, evaluate renal function, and potentially show the position of the stone. IVP has similar sensitivity to that of ultrasound. This examination generally is not used as a first-line diagnostic imaging examination. MRI of the abdomen and pelvis is seldom used for nephrolithiasis. MRI poorly detects stones. Currently, MRI is used in nephrolithiasis in pregnant patients with hydronephrosis on ultrasound. In these patients

it can help determine the location of the obstruction, while not subjecting these patients to radiation.

MANAGEMENT AND TREATMENT

Analgesia

When a patient presents with an acute stone episode, one of the main goals is relief from pain. The pain that renal colic patients experience is from an increase in collecting system pressure and urethral spasm, which is modulated via prostaglandins. Because of this theory, nonsteroidal anti-inflammatory drugs (NSAIDs) have been the preferred drug for treatment of renal colic. NSAIDs can decrease smooth muscle tone as well as inhibit prostaglandins. NSAIDs should be avoided in patients with a history of a gastrointestinal bleed or impaired renal function. Narcotics have also been found to be helpful in the treatment of renal colic pain. Narcotics do not help with inhibiting prostaglandins, and in fact some studies found that they increase ureteric muscle tone.

Hydration and Diuretics

Patients who are dehydrated from either vomiting or decrease in oral intake should receive intravenous hydration. In theory, increase in fluid flow through the affected kidney might expedite stone passage and thus improve the patient's symptoms. Studies have been performed to prove this hypothesis by high-volume fluid hydration with or without the addition of diuretics to increase urine output. The literature in fact does not support the use of diuretics and high-volume fluid therapy in acute renal colic.

Medical Expulsion Therapy

There have been several medical expulsion therapies (METs) that have increased the passage rate of ureteral stones, which include alpha blockers, calcium channel blockers, and antispasmodic agents. Treatments that increase stone passage would benefit the patient by decreasing the need for interventional procedures. The top two METs that have been studied for the treatment of renal colic are TAMSULOSIN (an alpha-adrenoceptor antagonist, a smooth muscle relaxant drug) and nifedipine (a calcium channel blocker). In 2018, a meta-analysis of 67 trials showed a small benefit of alpha-blocker therapy with stone passage than with a placebo control. The use of MET in improving the passage of ureteral stones needs further research. At this time, there is little downside in using tamsulosin in MET, the cost of treatment is low, and there are few side effects.

Urology Consultation

Patients who are not able to be treated conservatively, due to having any one or several criteria should consult an urologist in the ED for admission and possible urgent intervention **Box 2**. Patients with an obstructing stone and urinary infection should be admitted for intravenous antibiotics and decompression of the obstruction. Patients with intractable vomiting should be admitted for intravenous hydration and supportive care. As alike, patients with intractable pain who cannot be controlled on oral agents should be admitted for supportive care. Patients with one functioning kidney should also be admitted to the hospital.

BOX 2: Admission criteria for kidney and ureteral stones.

- Urosepsis
- Intractable vomiting
- Infection with stone obstruction
- Stone size <15 mm
- Bilateral obstruction
- Single kidney or transplanted kidney with an obstruction
- Intractable pain
- Significantly elevated creatinine level

TABLE 4: Rate of spontaneous stone passage based on stone size.

Size of stone (mm)	*Rate of spontaneous passage (%)*
1	87
2–4	76
5–7	60
7–9	48
≥9	25

PROGNOSIS

Stone passage is dependent on the size, shape, and location of the kidney stone. Most stones 4 mm or less in diameter pass spontaneously. For stones >4 mm in diameter, there is a progressive decrease in the spontaneous passage rate as the size of the stone increases (**Table 4**). Shape is also important, and in particular the width of the kidney stone predicts the likelihood of spontaneous passage. In addition, stones that have reached the distal ureter are more likely to pass without intervention. Only about half of the stones in the proximal ureter are expelled spontaneously, while approximately 80% will pass if at the ureterovesicular junction. Recurrence is common. In the absence of preventive measures, the probability of recurrence of symptomatic kidney stones at 5 years is 50% and 60% by 10 years. Fortunately, the recurrence rate can be decreased by up to 50% in those treated with medication or dietary intervention. Although renal failure and permanent functional injury to the kidney are uncommon with urolithiasis. Decreases in renal blood flow begin 5–18 hours after obstruction and the degree of reversibility is unclear. Few studies suggest irreversible damage after 4 weeks of obstruction.

COMPLICATIONS

Obstruction

Patients who have a ureteral stone obstruction should have relief of obstruction within 2 weeks. Studies have shown that time to relief of obstruction and the presence of infection were the only significant predictors of outcome of long-term renal damage. If the obstruction was delayed past 2 weeks, renal outcome worsens progressively. Thus, urologists can closely monitor patients with an obstruction that does not have a concurrent infection, if they have a functioning contralateral kidney.

Infection

An infection in the presence of an obstructive stone is a urologic emergency. Antibiotics cannot be excreted unless there is relief of the obstruction. When there is a urinary tract infection with a nonobstructing stone, patients can be treated with oral antibiotics with close follow-up within 24 hours.

Stents

Patients with ureteral stents should be evaluated for obstruction, infection, and migration of the stents. This can be done by using abdominal and pelvic CT scan or a kidney, ureter, urinary bladder (KUB) ultrasound. Such patients should consult an urologist for their management and disposition.

SPECIAL CONCERNS

Pediatric

Stone disease in the pediatric population is uncommon, although its incidence is increasing especially in teens. The presentation of children with stone disease differs from that of an adult. Children usually present with a vague abdominal pain, not a unilateral colicky flank pain. Gross hematuria is present in 14–33% of patients and urinary tract infection affects 8–46% of stone pediatric patients. Ultrasound is the study of choice in the pediatric population due to concern over radiation exposure. Indications for admission are the same as for the adults. All children should be referred to an urologist and a workup for metabolic stone disease should be performed.

Pregnancy

There are anatomic and pathophysiologic changes in pregnancy that increase the risk of renal colic. There is urinary stasis secondary to compression and increase in progesterone levels. There is also hypercalciuria secondary to calcium supplementation and increase in glomerular rate. The renal ultrasound is the study of choice in pregnant patients secondary to the radiation exposure of CT scan. Narcotics are generally required for pain management because NSAIDs are contraindicated in pregnancy. METs can be safely used in pregnancy. Indications for admission are the same as for nonpregnant adults. Close follow-up with obstetrics as well as urologist is needed.

Geriatrics

The first important thing is to make the correct diagnosis. The differential diagnosis for this patient population includes acute myocardial infarction and abdominal aortic aneurysm. The average age of the first presentation for renal colic is 42 years, and it is uncommon for this first presentation to occur in patients older than 60 years. Thus, if a patient older than 60 years presents with no history of USD with symptoms that suggest renal colic, one must have high index of suspicion for an alternate diagnosis. The CT scan is the preferred imaging modality because it can evaluate both the renal collecting system and the aorta as well as other possible alternate diagnoses. The elderly population tend to have comorbid conditions and are on medications that may preclude them from the standard pain management of USD. For example, in patients who have renal failure or peptic ulcer disease, the use of NSAIDs is contraindicated.

SUMMARY

"Kidney and ureteral stones" is a frequent ED complaint. Either due to increasing identification or lifestyle changes, the prevalence of kidney and ureteral stones is increasing in all age groups. It is important for emergency physician to develop expertise in the diagnosis and acute management of this disease. The classic presentation of urolithiasis is an abrupt, unilateral flank pain that radiates to the groin. The diagnosis of urolithiasis includes a history and physical examination, evaluating the patient's risk factors, evolution of symptoms, the presence or absence of infection, and the exclusion of renal colic mimics. Noncontrast CT is the current diagnostic test of choice for ureteral stones. Most patients with acute renal colic can be managed conservatively with pain control and hydration. Emergent urological consultation in the ED is required for patients with urosepsis, renal obstruction with suspicion of a proximal urinary tract infection, acute renal failure, anuria, or intractable pain or vomiting.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Urinary Tract Infection

Krunal Desai

INTRODUCTION

Urinary tract infection (UTI) is the most common infectious disease which affect from neonate to geriatric age group population in worldwide. Emergency physician need to evaluate wide spectrum of UTIs ranging from uncomplicated pyelonephritis, cystitis, urethritis to complicated pyelonephritis, urethritis, cystitis, or even who present with sepsis and shock. Challenges are much more while evaluating the UTI in emergency with improper history, nonavailability of culture reports, and irregular follow-up. Priorities for emergency physician while evaluating the UTI are determine whether infection is complicated or uncomplicated, necessary laboratory and imaging required, and appropriate antibiotics for patient.

DEFINITIONS AND CLASSIFICATION

Urinary tract infection described as an inflammatory process of urinary epithelium (upper or lower or both urinary tract) which is triggered by microorganism. Presence of white blood cells (WBCs) in urine is termed as pyuria, presence of bacteria in urine termed as bacteriuria.

Urinary tract infections can be classified on anatomical site, structural, and functional basis.

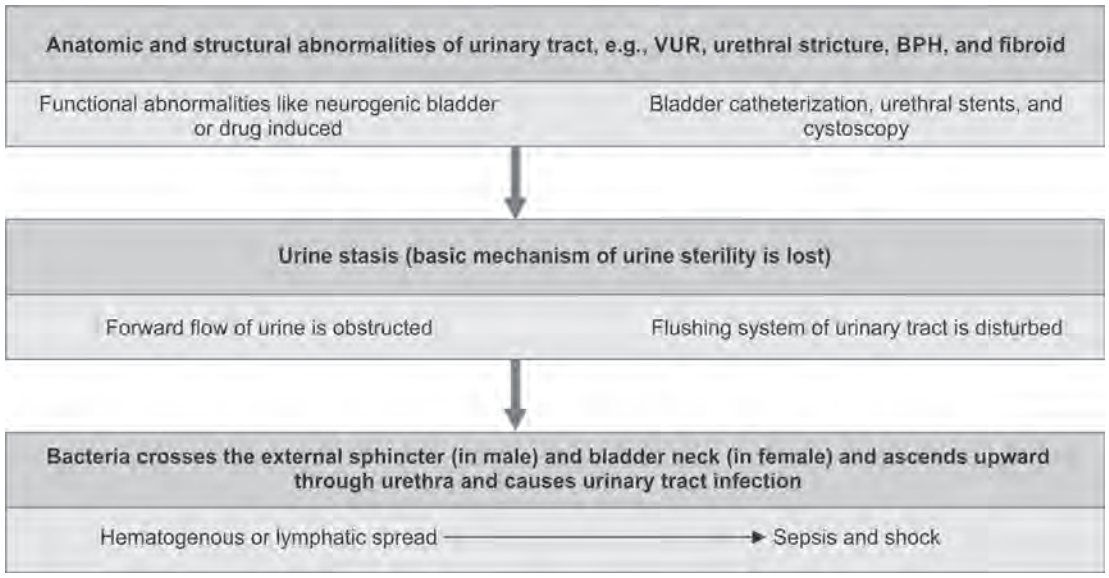
- *Upper UTI* involves ureter and kidney called as pyelonephritis.
- *Lower UTI* involves bladder called as urethritis and cystitis.
- *Uncomplicated UTI*: Uncomplicated UTI refers to occurs in young, healthy, and nonpregnant with normal structural and functional genitourinary tract.
- *Complicated UTI*: Complicated UTI refers to occurs in male, pregnant women, and any individual with structural and functional abnormality of genitourinary tract such as urolithiasis, neurogenic bladder, vesicoureteral reflux (VUR), malignancy, immunocompromised status, catheter, or stents.
- *Catheter-associated UTI (CAUTI)*: Patient with signs and symptom of UTI + presence of indwelling urinary catheter with no other source of infection.
- *Recurrent UTI*: It is defined as two uncomplicated UTIs in 6 months or three or more uncomplicated UTIs in the preceding 12 months.
- *Relapse of UTI*: It is defined as recurrence of UTI within 2 weeks of treatment completion for same organism.
- *Reinfection*: It is a recurrence of UTI with different organism than previous one.

PATHOPHYSIOLOGY

In normal situation, forward flow of urine is maintained along the urinary tract and urine remains sterile because of this flushing system of urinary tract. Urine remains sterile till external sphincter in male and till bladder neck in females. Mucosal barrier, immunological defense, and acidic nature of urine are the other factors helpful in prevention of UTI. Any disruption in anatomy, structure, and function of urinary tract leads to disruption of sterility of urine and infection. Pathophysiology of UTI is summarized in **Figure 1**. Incompetent ureterovesical valve leads to VUR and important cause of febrile UTI in children up to 24 month of age group. Spinal cord injury (SCI) patient with neurogenic bladder (dysfunction in bladder emptying) and patient with urologic surgery are also suffering from VUR. Calculi, masses or tumors either arising from urinary tract or outside like gastrointestinal tract or gynecologic structure obstruct the urine flow. Prostatic hypertrophy and urethral stricture are common causes in elderly men while fibroid, large pregnant uterus (in young female) and uterine prolapse (elderly female) are responsible for urinary obstruction. Medications such as anticholinergics, antipsychotic antidepressant, antiparkinson, and antihistamine are also responsible for urinary retention. Any instrumentation such as catheterization, cystoscopy, and transurethral surgery for stents placement and for calculi are high risk for UTI.

RISK FACTORS AND UROPATHOGENS

About half of the women experience UTI at least once in their lifetime. Lower rates of UTI are seen in men. Though elderly men are on higher risk due to prostate enlargement, use of catheterization, and debilitated state. Prior history of UTI, sexually active individual, and spermicidal use are the usual risk factors for UTI. *Escherichia coli* (75–95%) followed by *Staphylococcus saprophyticus* (5–15%) are the most common pathogens responsible for the complicated and


Anatomic and structural abnormalities of urinary tract, e.g., VUR, urethral stricture, BPH, and fibroid
Functional abnormalities like neurogenic bladder or drug induced
Bladder catheterization, urethral stents, and cystoscopy
Urine stasis (basic mechanism of urine sterility is lost)
Forward flow of urine is obstructed
Flushing system of urinary tract is disturbed
Bacteria crosses the external sphincter (in male) and bladder neck (in female) and ascends upward through urethra and causes urinary tract infection
Hematogenous or lymphatic spread
Sepsis and shock

(BPH: benign prostatic hyperplasia; VUR: vesicoureteral reflux)

FIG. 1: Pathophysiology of the urinary tract infection.

TABLE 1: Pathogens responsible for urinary tract infection (UTI).

Uncomplicated UTI	*Complicated UTI*	*Catheter-associated UTI*	*Recurrent UTI*
• *Escherichia coli* (75–95%)	• *Pseudomonas aeruginosa*	• *Proteus mirabilis*	• Antibiotic resistant *E. coli*
• *Staphylococcus saprophyticus* (5–15%)	• *Acinetobacter baumannii*	• *Candida* species	• *Enterococcus* species
• *Enterococcus* species	• *Enterococcus* species		• *Staphylococcus* species
• *Klebsiella pneumoniae*	• *Staphylococcus* species		

noncomplicated UTI. Gram-negative bacteria (*Klebsiella* and *Proteus mirabilis*) and gram-positive bacteria (*Enterococcus* and group B *Streptococcus*) can also responsible for UTI. Most common pathogens involved in complicated UTI are *Pseudomonas aeruginosa, Enterococcus faecalis*, and extended-spectrum β-lactamase (ESBL) producing bacteria. While polymicrobial and resistant organism involved in elderly men with urinary obstruction. Pathogens responsible for UTI are summarized in **Table 1**.

CLINICAL FEATURES

Urinary tract infection can present from localized symptoms to severe sepsis. In suspected case of UTI, detailed history and clinical features to classify the cause are most important. Patient can present with cystitis to urosepsis condition.

Cystitis

Cystitis is superficial infection of urinary bladder. Patient who has cystitis present with localized symptoms such as dysuria, urinary frequency, hesitancy, hematuria, or suprapubic pain. It is more common in woman than man. Usually patient with cystitis has no fever with only above-mentioned localized symptoms. It is necessary to evaluate regarding sexually transmitted disease (STD) by proper history such as urethral discharge, vaginal discharge, vaginal bleeding, new sexual partner, and sexual partner with STD. All these symptoms are more suggestive of STD than cystitis. Man, with >50 years of age, prostatic abnormality, and history of previous instrumentation can present with cystitis.

Pyelonephritis

Pyelonephritis is upper UTI which involves kidney and ureter. In contrast to cystitis, patient with pyelonephritis present with more systemic symptoms than local such as fever, vomiting, nausea, abdominal pain, and flank pain. For diagnosis of pyelonephritis, ultrasonography (USG), kidney, ureter, and bladder (KUB), or noncontrast computed tomography (NCCT KUB) should be done. Urine culture and blood culture should be sent from emergency before administration of antibiotic is ideal approach.

DIFFERENTIAL DIAGNOSIS

Being emergency physician, it is necessary to keep all differentials in mind for early confirmation, diagnosis, and management. History and clinical examination findings help to rule out all differentials and make confirm diagnosis. Common and life-threatening mimic of UTI can be differentiated as shown in **Table 2**.

DIAGNOSTIC EVALUATION

In emergency department, presumptive diagnosis of UTI by proper history and clinical examination should be confirmed by pathological-radiological investigations. Life-threatening

TABLE 2: Common and life-threatening mimic of the urinary tract infection.

Fever, nausea, vomiting, and abdominal pain	*Lower abdominal pain and urinary symptoms*
• Abdominal aortic aneurysm	• Spinal epidural abscess
• Cholecystitis	• Ectopic pregnancy
• Lower lobe pneumonia	• Ovarian torsion
• Appendicitis	• Pelvic inflammatory disease
• Diverticulitis	• Testicular torsion
	• Epididymitis/orchitis

differentials must be rule out first as mentioned above. For confirmed diagnosis of UTI, urine dipstick, routine microexamination, culture, USG are necessary. All these investigations should be used as per requirements. For urine test first most important thing is to collect urine by proper clean-catch method.

Technique for urine collection:

- Clean periurethral area, retraction of foreskin, and separation of labia: Collect midstream urine
- If patient cannot void urine: Sterile catheterization with no touch technique and collection
- If unable to catheterize patient: Suprapubic aspiration but invasive and painful

Once urine is collected, it should be analyzed as soon as possible because delay can make unreliable results.

Urine Dipstick

Urine dipstick test used in emergency department to find out presence of ketone, protein, glucose, nitrates, leukocyte esterase, bilirubin, pH, and specific gravity. For diagnosis of UTI, nitrite and leukocyte esterase test are important. Leukocyte esterase enzymes are released from WBCs, so presence of it indicates WBCs in urine. But drawback is WBCs can be vaginal source in female patients that cannot be ruled out. Results can be false positive in high glucose or protein concentration, use of glucocorticoids, and viral illness. So leukocyte esterase test has wide range of sensitivity from 70 to 95%. Other important test for UTI in emergency is nitrite test. In this test nitrates present in urine is converted to nitrite by microorganism but only by Enterobacteriaceae. So that other common organisms for UTI such as *S. Saprophyticus* and enterococci can be missed out. Nitrite test sensitivity alone is 81% but if both nitrite and leukocyte esterase positive then sensitivity increases up to 94%. False-positive results in nitrite test occur with contaminated specimen, drug, food that color urine red, and *Trichomonas* infection. False-negative results with recent antibiotic treatment, presence of glucose and protein in urine, and high specific gravity.

Urine Microscopy

After urine dipstick test, urine routine and microscopic examination are the most commonly used tests to diagnose UTI in emergency department. Urine microscopic examination provides information regarding presence of bacteria, WBC, red blood cell (RBC), and epithelial cells in urine. WBC count > 5 per high power field in symptomatic patient indicates abnormal result. If counts are less but history and clinical examination findings are suggestive of UTI, first rule out false-negative causes. Presence of WBC and RBC indicates other causes like vaginal bleeding or bleeding from genitourinary tract and do further diagnosis accordingly. Presence of epithelial cells indicates contaminated specimen.

Urine Gram Stain

Urine gram stain examination finds out gram-positive and gram-negative organism. So on that basis clinician can suspect organism and start empirical antibiotics. Major drawback is not available in most of emergency departments.

Urine Culture and Sensitivity

Urine culture and sensitivity frequently used at intensive care unit (ICU) when bedridden patient with prolong catheterization and multidrug-resistant organism in different cultures. In emergency it is used in selected patients. If patient with clinical history and examination suggestive of UTI, positive urine dipstick, microscopic examination does not need to do culture. Such patient responds well to empirical antibiotics. Patient with sepsis, male patient, pregnant, pyelonephritis, immunocompromised individual, recurrent UTI, and complicated UTI needs urine culture examination. It should be done before administration of antibiotic. Collection should be done with proper care.

Imaging

Patients with UTI generally do not need imaging in diagnostic evaluation. But in some conditions, renal imaging required to find out causes. USG KUB is primary modality of investigation. It is easy to perform, rapidly available, and can direct pathologies such as calculi, hydroureter, and kidney size and shape. CT scan is the investigation of choice for any renal pathology. It shows size, shape, pyelonephritis, calculi, obstructive changes, abscess, and emphysematous changes. In suspicious cases, CT KUB with contrast can be done to find out renal artery, vein stenosis due to thrombus or embolism.

TREATMENT

General Consideration

For treatment of UTI, first it is necessary to confirm type of UTI. There are basic steps which have to be considered by emergency physician for treatment of UTI:

- Confirm type of UTI
- Proper hydration
- Change catheter if suspect CAUTI
- Decide to admit or outpatient treatment
- Send culture reports, if indicated
- Start symptomatic treatment
- Start antibiotic as per antibiogram
- Follow-up

Principle of Antimicrobial Management

Antibiotics are typically recommended for UTI to eliminate the pathogen from the urine. While choosing the antibiotics, two important factors are important; one pathogen should

be susceptible to antibiotics and second its concentration in urine should be at high level [above the minimum inhibitory concentration (MIC)] to eliminate the pathogen. Dose adjustment of antibiotics is required in acute as well as chronic renal insufficiency. Eradication of pathogen is challenging in end-stage renal disease due to inability to maintain antimicrobial concentration in the urine. Urinary obstruction can also affect the antibiotic concentration in the urine so this should be addressed as early as possible.

Antibiotic therapy should be decided on the basis of the diagnosis, comorbidities, hemodynamic status of the patient, and the local/institutional antibiogram. While evaluating the UTI patient in emergency department urine culture is rarely available, so antibiotics should be started empirically and hospital antibiogram is useful to understand resistance pattern and antibiotic selection. History of medication allergies, compliance of the drug, cost of medication, and availability should also be considered.

Patient with hemodynamic instability and with urosepsis should be treated with intravenous (IV) fluid, vasopressors along with IV antibiotics. Proper evaluation is required in patient of urinary obstruction who presented with shock because these patients may require emergency urologic intervention. In view of source control strategies in management of UTI, percutaneous or endourologic drainage of hydronephrosis and renal abscess may require. Emphysematous pyelonephritis may require immediate partial or total nephrectomy.

Asymptomatic Bacteriuria

Condition where patient is asymptomatic but has bacteria in urine or urine culture (clean midstream catch) report is showing quantitative count of at least 10^5 cfu/mL (in single specimen for men and two consecutive specimens with same species for women). In emergency department, patient usually comes after obtaining previous report as emergency physician do not prescribe urine culture in asymptomatic patient. These groups of patients where bacteria are visualized in microscopy should be kept under observation, and usually not treated with any antimicrobial because they often clear. Pregnant women should be treated with antimicrobial for 3–7 days because of risk of preterm, low birth weight, or situation may progress to pyelonephritis.

Acute Uncomplicated Cystitis

Patient presenting with acute uncomplicated cystitis can be treated as outpatient treatment. Emergency physician should start antibiotics as per local resistance and antibiogram. Mostly drugs which get concentrated in urine considered as choice of antibiotics. There are three antibiotics which are used in treatment: Nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX), and ciprofloxacin.

Nitrofurantoin is used in treatment of uncomplicated cystitis because it is highly active against *E. coli* and achieves high urinary concentration. But major drawback is prolonged treatment, does not penetrate to tissue so cannot be used in pyelonephritis.

Dose: Nitrofurantoin 100 mg twice a day for 7 days.

Due to gradually increasing resistance of *E. Coli* to TMP-SMX, if local resistance <10–20% it can be used as empirical treatment in cystitis. If resistance >20%, nitrofurantoin should be considered.

Dose: TMP-SMX one DS (double strength) twice a day for 3 days.

If patient is allergic and resistance to nitrofurantoin and TMP-SMX, fluoroquinolones should be considered. As fluoroquinolones are used in multiple conditions such as pneumonia, complicated UTI, and tuberculosis, it should not be start as empirical antibiotic because of chance to develop resistance in community.

Dose: Ciprofloxacin 500 mg twice a day for 3 days.

Pyelonephritis

In most cases, infection begins as cystitis. If bacteria ascend through urinary tract and reaches infected kidney parenchyma, the condition is called pyelonephritis. Some cases also occur through hematogenous spread by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella*, and *Candida*. Fever, vomiting, flank pain, and costovertebral angle tenderness are the presenting features. Urine culture and blood culture along with diagnostic imaging are recommended if kidney, ureteral stone, masses, abscess, and emphysematous pyelonephritis are suspected. Antibiotics and supportive care (antipyretics, antiemetics, and IV fluid) are mainstay of the treatment. While initiating the antibiotics in emergency department, coverage should include against *E. coli* which is responsible for majority of cases. Patient should be admitted if vomiting and signs of dehydration, sepsis, pregnancy, postrenal transplant, presence of calculi, urethral stent, and catheters are present.

Acute Uncomplicated Pyelonephritis

As pyelonephritis is infection on renal parenchyma, antibiotics which penetrate in tissue can be considered as initial treatment. Fluoroquinolones are initial choice of antibiotic. But being emergency physician must consider to start outpatient or inpatient treatment. Indications for admission are inability to maintain oral hydration, unable to take oral medicines, severe sepsis, acute renal failure, immunocompromised, pregnancy, etc. If patient is allergic to fluoroquinolones, oral or IV amoxicillin can be started if low local resistance to organism.

If the patient can be treated as outpatient treatment oral fluoroquinolone is initial treatment of choice.

Oral Medicines

- Ciprofloxacin 500 mg twice a day for 7 days
- Amoxicillin 500 mg three times a day for 10 days
- Cefpodoxime 200 mg twice a day for 14 days

Intravenous Medicines

- IV ciprofloxacin 400 mg twice a day for 7 days
- IV ceftriaxone 1 g once a day for 14 days

Acute Complicated Pyelonephritis

As mentioned before, patient with pyelonephritis associated with structural and functional abnormality of genitourinary tract, immunocompromised status, signs of sepsis considered as complicated pyelonephritis. These patients required as early as possible broad-spectrum IV antibiotics. Take culture before administration of antibiotics. Recently, ceftolozane/tazobactam and ceftazidime/avibactam are newer antibiotics on trial for complicated UTI.

Doses

- IV cefepime 1 g twice a day
- IV piperacillin/tazobactam 4.5 g three times a day
- IV imipenem 500 mg four times a day
- IV ciprofloxacin 400 mg twice a day
- IV vancomycin 15 mg/kg twice a day

Recurrent Urinary Tract Infection

Many patient visits emergency department with same complains of UTI frequently. Usually these patients can be managed with antibiotics according to previous culture and treatment. In these patients it is necessary to find out cause or risk factor for recurrence. Risk factors are structural and functional abnormality of genitourinary tract, new sexual partner, use of a diaphragm or spermicide. It is also necessary to find out which patients need further investigations of recurrent UTI.

Indication for further investigation of recurrent UTI:

- Prior urinary tract surgery
- Obstructive symptoms
- Prior abdominopelvic surgery
- Immunocompromised status
- Repeated pyelonephritis

Two treatment modalities can be used in recurrent UTI:

1. Postcoital antibiotics
2. Self-start therapy

Postcoital antibiotic can be started in female patients with recurrent UTI when sexual activity is risk factor for UTI. Low dose antibiotics should be started within 2 hours after coitus. TMP-SMX, ciprofloxacin, nitrofurantoin, norfloxacin, and ofloxacin are generally prescribed.

Self-start antibiotic is another modality in women who can able to recognize her symptoms of UTI. Three days course of antibiotics should be given to such patients and advised to start treatment if symptoms present. If symptom dose not resolve within 2 days then it is advised to contact physician for further treatment.

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is a severe necrotizing infection of renal parenchyma and perirenal space caused by *E. coli* mostly in uncontrolled diabetic patient. Emphysematous pyelonephritis considered as urologic emergency and severe spectrum of clinical pyelonephritis, with high mortality rate 20–40%. It is believed that high blood sugar in tissue provide favorable environment for *E. coli* which ferment sugar and produce carbon dioxide. Computed tomography of abdomen and pelvis is used to confirm the diagnosis. Emergency department management consists of board-spectrum antibiotics, IV fluid, and urgent urology consultation. In modern management, conservative approach of percutaneous drainage along with medical management (antibiotics) is considered. Nephrectomy may be required in severe cases.

Renal Abscess and Perinephric Abscess

Purulent infectious collection of renal parenchyma is known as renal abscess, typically caused be gram-negative bacteria and suspected when patient with pyelonephritis is not responding to antimicrobial therapy. Perinephric abscess results from rupture of cortical abscess in to perinephric space. Imaging modality of choice is computed tomography. Supportive and noninvasive approach can be opted for hemodynamically stable small abscess (3–5 cm) and can be treated with antibiotics. Antibiotic therapy should be targeted against gram-negative organism. Open or percutaneous surgical drainage is considered for larger abscess.

Catheter-associated Urinary Tract Infection

Catheter-associated UTI is one the common healthcare-associated infection and bacteriuria is observed in about 10% in catheterized individual. Urinary catheter system provides an environment for *Pseudomonas*, *Proteus*, *E. coli*, and *Enterococcus* bacterial growth. Fever, suprapubic tenderness, and sepsis hypotension are usually present. Urine culture result is obtained if CAUTI is suspected, catheter should be replaced or removed and antibiotics should be started immediately.

Spinal Cord Injury Patient and Urinary Tract Infection

Patients of SCI are more prone for UTI and most common cause of fever. Catheterization of bladder, impaired bladder emptying, and decreased fluid intake altered defense mechanism of body due to chronic illness. Decubitus ulcers are the predisposing factors for UTI in SCI patient. Fever fatigue with vague abdominal discomfort are the usual presenting feature, they are not experiencing classic feature of UTI (dysuria, frequency, and urgency) because of loss of sensation. *Enterococcus*, *Proteus*, and *Pseudomonas* are common pathogens. Aminoglycosides plus penicillin or third-generation cephalosporine is considered for UTI in patient with SCI.

Urinary Tract Infection and Sexually Transmitted Infection

Urinary tract infection and sexually transmitted infection (STI) are sometime difficult to differentiate as in both conditions symptoms like dysuria may overlap and are present in sexually active persons. STI present with vaginal discharge, lower abdominal pain, pruritus, dyspareunia, and history of multiple sexual partner. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are most common causative organisms for cervicitis, pelvic inflammatory disease, epididymitis, and prostatitis. If suspected, both UTI and STI can be treated concurrently.

Special Population

Pregnancy

Pregnant women are more prone to get UTI due to hormonal and mechanical changes during pregnancy. In pregnancy, asymptomatic bacteriuria also should be treated because there are chances to develop severe sepsis, premature labor, low birth weight, etc. Most common organism is *E. coli*. Nitrofurantoin, beta-lactam antibiotics, second- and third-generation cephalosporins are generally used for treatment. But all medicines used according to trimester and considering

its side effects. Fluoroquinolones and tetracyclines are contraindicated in pregnancy. Nitrofurantoin should be avoided in first-trimester and near-term period because of its effect on organogenesis, potential to cause hemolytic anemia in newborn. Ceftriaxone causes kernicterus by bilirubin displacement. Obstetrician opinion is necessary.

Elderly

Diagnosing and managing the UTI in elderly is challenging because of limited history and typical symptoms may not be present or not well communicated. Bacteriuria and pyuria along with nitrite positive are indicative of active infection. Initiation of antibiotics in elderly needs caution. IV antibiotics are required in UTI with sepsis or altered sensorium. Oral antibiotics should be carefully prescribed in those elderly who can be discharged home. Nitrofurantoin is usually the first choice but must be avoided in renal insufficiency.

DISPOSITION

Majority of patient of uncomplicated and few of complicated UTI can be discharged home. Pyelonephritis patient with fever, vomiting, dehydration, and hemodynamic instability need hospitalization for stabilization with IV fluid, antibiotics, antiemetics, later they can also be discharged with close follow-up.

SUMMARY

Being an emergency physician, based on clinical symptoms, history, and examination do appropriate evaluation for UTI. Use antibiotic as per hospital antibiogram and local resistant pattern. Summary of empirical use of antibiotics is given in **Table 3**. With increasing resistance pattern, it is necessary to follow recent guidelines for management of such cases.

TABLE 3: Summary of empiric antibiotic therapy in UTI.

Condition	*Antimicrobial agents*	*Dose/route*	*Duration of therapy*
Acute uncomplicated UTI	Nitrofurantoin	100 mg/oral twice/daily	5 days
	TMP-SMX	160–800 mg 1 DS/oral/twice daily	3 days
	Fosfomycin trometamol	3 g/oral	One dose
	Ciprofloxacin	500 mg/oral/twice daily	7 days
	Levofloxacin	750 mg/oral/once daily	5 days
	Amoxicillin-clavulanic acid	500–125 mg oral thrice daily	3–7 days
	Cefpodoxime	100 mg/oral/twice daily	7 days
	Cephalexin	500 mg/oral/twice daily	7 days
	Cefaclor	500 mg/oral/three times daily	7 days
	Cefuroxime	250 mg/oral/twice daily	7–10 days
Pyelonephritis (outpatient)	Ciprofloxacin	500 mg/oral/twice daily	7 days
	Levofloxacin	750 mg/oral/once daily	5 days
	Cefpodoxime	200 mg/oral/twice daily	10–14 days
	TMP+SMX (DS)	160–800 mg 1 DS/oral/twice daily	10–14 days
	Amoxicillin-clavulanic acid	875–125 mg oral thrice daily	10–14 days
	Ceftriaxone	1 g/IM or IV	One dose
	Ciprofloxacin	400 mg IV	One dose
	Gentamycin	5 mg/kg IM or IV	One dose
Pyelonephritis (inpatient)	Ciprofloxacin	400 mg IV	Every 12 hourly
	Levofloxacin	500 mg IV	Every 24 hourly
	Ceftriaxone (± aminoglycoside)	1 g IV	Every 12 hourly
	Gentamycin (± ampicillin)	5 mg/kg IV	Every 24 hourly
	Piperacillin-tazobactam (± aminoglycoside)	3.375 g IV	Every 6 hourly
	Meropenem	2 g IV	Every 8 hourly

(DS: double strength; IM: intramuscular; IV: intravenous; TMP-SMX: trimethoprim-sulfamethoxazole; UTI: urinary tract infection)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Penile Emergencies

Puneet Ahluwalia, Devendra Richhariya

INTRODUCTION

The penis is a very sensitive organ in the body and even minor discomfort or injury to penis compels the patient to consult the physician either in outpatient or in emergency department. Emergency physician should be aware of the penis-related conditions and emergencies because delay intervention may lead ischemia and necrosis of the penis. Emergency physician should be able to manage ischemic priapism, phimosis, paraphimosis, entrapment (zipper) injury, and penile fracture. Any penile trauma should be considered as an emergency until proven otherwise. This chapter includes various penile complaints in adults, with emphasis on the most serious (penile fracture) and common conditions such as phimosis, paraphimosis, balanitis, and posthitis.

ANATOMY

The penis consists of the paired corpora cavernosa, or erectile bodies, that lie dorsal to the corpus spongiosum (**Fig. 1**). The corpus spongiosum surrounds the penile urethra. The corpora cavernosa and corpus spongiosum are wrapped in a thin connective tissue layer, the tunica albuginea. The glans is the distal head of the penis. The distal foreskin, or prepuce, in uncircumcised men lies over the glans and can be retracted proximally to expose the glans. The coronal sulcus distinguishes the glans penis from the penile shaft.

PRIAPISM

Priapism is defined as prolonged erection of the penis, generally lasting >4 hours, in the absence of sexual desire or stimulation. This medical condition was named after Priapus, an ancient Greek god of fertility and horticulture who was endowed with oversized genitalia. Ironically, one cause of priapism is prolonged effects of erectile dysfunction medications, making a pleasurable emulation of Priapus a painful one. More than one-third of patients with severe priapism may experience permanent erectile dysfunction despite treatment, resulting in obvious infertility or other emotional or functional sequelae.

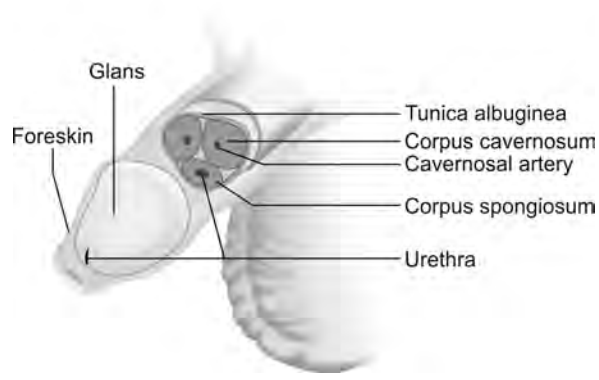


FIG. 1: Anatomy of the penis.

Etiopathogenesis

Priapism can be divided into two main categories. Ischemic priapism, also known as low-flow priapism, is the most commonly seen variant and is caused by painful venous engorgement of the corpora cavernosa and requires emergency treatment. Nonischemic (high-flow) priapism is rare and is often painless. It is caused by increased arterial inflow to the penis from traumatic arterial-cavernosal fistulae and does not require urgent treatment. Ischemic priapism can be considered as a compartment syndrome of the penis. The corpora cavernosa become engorged with stagnant, oxygen-depleted venous blood from either an intraluminal obstruction of venous blood flow or an inability of the penile muscle tissue to adequately contract and augment venous outflow. The causes of ischemic priapism are multiple and varied (**Box 1**).

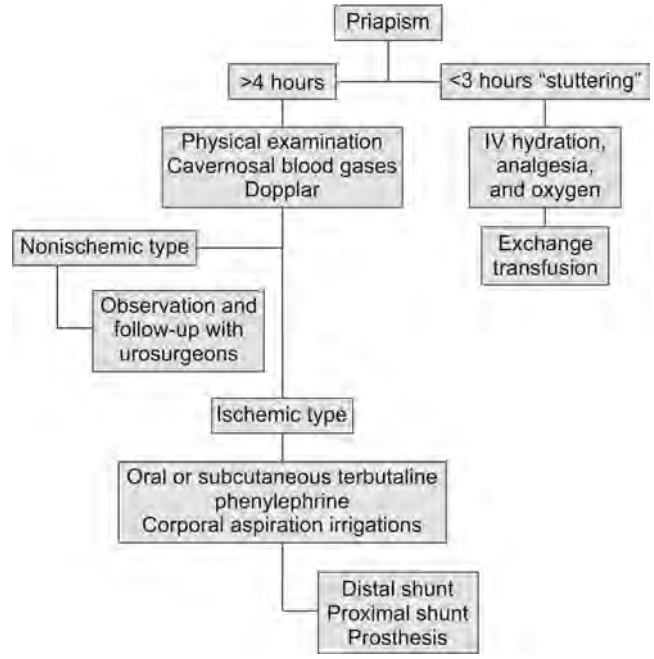
Differentiating Ischemic and Nonischemic Priapism

Evaluation of the patient with priapism may involve several steps before a final cause can be identified. *Patient history* can help differentiate between ischemic and nonischemic priapism. Ischemic priapism is painful, nontraumatic,

BOX 1: Causes of ischemic priapism.

- *Medications*
- Impotence agents; intracavernosal therapies (prostaglandin E1, papaverine, and phentolamine); and oral agents (i.e., sildenafil)
- *Antihypertensives*: Hydralazine, prazosin, doxazosin, and α-adrenergic blocking agents such as tamsulosin
- *Antidepressants*: Trazodone, fluoxetine, sertraline, and citalopram
- Antipsychotics (phenothiazines) and atypical antipsychotics (ziprasidone)
- *Substance abuse*: Cocaine, marijuana, and alcohol
- *Others*: General anesthetics, hydroxyzine, metoclopramide, omeprazole, anticoagulants, testosterone, immunosuppressants (e.g., tacrolimus), and total parenteral nutrition
- *Hematologic disorders*
- Sickle cell disease, leukemia, and myeloma
- *Central nervous system*
- *Brain*: Cerebrovascular accident
- *Spinal cord*: Spinal stenosis, spinal cord injury, lumbar disk herniation, cauda equina syndrome, spinal disk disease, epidural anesthesia, and neurosyphilis
- *Hip arthroplasty*: Presumably caused by intraoperative nerve injury
- *Others*
  - Infections, malaria, and rabies
  - Toxins—scorpion
  - Carbon monoxide and idiopathic hypertriglyceridemia

and may be associated with a history of priapism, hemoglobinopathy, or vasoactive drug use, whereas nonischemic priapism is typically painless and caused by traumatic injury. Patients with ischemic priapism often present shortly after onset of symptoms because of pain, whereas patients with nonischemic priapism may present after several hours or days of symptoms. On physical examination, ischemic priapism will present with a rigid penile shaft but soft glans. Patients with nonischemic priapism will often have a partial erection, but the entire penis, including the glans, will be firm. The presence of the *"peisis sign",* which is partial or complete resolution of the erection during compression of the perineum, may also help support the diagnosis of nonischemic priapism. Any patient presenting with the first episode of priapism and who is not known to have sickle cell disease should have a sickle cell preparation and a complete blood cell count, regardless of ethnicity. *Aspiration of the corpora cavernosa* is helpful in distinguishing ischemic from nonischemic priapism. The blood gas of ischemic priapism will be grossly dark in color and have a pH < 7.25, a partial pressure of oxygen (PaO_2) < 30 mm Hg, and a partial pressure of carbon dioxide (pCO_2) > 60 mm Hg. In contrast, corporal blood gas from nonischemic priapism will appear much closer to normal arterial blood gas, typically with a pH > 7.30, PaO_2 > 50 mm Hg, and pCO_2 < 40 mm Hg. Finally, *color duplex ultrasound* of the penis and perineum may be useful in assessing for the presence or absence of blood flow through the cavernosal arteries. Absent blood flow will confirm the diagnosis of ischemic priapism. Normal or increased blood flow will support the diagnosis of nonischemic priapism. *Arteriography* may be indicated for nonischemic priapism, but it is often performed when embolization treatment is planned rather than as an initial diagnostic modality.



FLOWCHART 1: Treatment summary of priapism.

Management

A urologic surgeon typically manages treatment of acute priapism. However, treatment for ischemic priapism will frequently need to be initiated in the emergency setting while awaiting specialty consultation **Flowchart 1**.

The classic teaching is that the initial treatment—*oral (or subcutaneous) terbutaline a ß2-adrenergic agonist,* is thought to increase venous outflow from the engorged corpora through relaxation of venous sinusoidal smooth muscle. Terbutaline has an unproven benefit. If terbutaline fails to work rapidly, the next step in the treatment of priapism is *corporal blood aspiration*, saline irrigation, and injection of α-adrenergic receptor agonist such as dilute phenylephrine. Phenylephrine should be diluted in normal saline to a concentration of 0.1–0.5 mg/mL, and 1-mL injections made every 3–5 minutes for 1 hour. Lower concentrations in smaller volumes should be used in children and patients with severe cardiovascular disease. Use of a preprocedural penile block is essential. In addition to the treatment directed at acutely relieving the symptoms, other underlying causes, if they exist, should be treated. For example, patients with sickle cell disease may benefit from intravenous fluids and supplemental inhaled oxygen. Certainly any potentially offending medications should be discontinued.

Treatment of stuttering priapism includes *preventative daily antiandrogen therapy*, such as cyproterone acetate, or gonadotropin-releasing hormone drugs, such as leuprolide, which paradoxically reduce the frequency of priapism but do not inhibit sexual activity. A promising new treatment is daily treatment with low-dose inhibitors of the enzyme phosphodiesterase type 5. These agents may reduce cellular nitric oxide action and decrease vasodilation, thus reducing erection duration. However, even patients with stuttering priapism may require emergency treatment for typical ischemic priapism in the setting of particularly severe symptoms or a markedly prolonged erection.

Surgical shunt procedures are used as a last resort in patients with low-flow priapism unresponsive to the aforementioned treatments, regardless of the precipitating cause of ischemic priapism. Treatment of nonischemic priapism requires less urgency. No risk of long-term damage is associated with the absence of immediate treatment and, although the condition is distressing, pain is not a prominent feature**.** *Conservative therapies*, such as rest, ice packs, and observation for several days, will help resolve the inciting arteriovenous fistulae in >60% of cases. If conservative management fails or is otherwise nonfeasible**,** *embolization is the next step***.** Embolization has >90% success rate in treating priapism, but still nearly 10% of patients may have erectile dysfunction after this procedure**.** *Surgical ligation of the cavernosal artery* or ligation of the fistula may be required if embolism fails. However, after ligation, close to half of patients experience erectile dysfunction. Alternative methods to treat nonischemic priapism include *injection of thrombin or methylene blue into the corpora cavernos*a in an effort to occlude the arteriovenous fistula, but these should be considered less favored alternatives to embolization.

ZIPPER INJURY AND PENILE ENTRAPMENT

Zipper injuries are more common in children than adults. Often the patient is uncircumcised and the foreskin gets caught and crushed when the zipper is closed. Lubricants such as mineral oil can be used to free the skin from the zipper, but this does not always work. Cutting the median bar of the zipper will separate the zipper, allowing the two sides of the zipper to fall apart. The median bar is the small piece of metal that connects the anterior and posterior plates of the zipper. A bone or wire cutter is needed to divide the median bar (**Figs. 2A** and **B**). If these tools are unavailable, another method is to grasp opposite sides of the zipper, one inferior and one superior to the site of zipper entrapment, and slowly separate the teeth by pulling in opposite directions. Local anesthesia is recommended before using this method.

If these methods fail to release the entrapped foreskin, emergent partial or complete circumcision to separate the prepuce from the zipper may be necessary. Glans edema mimicking paraphimosis can occur in circumcised or uncircumcised men in penile entrapment injuries. In these instances, external objects may constrict the mid to distal shaft, leading to the same pathophysiologic derangements seen with paraphimosis. Objects may either be placed intentionally for sexual stimulation or may occur sporadically, as in the case of a hair tourniquet in male infants. Hair tourniquets may be particularly difficult to diagnose, because the offending hair may be nearly invisible within an engorged and edematous coronal sulcus. An occult hair tourniquet should be considered, along with testicular torsion, in male infants who are crying inconsolably. In adolescent or adult men, rings or other constricting bands may be used for self-stimulation or to maintain an erection.

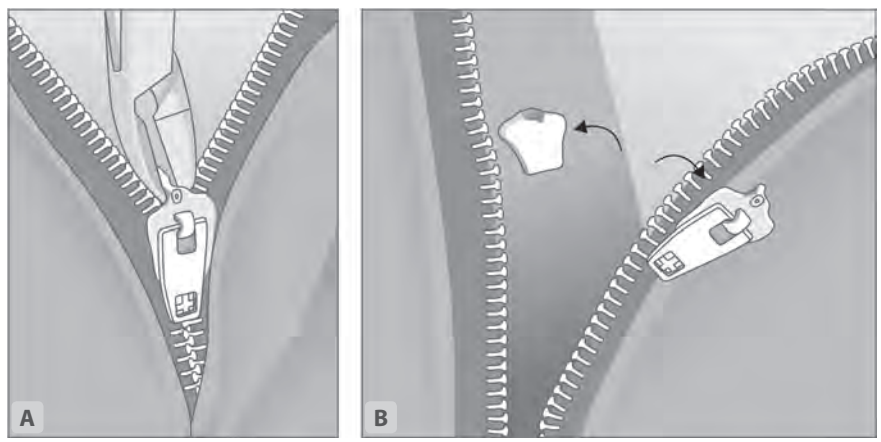
Depending on the object and degree of entrapment and distal edema, release may be challenging. Occasionally, constricting objects may be removed without the need for cutting or sawing. One method is the string method. Similar to that used to remove a ring from a finger, a flat string is passed under the ring so that it protrudes proximally. Then the distal end of the string is wound around the penis and when the proximal end of the string is pulled up and distally, with luck the ring will move distally, little by little, until it is removed. Glass saws may be helpful for removing glass bottles, but plastic bottles are not easily cut by a glass saw or scalpel. Rather, an oscillating cast saw is recommended for an entrapped plastic bottle.

Using a splint device, such as a wooden tongue depressor blade, between the bottle and the skin of the penis is recommended. Metal devices may be removed with ring cutters, but may require heavy equipment such as pneumatic saws used by fire department personnel to extricate victims from crushed automobiles. One challenge in using these machines is that the skin entrapped under the device must be protected from the blade.

In some cases, aspiration of blood from the entrapped corpora cavernosa may relieve enough edema so that a protective device can be placed before engaging the saw. Because a great deal of heat is often generated from these saws, continuous irrigation of the area with cold water or saline is also necessary to protect the penis from thermal injury. Time is critical when removing entrapped objects. With prolonged duration of entrapment, ischemia or gangrene of the distal penis may occur, in the most severe cases placing the penis at risk for possible amputation. This surgical cure is invasive and skin grafting is frequently necessary to close the wounds.

BALANITIS AND POSTHITIS

Balanitis is inflammation of the glans penis, and posthitis is inflammation of the penile foreskin. Often both the glans and foreskin are inflamed, *termed balanoposthitis*. Glans or prepuce



FIGS. 2A AND B: Zipper removal.

inflammation is often caused by infection. Uncircumcised men are at risk for developing infection because the tight foreskin, together with poor hygiene and smegma build-up, creates an environment conducive to the development of inflammation. Patients with this condition typically complain of a red, edematous glans or foreskin, often with discharge. Determining the causal agent may be challenging. *Candida albicans* is the causal agent in nearly one-third of balanitis cases. The typical findings of candidiasis are erythema and papules with "satellite" lesions. Burning and pruritus may also be present. Candida can be contracted from sexual activity with an infected partner. Diabetic patients or other immunosuppressed patients are at risk for candida balanitis or posthitis. Treatment with topical azole antifungal agents and effective hygiene typically is sufficient, but in severe cases a single oral dose of 150 mg of fluconazole may be necessary. Other common infectious causes include streptococcal and staphylococcal species, which typically require oral antimicrobial treatment. Sexually transmitted diseases, including chlamydia and syphilis, may also cause balanitis and posthitis. Therefore, cultures or other diagnostic testing for suspected causal agents may be necessary to help guide treatment. Balanoposthitis may be complicated by phimosis, cellulitis of the penile shaft, or abscess formation. Noninfectious causes of balanoposthitis occur less frequently overall, yet remain important considerations. Contact dermatitis may occur from condoms, spermicidal, or lubricating gels associated with condom use. Lichen planus is an inflammatory dermatosis that affects only the glans (balanitis), causing itchy red and whitish plaques. It is treated with high-potency topical steroids. Balanitis xerotica obliterans (BXO) is a rare condition of unknown origin that causes chronic inflammation of the glans, dry skin, and pruritus, and may be associated with endarteritis.

PEYRONIE'S DISEASE

Peyronie's disease was first reported in 1743. It is a connective tissue disorder in which plaques or scars form in the tunica albuginea, resulting in penile pain, induration, palpable plaques on the shaft that cause abnormal curvature of the erect penis, and ultimately erectile dysfunction. The characteristic scar formation can occur after major trauma and minor "microtrauma" during intercourse. In many cases, patients will not recall any distinct precipitating traumatic event. Patients with Peyronie's disease are thought to have a genetic predisposition for abnormal scar formation. Patients should be referred for nonurgent urologic surgery follow-up. Typical therapies range from tocopherol (vitamin E) pills to plaque injections with interferon alpha.

PENILE CALCIPHYLAXIS

Penile calciphylaxis is a rare disorder. Patients may present with severe penile pain from ischemia caused by calcification and fibrosis of the penile arteries. In its most extreme form, it may progress to gangrene, requiring penectomy. The underlying cause is often secondary hyperparathyroidism associated with end-stage renal disease. Affected patients may also have concurrent calciphylaxis of the limbs. Emergency urologic surgical consultation is needed for infection or necrosis requiring debridement.

PHIMOSIS

Phimosis is the condition in which a narrowed prepuce (foreskin of penis) cannot be retracted over the glans penis. It is derived from a Greek word *"phimos"* which means "muzzle". At birth almost 96% of male newborns have phimosis which resolves over time, so that normal retractable prepuce is seen in around 50% by the end of 1st year, 90% by 3 years, and in 99% by 14 years of age.

Etiology

Phimosis can be divided into physiological and pathological (true) phimosis.

Physiological (Primary) Phimosis

During neonatal development, the inner epithelial lining of prepucial skin is attached to the underneath glans. These naturally occurring adhesions and narrow prepuce inhibits retractability of prepuce over glans leading to physiological phimosis. As the child grows, epithelial debris get formed and accumulated under the prepuce causing its separation from glans (**Fig. 3**). This along with intermittent erections of penis leads to normal retractable foreskin, over the variable period of time ranging from birth to 18 years of age or may rarely be even more. However, around 2% individuals may not achieve this normal retractability even throughout their lives.

Pathological (Secondary) Phimosis

The pathological or true phimosis is due to scarring of distal prepucial skin (**Fig. 4**). The various reasons for such scarring could be poor hygiene leading to recurrent balanitis (inflammation of glans penis) or posthitis (inflammation of prepucial skin). Even overzealous attempts of forceful retraction of prepuce in physiological phimosis may lead to microtears, bleeding, inflammation, and healing with scarring.

The incidence of pathological phimosis is around 0.4 per 1,000 boys per year, much lesser compared to physiological. Another causative factor for pathological phimosis is BXO, a penile form of lichen sclerosus et atrophicus. BXO is a chronic inflammatory condition with unknown etiology affecting skin and mucous membrane, especially prepuce, glans penis,

FIG. 3: Phimosis in a child. ***(For color version, see plate 12)***

FIG. 4: Phimosis in an adult. ***(For color version, see plate 13)***

meatus, and distal urethra, accounting for the most common cause of secondary phimosis in children.

Clinical Presentation

It is important to differentiate between physiological and pathological phimosis as the treatments for both are different.

In physiological phimosis, the child is usually brought by anxious parents but the child himself may not be having any bothersome complaints, except for nonretractability of foreskin or ballooning of foreskin during voiding. The local symptoms, such as pain, swelling, and redness are absent. Urinary flow is good. This is contrary to pathological phimosis in which child may present with preputial pain and irritation, local infections leading to swelling and redness of skin, minor bleeding and sometimes dysuria, and recurrent episodes of urinary tract infections (UTIs). The parents may notice poor urinary stream, especially in cases with associated BXO. Few grading classifications according to the severity of phimosis have been proposed by various authors (**Box 2**).

BOX 2: Grading (classification) of phimosis based on severity.

Meuli et al. grading of phimosis

Grade 1: Fully retractable prepuce and stenotic ring in the shaft

Grade 2: Partially retractable prepuce with partial exposure of the glans

Grade 3: Partially retractable prepuce with exposure of only meatus

Grade 4: No retractability

Kikiros et al. grading of phimosis

Retractability of foreskin Score:

0. Full retractability, not tight behind glans, or easy
1. Full retraction of foreskin, tight behind the glans
2. Partial exposure of glans, prepuce (not congenital adhesions) limiting factor
3. Partial retraction, meatus just visible
4. Slight retraction (neither meatus nor glans can be visible)
5. Absolutely no retraction

Appearance of foreskin Score:

0. Normal
1. Crack in prepuce, "skin-splitting" on gentle retraction
2. Small white scar, partial circumferential
3. Balanitis xerotica obliterans or severe scarring ± bleeding

Evaluation

Phimosis is a fairly obvious clinical condition, requiring no specific laboratory tests or imaging modalities for diagnosis.

History

Though usual presenting complaint is ballooning of prepuce during voiding, a detailed history of all associated symptoms is vital in ruling out the likely complications.

History should also include episodes of recurrent fever, stream of micturition, and urinary problems.

Physical Examination

In physiological phimosis, the distal prepucial skin is healthy, pliant with typical pink mucosa seen pouting or flowering on gentle traction. However, in pathological phimosis, on gentle traction, there is abnormal scarring of prepuce and a cone-shaped structure is seen with a narrow white fibrotic ring at the tip. This clinical differentiation is very vital so as to avoid anxiety in parents and unnecessary surgical procedures.

Treatment

First and foremost thing in management of phimosis is to confirm whether, it is physiological or pathological. Management depends on age of child, type and severity of phimosis, and associated complications. Once it is confirmed that the phimosis is physiological, the most important thing is to reassure parents about the normalcy of the condition. Parents should be taught about the care of foreskin.

Treatment of phimosis can be divided into nonsurgical or conservative and surgical treatment. Though traditionally circumcision is considered as the standard treatment for phimosis, many topical ointments have been tried in recent years with a good success rate. In few recent trials, it was shown that only 8–14.4% of the total referrals had actual pathological phimosis requiring surgical intervention. Rest all could be managed conservatively and thus over-referrals could have been avoided.

Topical Preparations

Various topical preparations have been tried till date in form of steroids, estrogen, and nonsteroidal anti-inflammatory drugs (NSAIDs). Among these, steroids have been most widely used and have shown more promising outcomes.

Topical Steroids

Many studies in past few decades have shown a favorable success rate of topical steroid therapy, ranging from 70% to 95%, as shown in **Box 1**. The mechanism of action of topical steroids is believed to be local anti-inflammation and immunosuppression. They also reduce the dermal synthesis

of glycosaminoglycans, epidermal proliferation and stratum corneum thickness thereby causing skin thinning. *Most commonly used preparation is betamethasone 0.05% twice daily for a period of 4 weeks*. Other concentrations of betamethasone such as 0.1% and 0.06% have also been tried with almost similar success rates. Other steroids such as clobetasol propionate, triamcinolone, mometasone dipropionate, and fluticasone showed comparable results (**Table 1**).

Very few studies have mentioned the recurrence rates because of the short follow-ups in rest of the studies. The reported recurrence rate ranges from 2 to 14%, poor compliance being the most common reason. Almost all studies, who have reported the recurrence, have observed success after retreatment for few more months with same agent, and therefore reduction in need for circumcision.

Prepucial Stretching

The nonsurgical adhesiolysis by frequent manual retractions of prepuce has found to be a safe and effective treatment option for phimosis regardless of the age of the boy. Combination of topical steroids along with stretching adds to the improvement of overall outcome.

Surgical Treatment

Circumcision

Male circumcision is one of the oldest surgical procedures known to humans. It is also one of the most commonly performed surgical procedures worldwide to the extent that approximately 37–39% of men are circumcised worldwide.

Though sometimes treatment of phimosis is as per the parent's preference, the absolute indication of circumcision is secondary phimosis. However, circumcision may be indicated in some cases of primary phimosis such as recurrent balanoposthitis and recurrent UTIs, especially in patients with urinary tract abnormalities. The contraindications for circumcision are an acute local infection and congenital anomalies of the penis, like hypospadias, where the foreskin should be preserved as it may be helpful for a future reconstruction. Following techniques are used for circumcision.

- *Circumcision using devices*: Various devices are available nowadays for circumcision. *Gomco clamp* is a 4-piece device, designed with a structure which protects the glans, provides hemostasis, and does not require any additional suturing. In this method, glans is exposed by retracting the prepuce and adhesiolysis, followed by placement of a metal bell over the glans to protect it from damage. The prepucial skin is repositioned back over the bell and circumcision is done with a scalpel. The compression by an outside ring over the bell achieves the hemostasis. *Plastibell* is a device which works on a similar principle except that instead of an outer ring, a thread is tightly tied over a plastic bell covering the prepuce which achieves hemostasis. The skin sloughs after few days and Plastibell falls off. Another device named *Mogen clamp*, is applied across the stretched prepucial skin, after ensuring that the glans is free below the clamp. The hemostasis is achieved by the compression by the V-shaped clamp. The anesthesia for all these devices is usually regional, i.e., penile block. The complications are usually because of the technical factors and include injury to glans, insufficient or excess skin removal or asymmetric redundancy of skin and sometimes bleeding due to improper clamping.

TABLE 1: Role of various topical steroid in phimosis.

Author, year	*Number*	*Topical agent*	*Duration*	*Success rate*
Wright, 1994	139	0.05% betamethasone	1–2 months	80%
Golubovic, 1996	20	0.05% betamethasone	1 month	95%
Chu, Chen, and Diau, 1999	276	0.06% betamethasone	2 weeks	95%
Monsour, 1999	25	0.05% betamethasone	1 month	95%
Orsola, Caffaratti, and Garat, 2000	137	0.05% betamethasone	1–2 months	90%
Ashfield, 2003	228	0.1% betamethasone	6 weeks	87%
Yang, 2005	70	0.06% betamethasone valerate or clobetasone butyrate 0.05%	4–8 weeks	81.3% for betamethasone and 77.4% for clobetasone
Jorgensen and Svensson, 1993	54	0.05% clobetasol propionates	1–3 months	70%
Lindhagen, 1996	30	0.05% clobetasol propionate	1–2 months	89%
Pileggi and Vicente, 2007 Double-blind study	110 (56 mometasone, 54 placebo)	0.1% mometasone furoate versus placebo	8 weeks	88% with mometasone, 52% placebo
Esposito, 2008	240	Mometasone furoate 0.1% versus placebo	4 weeks	65.8% for mometasone and 16.6% for placebo
Letendre, 2009 randomized, double-blind, placebo controlled	43	0.1% triamcinolone versus placebo	2 months	76% with triamcinolone and 39% placebo
Zavras, 2009	1,185	0.05% fluticasone propionate	1–2 months	91.1%
Muller and Muller, 1993	30	0.1% estrogen	20 days	93%
Yanagiswa, 2000	15	Estrogen	2–8 weeks	87
Atila et al., 1997	32	Diclofenac sodium	1 month	75%

- *Free-hand circumcision*: This is done in operation theatre preferably under general anesthesia or penile block and includes excision of phimotic prepuce and suturing after hemostasis.
- *Sleeve technique*: In this technique, first a circumferential incision is marked on the outer prepucial skin, equidistant from corona. The inner prepuce is separated from glans by adhesiolysis using artery forceps. The prepucial inner mucosa is separated from the skin. The foreskin is excised preserving the mucosa, and remaining prepuce closed with absorbable sutures after achieving hemostasis.
- *Dorsal-ventral slit technique*: In this type, after initial adhesiolysis, two slits are taken, one on dorsal and one on ventral aspect and then these incisions are connected circumferentially, leaving the two free-edges which are then closed with absorbable sutures.
- *Preputioplasties*: Over the years many prepuce-preserving techniques have been described in literature: V-flap, Z-flap repair, triple incision plasty, limited dorsal slit, multiple Y-V plasty, and triple T. All have claimed their technique to be a better alternative to circumcision, especially for the patients who do not want their glans exposed. However, no comparative trial has been done to recommend their routine use in clinical practice. In short, the choice of surgical procedure depends upon surgeon's expertise and patient's/parent's preference.

Complications of circumcision: As complications can happen in any surgical procedure, circumcision is no exception. In one large systematic review of complications of circumcision, Weiss et al. found that the median frequency of any adverse event and any serious adverse event was 1.5% (range 0–16%) and 0% (range 0–2%), respectively. They also found that complications occurred more frequently in circumcision for older children than in neonates and infants.

- *Early complications*: By and large the complications of circumcision procedure are usually minor and treatable such as bleeding, surgical site infection or swelling, and inadequate skin removal. Other serious early complications include excessive bleeding, chordee, iatrogenic hypospadias, necrosis of glans, and amputation of glans. The excessive bleeding during or after circumcision, requiring blood transfusion, may occur in children with bleeding disorders like hemophilia. Therefore, it is very important to ask regarding any family history of such disorders before surgery.
- *Late complications*: These include chordee, epidermal inclusion cysts, excess redundant foreskin, prepucial adhesions or skin bridges, iatrogenic hypospadias recurrent phimosis, buried penis, suture sinus tracts, urethrocutaneous fistulae, and meatal stenosis. Most of these are treatable but require an additional surgical procedure, indicating the importance of proper operative technique.

A meta-analysis to assess sexual functions following adult male circumcision has concluded that the circumcision does not have any adverse effect on sexual function or penile sensitivity when compared with uncircumcised men.

Medical benefits of circumcision: Most of the studies in literature showed that uncircumcised males were more prone to sexually transmitted diseases such as syphilis, chancroid, herpes simplex, and human papillomavirus (HPV), whereas circumcised men were more prone to urethritis. Few randomized controlled trials (RCTs) done in African patients have shown protective effects of circumcision against human immunodeficiency virus (HIV) with almost 50% risk reduction.

There is no direct causal association of phimosis with penile carcinoma. However, indirect benefit by reduction in HPV infection, which is a causative factor for penile carcinoma, may be expected. Still routine neonatal circumcision to prevent penile carcinoma is not indicated.

The protective effect of circumcision against UTIs may be seen only in cases of recurrent UTIs and children with congenital urinary tract abnormalities such as high-grade vesicoureteral reflux.

Phimosis is the nonretractability of prepuce over the glans penis. Most of the newborns have phimosis due to natural adhesions between prepuce and the glans, and this is physiological and as the child grows he achieves normal retractability over a variable period of time. Secondary phimosis is a pathological condition, which must be differentiated clinically from primary phimosis. While primary phimosis can manage conservatively or by manual stretching and topical steroids, secondary phimosis definitely requires some form of treatment mostly surgical. There are various forms of treatment options available. The topical steroid applications along with repeated manual stretching of prepuce are quite safe and have a good success rate. The absolute indication for circumcision is pathological phimosis (BXO) or sometimes primary phimosis with recurrent balanoposthitis or UTIs. Various devices are now available for circumcision with almost equal success rates as conventional free-hand circumcision and with comparable complication rates. Complications associated with circumcision procedure are usually minor and treatable. Medical benefits offered by circumcision include protection against some sexually transmitted disease including HPV, HIV, and against recurrent UTIs, especially in cases of congenital urinary tract anomalies.

PARAPHIMOSIS

Paraphimosis is a urological emergency in which foreskin is left retracted due to its entrapment behind the glans penis. This leads to strangulation of glans and lymphovascular compromise of the prepuce leading to venous engorgement, inflammation, pain, and even necrosis, further impending the reduction of foreskin.

Etiology/Causes

The cause is most often iatrogenic. It occurs when the foreskin is retracted for urethral catheterization, penile examination, or during per urethral procedure like cystoscopy or meatal dilatation. Failure to reposition the retracted foreskin back over glans results in paraphimosis. Less commonly it may be due to trauma during sexual intercourse or self-inflicted injuries.

Pathophysiology of the Condition

When retracted foreskin remains trapped behind glans penis prolonged time, the blood and lymphatic flow to and from prepuce and glans is obstructed. This leads to vascular engorgement and subsequent edema of prepuce. Paraphimosis is a urological emergency which, if left untreated, may ultimately result in glans necrosis and rarely autoamputation.

Clinical Presentation

Though paraphimosis can occur in any age group, its incidence is lesser in young children (0.2%) compared to other penile lesions such as balanitis (5.9%) and phimosis (2.6%). Most common occurrence is in adolescent males with 1% incidence in all adult males above 16 years of age. The preceding event in adults is usually a Foley catheter insertion and in children, a forceful retraction of foreskin for examination or for cleaning. Whatever may be the reason, failure to return the retracted foreskin to its normal position over the glans remains the main culprit. Patient presents with a swelling in foreskin, usually with pain. The diagnosis is often confirmed on physical examination of prepuce and the glans, both of which are markedly edematous and congested. The proximal penile shaft usually remains unremarkable. The reduction of prepucial skin becomes difficult and painful due to the swollen prepuce and constricted band of edematous tissues behind the glans (**Fig. 5**).

Evaluation

History and Physical Examination

A detail history should be taken concerning foreskin retraction, urethral instrumentation, or presence of urinary symptoms. The external genitalia should be examined in detail with a focus on the color and consistency of the glans and prepuce, the severity of constriction around the penile corona and condition of proximal penile shaft. Though glans remains pink healthy in most of the cases, long standing cases may have dark red, dusky or even black glans indicating its ischemic necrosis. The viability of glans can also be confirmed by its palpation, as normal healthy glans is soft and pliable and becomes firm and inelastic after necrosis.

Treatment

The main aim of treatment of paraphimosis is reduction of preputial and glans edema and restoration of prepuce to its original position. There are many different methods of reduction of paraphimosis as described below.

Manual Reduction

Manual reduction method may be tried in mild, early, and uncomplicated cases. Because of the pain which gets further aggravated during manipulation, it may require some form of anesthesia such as topical lignocaine gel, oral narcotics, penile nerve block, or sedation. Manual reduction is done by giving circumferential compression over edematous prepuce and glans with gloved fingers in order to disperse the edema fluid. The reduction can simply be achieved by pulling the foreskin upwards towards the phallus, while maintaining the circumferential compression. Application of ice packs may also facilitate in reducing the edema; however, some surgeons discourage this method as it may further compromise arterial inflow to the already ischemic portion of the penis. Manual compression can also be achieved by tightly wrapping a compressive elastic dressing around edematous portion of the penis from the glans towards the base for 5–10 minutes.

FIG. 5: Paraphimosis in a child. ***(For color version, see plate 13)***

Pharmacological Therapy

Another way of reducing the preputial edema is application of mannitol (20%) soaked gauze around prepuce for a period of 30–45 minutes, with or without intermittent compression. This works on the principle of transfer of edema fluid from edematous prepuce down the osmotic gradient to hypertonic mannitol, reducing the edematous swelling. In another reported technique, Eutectic Mixture of Local Anesthetic (EMLA) cream containing 2.5% lidocaine and 2.5% prilocaine is applied to the glans in a glove covering for around 30 minutes and trapped foreskin can then be reduced with gentle traction. Injection of hyaluronidase (1 mL of 150 U/cc) also helps in reducing the edema. Hyaluronidase degrades the viscous hyaluronic acid and thereby increases the dispersion of edema fluid.

Minimally Invasive Therapy

This includes the most widely practiced method of multiple puncture technique, also known as Perth–Dundee technique. In this method, multiple (approximately 20) punctures with 26-gauge needle are made in edematous prepuce and the prepuce is then compressed to express out the edema fluid. As this is a painful method, it requires some form of anesthesia usually topical or penile block. Once the edema has subsided with the help of above described methods, paraphimosis can be reduced. For this, both the thumbs are placed on glans and rest all fingers are wrapped around the trapped prepuce. A gentle steady force is applied by thumb over glans along with countertraction achieved by constant pulling of prepuce outwards back over the glans.

Surgical Treatment

Surgical intervention is required when above described methods have failed to reduce the paraphimosis. This involves longitudinal dorsal slit cutting of prepuce at 12 O'clock till constricting band site and reduction of trapped prepuce back over the glans. The cut edges are over sewn with absorbable suture without approximating them. Circumcision is usually the last resort done reserved for recurrent episodes.

Paraphimosis is a urological emergency in which foreskin is left retracted due to its entrapment behind the glans penis causing inflammation, strangulation of glans. It usually occurs after failure of prompt repositioning of foreskin after its retraction. Urgent medical attention is necessary to avoid further damage which may even cause ischemic necrosis of glans in long-standing cases. Paraphimosis can occur in any age group. The diagnosis is clinical, no tests are required. The treatment options include manual reduction,

compression dressing, multiple puncture technique, dorsal slit and lastly circumcision. Patients should be taught regarding the reduction of foreskin every time it is retracted.

PENILE FRACTURE

Penile fracture is defined as disruption of the tunica albuginea with rupture of the corpus cavernosum secondary to trauma to penis in tumescent state. Penile fracture usually occurs during vigorous sexual intercourse or an aggressive manipulation of penis in an erect state. This is a urological malignancy and the rupture may extend to involve corpus spongiosum and urethra. The first case of penile fracture was reported by an Arab physician, Abu al-Qasim al-Zahrawi in Cordoba, more than 1,000 years ago.

Epidemiology

The incidence of penile fracture varies among different geographical areas, with higher incidence in Middle East and African regions compared to Western countries or Asian continent. The incidence of penile fracture is under reported as patients avoid to seek medical attention due to embarrassment. The reported incidence is around 1 in 175,000. The age distribution also varies in different geographical areas with mean age in Africans 26.4 years, in Asians 33.7 years, in Europeans 38.7 years, and in North Americans 37.6 years with a range of 12–82 years.

Etiology/Causes

Overall, the most common cause of penile fracture is the blunt trauma during a vigorous sexual intercourse, when the erect penis slips out of the vagina and hits the perineum or pubic bone, giving rise to a buckling injury. Again, causative factors differ according to the region. Trauma during sexual intercourse is more common cause in Western countries while in Middle East countries common causes include penile manipulations including kneading during masturbation, forceful bending of a tumescent penis during masturbation in order to achieve sudden detumescence known as "Taghaandan maneuver", or even tucking the erect penis into underwear. Taghaandan maneuver alone is responsible for >50% of cases in Middle East countries, while it accounts for only 8% of cases in Western population. Other reported causes are fall from bed during sleep on an erect penis, roll over injury during nocturnal tumescence, sudden change of position by female partner while an erect penis is still inside vagina causing its acute bend. "Woman on top" or reverse coitus is reported to be the riskiest position causing fracture penis.

Pathophysiology of the Condition

Tunica albuginea is a bilaminar structure covering both the corpora cavernosa. In flaccid state, the thickness of tunica albuginea is 2 mm, which decreases to 0.25–0.5 mm in tumescent state. It also has a high tensile strength which can resist intracavernous pressures up to 1,500 mm Hg. However, when erect penis is bent abnormally, there is sudden rise in intracavernosal pressure exceeding the tensile strength of the tunica albuginea. This leads to rupture of already thinned tunica, most commonly at ventrolateral aspect which is the thinnest part of tunica albuginea. The rupture of tunica albuginea is usually unilateral and transverse, involves overlying corpus cavernosum and may extend to corpus spongiosum and urethra. After penile fracture, penis becomes detumescent suddenly and a local hematoma develops over penile shaft confined by Buck's fascia. When Buck's fascia is disrupted, this hematoma may spread to the scrotum, perineum, and suprapubic region.

Clinical Presentation

Patient typically presents with a history of a cracking or popping sound in erect penis followed by immediate detumescence and development of pain and swelling in penis. Blood at tip of meatus, hematuria, and acute urinary retention give the hint of associated urethral rupture. Urethral injury incidence also varies region to region, with United States and Europe (20%) having higher incidence compared to Middle East and Asia (3%), may be related to the cause of trauma (intercourse related versus self-inflicted). Due to embarrassment, patients usually do not present to emergency room or present very late.

Evaluation

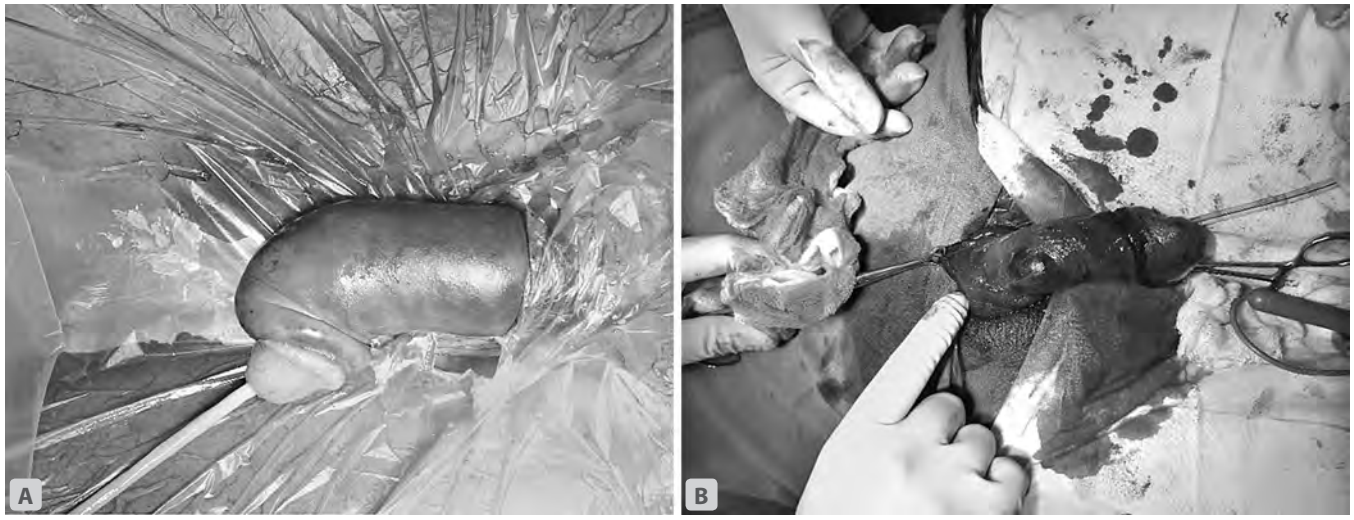
History and Physical Examination

Diagnosis of penile fracture is a clinical one with history and physical examination playing important role in establishing it. In history, one should ask regarding the time and type of trauma, presence of sudden detumescence, and presence of blood at tip of meatus, hematuria or any voiding disturbance.

On inspection, the most common finding is presence of penile swelling due to *penile hematoma*, bruising and deviation to one side, giving *an "eggplant" appearance, also* known as *"aubergine sign"* (**Figs. 6A** and **B**). The deviation of swollen penis is opposite to the side of tear, because of the mass effect of hematoma. This defect can sometimes be palpable with a blood clot over it and can be rolled under the fingers—known as *"rolling sign"*. A butterfly hematoma in perineum suggests rupture of Buck's fascia or associated urethral injury. Rest physical examination remains unremarkable. Patients late after trauma usually have present with erectile dysfunction, penile curvature, palpable plaques like Peyronie's disease and rarely urethrocutaneous or urethrocavernous fistula. Differential diagnoses include rupture of penile vessels (superficial or deep dorsal vein, dorsal or deep cavernous artery), lymphangitis of penis and Mondor's disease.

Investigations

Though the diagnosis of penile fracture is made clinically, few radiological investigations help in confirmation of diagnosis, to locate the exact site of tear and to diagnose-associated complications. Penile ultrasound is the preferred modality as it is readily available in emergency, cheap, noninvasive, and useful in locating exact site of tear and in ruling out fracture in suspicious cases. In case of clinical suspicion of urethral injury, retrograde urethrography can be done before surgery. However, because of possibility of inaccuracy and its time-consuming nature, on table flexible cystoscopy just before catheter placement is preferable. Magnetic resonance imaging and cavernosography are not routinely used because of the high expenses, limited availability, and time-consuming nature.



FIGS. 6A AND B: Examination of penile fracture. (A) Eggplant appearance of penile fracture; (B) Hematoma on ventrolateral aspect. ***(For color version, see plate 13)***

Treatment

Treatment can be conservative or surgical. Conservative approach may be advocated in cases of intact tunica on imaging but strong clinical suspicion. It includes cold fomentation, anti-inflammatory agents, fibrinolytics (trypsin and streptokinase), and antiandrogens (like stilboestrol, to prevent erections). However, conservative approach is not recommended because of the long-term complications such as corporeal fibrosis, delayed chordee with resultant shaft deformation (in up to 16% of cases), and plaque formation (in up to 50% of cases). Many studies and reviews of literature have shown that prompt surgical is associated with fewer complications and better long-term results in terms of erectile function compared to conservative treatment.

Surgical Approach/Surgical Repair

The most common and preferred approach is subcoronal circumferential incision with degloving of penis. Apart from being cosmetic, this allows surgeon for complete inspection of corpora and helps in identifying extra, small corporal, and urethral tears. Other reported incisions are longitudinal incision directly over the site of tear, inguinoscrotal and high scrotal midline raphe, though experiences with last two incisions are limited. The choice of incision is operator dependent.

Technique

Many surgical approaches have been described in literature. However, the surgical principles remain more or less universal, which includes identification and evacuation of hematoma and ligation of torn vessels, debridement of devitalized tissue, and repair of lacerations of the tunica albuginea (**Figs. 7A** and **B**). Though debridement of lacerated tissue is important, care must be taken to avoid excessive debridement of delicate and normal erectile tissue. Tunica tears are usually transverse and located ventrolateral where the tunica is thinnest, however laceration can occur at any site. Small or nonapparent tears can be localized by intracorporeal injection of normal saline and thereby inducing artificial penile erection (also known as Gittes test). This test also helps in confirming the integrity of repair.

Suture Material

Intermittent or continuous repair with absorbable sutures (2-0 or 3-0) is recommended by most of the surgeons worldwide. Though repair with nonabsorbable sutures provide equally good results, it may result in painful palpable knots. This problem can be solved by taking inverted knots.

Urethral Injury Repair

In cases of clinically suspected urethral injury, retrograde urethrography, ultrasonography, or preferably flexible urethroscopy should be done. However, in many cases (almost 50%) urethral injury can be clinically nonevident and be found intraoperatively. Partial urethral tears can be over sewn with fine absorbable sutures over a urethral catheter. Complete urethral disruption requires proper debridement, mobilization, and tension-free repair over a Foley catheter.

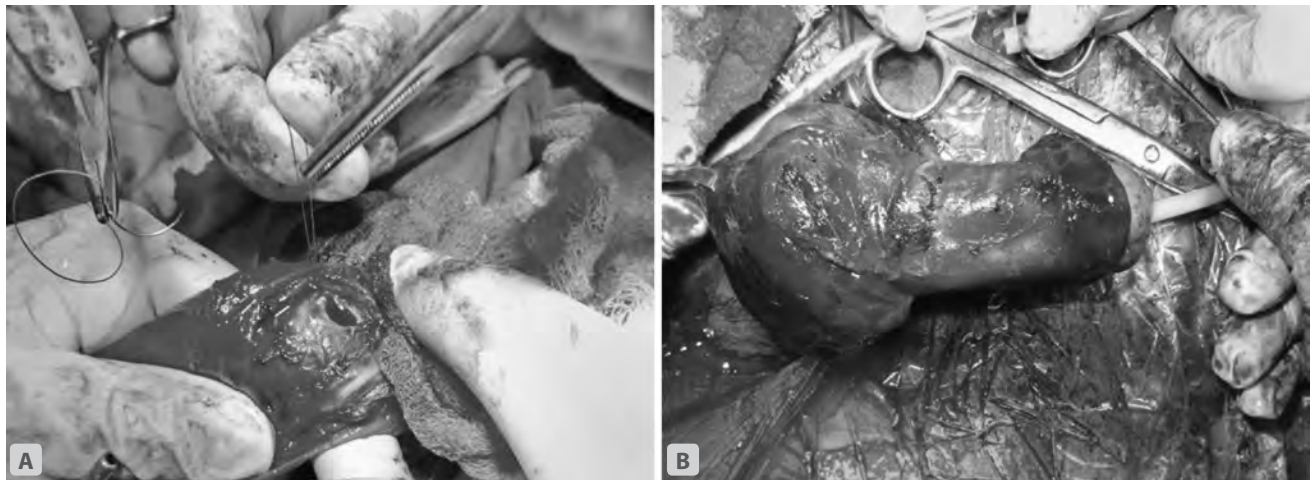
Timing of Surgical Repair

It has been shown in some of the reports and reviews from the literature that prompt repair is associated with good functional results compared to delayed repairs. However, timing of repair does not significantly affect rates of erectile dysfunction and penile plaque formation. Therefore, cases presenting even after few days should not be denied for surgical repair as they can have a good functional results in long-term. The dressing should be loose so that glans can be checked for early ischemic color changes. Patient should be instructed to avoid sexual activity for a period of 4–6 weeks to allow complete healing of the repair. A patient should be educated about the predisposing factors so to avoid recurrence. He should be instructed to avoid vigorous sexual intercourse, aggressive sudden penile manipulations, and unusual positions of intercourse like reverse coitus.

Complications

Long-term complication rates after a surgical repair are not very high. Reported complications include penile deviation due to fibrosis, skin necrosis, painful erections, and rarely erectile dysfunction.

Penile fracture is rupture of tunica albuginea due to trauma to penis in a tumescent state. Common causes vary geographically and include aggressive sexual intercourse,



FIGS. 7A AND B: Surgical correction of penile fracture. (A) Closure of tunica tear in process; (B) After completion of closure. ***(For color version, see plate 13)***

forceful penile manipulations, fall from bed, or roll over injury during nocturnal tumescence. Though the diagnosis is clinical imaging like ultrasound gives better idea on the number and site of tunica tear. Once diagnosis is confirmed, patient should be offered surgical repair at earliest and patients presenting even after few days should also be treated in same way. Surgical principles include evacuation of hematoma, identification and repair of tunica tear with running or interrupted absorbable sutures, and repair of associated urethral injury. Long-term results are better in surgical repair group compared to conservative. However, no significant difference in erectile function could be found in early versus delayed treatment. So all patients should be offered surgical management, irrespective of time between fracture of penis and presentation to hospital. Reported long-term complications include penile curvature, skin necrosis, painful erections, and rarely erectile dysfunction.

SUMMARY

As an organ of central importance to both the urologic and reproductive systems, penile emergencies have the potential to lead to significant morbidity for patients. Although there is generally considered to be a defined set of pathologies affecting the penis in the acute setting, recognition and prompt diagnosis of these conditions often can be challenging for clinicians. Because of the organ's anatomy and physiology, failure or even moderate delays in identifying these acute conditions may result in permanent dysfunction and morbidity. In the broadest sense, penile emergencies can fall into one of two major categories: Physiologic (relating to the venous outflow) or anatomic (relating to pathologies of the organ's complex tissue structure). Specific disease states include priapism, penile calciphylaxis, paraphimosis, phimosis, balanitis, posthitis, Peyronie's disease, and penile tourniquet syndrome.

Penile emergencies most commonly result from pathologic processes related to the unique anatomic structure and physiologic function of the organ. As the organ itself is essential for excretory and reproductive function, its pathologies can lead to devastating morbidity and in some cases mortality. Even with prompt diagnosis and treatment, penile emergencies can lead to permanent organ dysfunction. Prompt diagnosis, management, and urologic consultation are essential for having the best chance of minimizing sequela of these conditions.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Acute Scrotal Emergencies

Devendra Richhariya

INTRODUCTION

Scrotal emergencies, however uncommon, can be life and fertility threatening. Testicular torsion, Fournier gangrene, and scrotal trauma are all considered emergent urologic conditions. These conditions need to be separated from the wide differential diagnoses presenting as acute scrotal pain to the emergency department. Diagnosis of testicular torsion is time sensitive. Testicular torsion has a >90% salvage rate if surgery is performed within the first 6 hours of symptom onset. After 6 hours, there is a time-dependent increase in the rate of testicular atrophy and orchiectomy. It is important to establish the diagnosis early and advocate for definitive management with urology colleagues.

ANATOMY

Knowledge of the relevant anatomy is important to understand the differential diagnosis and subsequent steps in the evaluation (**Fig. 1**). The testes are ovoid-shaped organs roughly 3–5 cm and vertically-oriented. The tunica albuginea covers them with continuous internal septations converging into a mediastinum tests which acts as the structural support for the organ. This, in turn, is enveloped by the tunica vaginalis. Epididymis is a curved structure roughly 6–7 cm in its longest dimension and posterolateral to the testis. The efferent ductules converge to form the ductus epididymis and eventually the vas deferens.

The vascular anatomy of the scrotal contents is also important to know. The testes receive a supply of blood from the testicular artery, deferential artery, and the cremasteric artery. Deferential artery and the cremasteric artery are branches of the inferior vesical and inferior epigastric artery, the testicular artery branches directly from the abdominal aorta. The testes are drained into the testicular vein via the pampiniform plexus. The testicular vein drains directly into the inferior vena cava on the right while it drains into the left renal vein on left. The vascular structures, vas deferens, and nerves are all encased within the spermatic cord, a conduit allowing passage from the peritoneum to the scrotum through the inguinal canal. The cremaster muscle is also found within the spermatic cord. Only small part of the testis and epididymis is surrounded by the tunica vaginalis and then attaches posteriorly to the scrotal wall. Here one should be aware about the congenital deformity known as the bell clapper deformity (incidence 12%) in which tunica vaginally surrounds the testis and part of the spermatic cord; the testicle is failed to fixed with the scrotal wall and able to twist freely and prone for the torsion (**Fig. 2**).

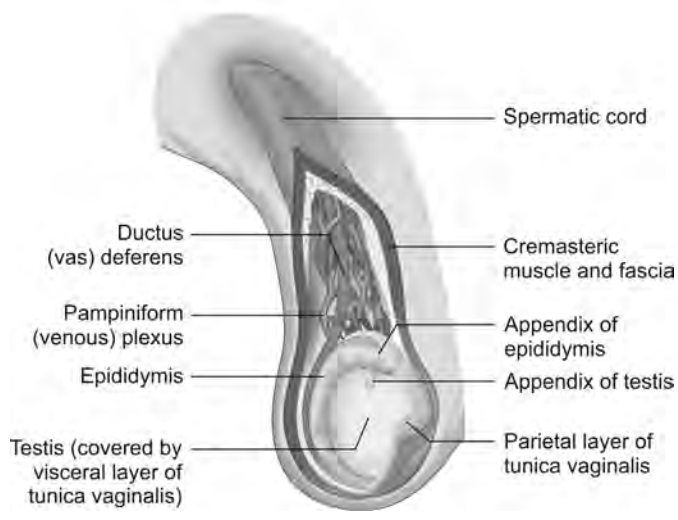

FIG. 1: Anatomy of scrotum.

ETIOLOGY OF ACUTE SCROTUM

An acute scrotum is defined as acute pain of the scrotum. Pain is typically accompanied by local signs, such as swelling or tenderness, and/or generalized symptoms, such as vomiting or fever. There is a large differential diagnosis for acute scrotal pain. True emergencies should be separated from urgencies. True urologic emergencies include testicular torsion, Fournier gangrene, and testicular trauma. Other abdominal emergencies to keep in mind that may present as scrotal pain include, but are not limited to, an incarcerated inguinal hernia, appendicitis, or referred pain from an abdominal aortic aneurysm. Torsion should be differentiated from appendage torsion and epididymitis, whereas Fournier gangrene should be ruled out in infectious presentations of scrotal pain, including scrotal cellulitis and scrotal abscesses. In the setting of trauma, it is important to identify penetrating trauma and

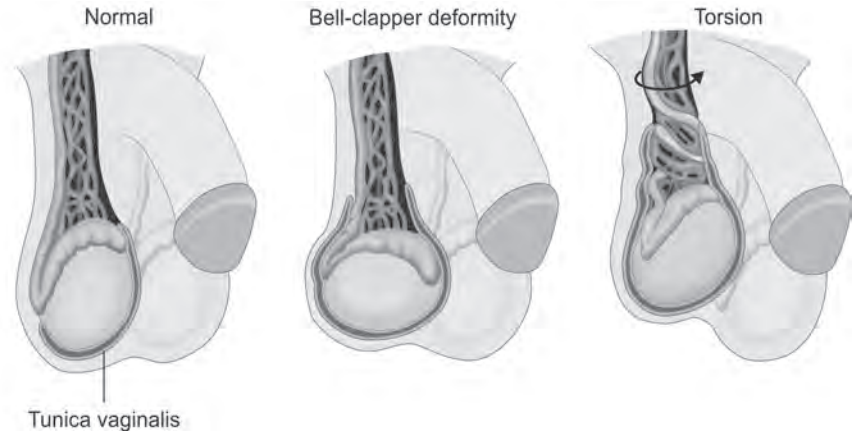

FIG. 2: Demonstration of normal testis, bell clapper deformity, and testicular torsion.

TABLE 1: Differential diagnoses for acute scrotal pain.	
Ischemic	Testicular torsion, torsion of the testicular appendage
Infectious	Epididymitis, epididymo-orchitis, orchitis, scrotal cellulitis, scrotal abscess, Fournier gangrene, Hansen disease, and filariasis
Traumatic	*Blunt*: Testicular contusion, testicular rupture, penetrating, testicular rupture, hematocele, and scrotal DE gloving
Inflammatory	Henoch–Schönlein purpura
Idiopathic	Idiopathic scrotal swelling
Oncologic	Testicular tumors
Other	Strangulated/incarcerated inguinal hernia, referred pain from abdominal pathology, for example, ruptured abdominal aortic aneurysm or nephrolithiasis

testicular rupture from simple testicular contusions. **Table 1** summarizes the list of the differential diagnoses for acute scrotal pain.

The presentation of an acute scrotum can be broken down into four subcategories: *The painful swollen testicle, the painless swollen testicle, the erythematous testicle, and the traumatic testicle.* Within each of these groups there is a diagnosis that cannot be missed. However, not all scrotal emergencies present with pain in the genital area. It is important to rule out scrotal emergencies in patients presenting with lower abdominal pain.

PAINFUL SCROTUM

Testicular Torsion

Testicular torsion occurs when the spermatic cord twists causing venous congestion, decreased arterial blood flow and eventually ischemia of the testicle. *There are two types of torsion: extravaginal and intravaginal*. Extravaginal torsion occurs in the perinatal period, it occurs with twisting of the entire tunica vaginalis. It may present as a vanishing testicle or painless swollen hemiscrotum. Intravaginal torsion is the twisting inside the tunica vaginalis, occasionally as the result of a *congenital bell clapper deformity***.** The deformity occurs when the testicle is not fully fused to the posterior scrotal wall. This results in the testicle being suspended horizontally, which predisposes it to torsion. This deformity is estimated to be present in approximately 12% of men. Testicular torsion can occur at any age, although it is most common at two peaks in life: During the first year of life and around puberty (12–18 years old). Testicular torsion generally presents as acute onset scrotal pain with associated nausea or vomiting. It can occur after minor trauma or during periods of testicular growth (i.e., puberty); however, it usually occurs in the absence of a preceding event. It is important to keep in mind that intermittent torsion may also precede complete torsion. Testicular torsion can often be hard to differentiate from appendage torsion and epididymitis. There are two features of the clinical history that have been shown to increase the likelihood of diagnosis. Presence of nausea and/or vomiting and <24 hours since the onset of pain have both been proven to be associated with testicular torsion more often than the latter diagnosis. One study demonstrated that, in patients with acute scrotal pain from testicular torsion, the presence of nausea and vomiting had a specificity of 93% and a sensitivity of 69%. Thus, in the setting of acute scrotal pain, systemic symptoms of nausea and vomiting make testicular torsion more likely.

In all cases of scrotal pain or lower abdominal pain in boys or men, a thorough genitourinary examination should be performed to assess for scrotal swelling, tenderness to palpation, location of tenderness, vascular swelling, discoloration, erythema, drainage, or warmth.

There are several *physical examination findings* that increase the likelihood of testicular torsion being the source of the painful scrotum. Multiple studies found that *abnormal cremasteric reflex and high position of the testicle* were more commonly found in patients with testicular torsion. The cremasteric reflex is defined as ipsilateral elevation of the testicle after stroking of the medial thigh. If absent, torsion may be more likely; however, if present, this by no means rules out torsion. The reflex can be absent in a significant percentage of normal men, as well as in those with upper and lower motor neuron disorders, spinal cord injuries, or nerve injuries after hernia repair. Absence of the cremasteric reflex has been shown to have a negative predictive value of 98%, meaning if the reflex is present, torsion is less likely. Another helpful physical examination finding *is anterior rotation of the epididymis*, which was found to have a 98% specificity in testicular torsion. Elevation of the testicle and transverse location of the testicle also had high negative predictive values of 95%.

When testicular torsion is suspected, a *wide-based gait* may be seen, because patients try to avoid leg contact with the tender scrotum. In perinatal torsion, it is possible that the contralateral side may also be torsed, without evidence or abnormal findings on clinical examination. Combination of history and physical examination can help narrow the diagnosis as well as differentiate between testicular torsion, torsion appendage, and epididymitis.

Appendage torsion: On examination, isolated superior pole tenderness has a strong correlation with torsion of the testicular appendage. Patients may also have the blue dot sign, which is visualization of the infarcted appendage through the scrotal skin appearing as a blue dot. This sign is pathognomonic for appendage torsion. **Table 2** presents comparison with testicular torsion and epididymitis.

Appendage Torsion

Appendage torsion, although not a scrotal emergency in itself, must be differentiated from testicular torsion. Appendage torsion is the twisting of a testicular or epididymal appendage, which is an embryologic remnant of the Müllerian ducts. Appendage torsion is usually seen in prepubertal boys 7–12 years old. Onset is acute to subacute. It is often difficult to differentiate appendage torsion from testicular torsion based on history because both groups may have acute onset testicular pain and swelling. However, patients with appendage torsion are less likely to have systemic symptoms, including nausea or vomiting (**Fig. 3**).

Epididymitis and Orchitis

Like appendage torsion, epididymitis and orchitis may present similarly to testicular torsion. Epididymitis and orchitis are inflammation of the structures within the scrotum. Epididymitis is inflammation of the epididymis, whereas orchitis involves the testicle. The most common cause of both is bacterial infection. The cause is generally broken down based on age group. In infants, epididymitis may be caused by sterile urine reflux secondary to a congenital anomaly. In children, a postviral infectious phenomenon is the most likely cause of the inflammation. Therefore, a careful history reviewing recent viral illness is important. In young boys under the age of 14 years, it is rare to have a bacterial cause. In young men under 35 years, the cause is most commonly sexually transmitted infection or complications from a sexually transmitted infection. In men over the age of 35 years, it is more commonly associated with benign prostatic hyperplasia. In the population of men who have sex with men, it is also important to consider *Escherichia coli* or fungal infections. Epididymitis may present with hemiscrotum pain and swelling, similar to testicular torsion or appendage torsion. It may also present with associated symptoms of abdominal pain, nausea, or vomiting. However, epididymitis, unlike testicular or appendage torsion, is more likely to present with dysuria and micturition complaints. Isolated orchitis is rare; it typically presents as a progression of epididymitis. When isolated, it is usually a result of a systemic viral infection (i.e., Coxsackievirus, Epstein–Barr virus, varicella, or echovirus). Mumps is the most common viral cause of orchitis. When the scrotum is involved, mumps presents as initial unilateral testicular involvement that later progresses to bilateral after 1–9 days. When the causative organism is bacterial, it is almost always epididymo-orchitis. Immunocompromised patients are also at risk of fungal infections.

On normal physical examination, the epididymis is found at the posterior-lateral aspect of the testicle. When palpated it feels soft and fleshy, similar to an earlobe. In epididymitis, the epididymis may be tender on palpation. Patients may not have testicular tenderness. The provider should also check for *Prehn sign*, which is relief of pain in the lateral recumbent position or with scrotal elevation. If orchitis is present, patients will have more testicular involvement, with increased testicular swelling and tenderness. Testicles should have a normal position in both disease processes (*see* **Table 2** for comparison with testicular torsion and appendage torsion).

Inguinal Hernia

In the differential diagnosis of painful scrotal swelling, it is important to consider an inguinal hernia. Inguinal hernias will not be elaborated further. It is mentioned here as a reminder

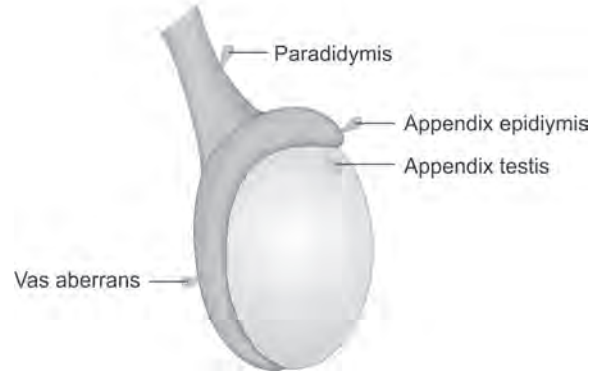

FIG. 3: Position of testicular appendage.

TABLE 2: Comparing testicular torsion, epididymitis, and appendage torsion.

History	*Testicular torsion*	*Epididymitis*	*Appendage torsion*
Age	Neonates and adolescents	Adolescents and young adults	Prepubertal
Pain onset	Acute	Gradual progressive	Acute to subacute
Associated symptoms	Nausea and vomiting	Dysuria	
Physical examination		Fever	
Cremasteric reflex	Absent	Present/absent	Present/absent
Testicles	Testicular swelling, progressive to diffuse hemiscrotal involvement, high riding, and transverse alignment	Epididymal swelling progressing to diffuse hemiscrotal involvement; normal position	Head of the affected testicle or epididymis; normal position

that the presentation of acute scrotal pain and swelling can be caused by pathologic conditions of the abdomen.

PAINLESS SWOLLEN SCROTUM

Hydrocele, Varicocele, and Spermatocele

Hydrocele is an accumulation of fluid around the testicle. It is the most common cause of painless scrotal swelling in children. The swelling is often more prominent while awake, standing, or crying. A varicocele is another cause of painless scrotal swelling. It most commonly occurs during puberty and on the left side due to a difference in venous drainage. A varicocele occurs when venous return from the scrotum is altered causing dilation of the spermatic cord veins, also known as the pampiniform plexus. Finally, a spermatocele can also cause painless testicular swelling. This occurs when a sperm-filled cyst arises in the epididymis.

On physical examination, hydrocele may be more prominent while awake, standing, or crying. It presents as posterior swelling behind the testicle. An otoscope can be used to shine light through the scrotal wall. A fluid-filled scrotum will allow light to shine through, whereas a thickened scrotal wall or enlarged testicle will not transilluminate. Varicoceles are often palpable on the posterior superior portion of the testes; often described as a "bag of worms". Finally, a spermatocele may feel like a painless cyst on the testicle. All painless masses should be differentiated from testicular malignancy.

Testicular Malignancy

Testicular malignancy is another cause of painless testicular swelling. However, this may be more easily distinguished from the above diagnoses on physical examination. It usually presents as an asymptomatic testicular mass. However, in rare cases, a mass may present with pain caused by acute bleeding within a tumor. Testicular malignancy generally presents as a firm nontender mass on examination.

ERYTHEMATOUS SCROTUM

Idiopathic Scrotal Edema

Idiopathic scrotal edema is a rare, self-limiting cause of an acute scrotum. It occurs between the ages of 3 and 9 years. It is defined as swelling of the scrotal skin without swelling of the deeper tissues. It is an important diagnosis to be aware of, because it needs to be differentiated from more malignant causes of scrotal edema and pain. Idiopathic scrotal edema generally presents as unilateral or bilateral scrotal swelling, erythema, and pain. It should be differentiated from scrotal abscess and deeper infections.

Scrotal Abscess and Fournier Gangrene

Scrotal infections can range from mild cellulitis to a surgical emergency, such as Fournier gangrene. Patients can develop superficial or deep infections. A scrotal abscess and cellulitis are examples of superficial infections. Scrotal abscesses are derived from simple hair follicles and only involve the scrotal wall. Deep infections involve deeper structures, such as the testes or epididymis. Fournier gangrene is a rapidly progressive polymicrobial necrotizing fasciitis of the perineal, perianal, or genital areas. Immunocompromised patients, particularly patients with a history of diabetes or alcohol abuse, are at higher risk for acquiring Fournier gangrene. The most important predictors of mortality are age >60 years or complications during treatment, such as need for mechanical ventilation or red blood cell transfusion.

Differentiating a scrotal abscess or cellulitis from Fournier gangrene may be difficult on first visualization. Patients may have overlying erythema or swelling. Crepitus and ecchymosis are common features in Fournier gangrene. Patients may also present with purulent discharge from the perineum or with fever. It is important to remember that fever may not always be present.

TRAUMATIC SCROTUM

Testicular Trauma

Isolated urologic trauma is relatively uncommon. It is more commonly found in patients with multiple traumatic injuries. Approximately 10% of all abdominal traumas also have a genitourinary injury. Traumatic injuries to the scrotum include blunt injuries, penetrating injuries, burns, bites, and scrotal avulsions. Blunt traumatic injuries may include scrotal hematoma, hematocele, testicular contusion, and complete testicular rupture. Scrotal hematocele occurs when the tunica vaginalis fills with blood, whereas disruption of the tunica albuginea is considered to be a ruptured testicle. Testicular rupture and penetrating injuries are true scrotal emergencies requiring surgical management. Testicular trauma commonly occurs playing sports or during motor vehicle accidents. Injury is more likely in motor vehicle accidents involving two-wheeled vehicles. Testicular dislocation is rare, but may occur with straddle injuries associated with motorcycle accidents. Half of all blunt testicular injuries occur while playing sports. Patients may present several days after blunt injury with symptoms similar to epididymitis. Traumatic epididymitis is a self-limiting inflammatory reaction after blunt trauma. Strangulation injuries, that is, entrapment in a zipper, are another source of testicular trauma. Zipper injuries more often occur in "impatient boys or intoxicated men". String, hair, or rubber bands can also cause strangulation injuries. In these cases, keeping child abuse on the differential is recommended. Scrotal trauma often presents with scrotal pain and swelling.

On examination patients may have scrotal discoloration or a tender, firm scrotal mass that fails to transilluminate. This could indicate a hematocele. An empty hemiscrotum in the setting of trauma is suggestive of testicular dislocation. In a patient with scrotal trauma, external signs may not correlate with internal injury. There should be high suspicion of testicular injury with any open wounds to the scrotum.

DIAGNOSIS

Aside from clinical diagnosis, ultrasonography is the diagnostic modality of choice for the presentation of acute scrotal pain. In general, ultrasonography is performed by a radiologist or ultrasonography technician; however, bedside ultrasonography by an emergency physician can also aid in diagnosis. Emergency physicians can accurately diagnose patients presenting with acute scrotal pain using bedside ultrasonography (**Box 1**). Ultrasonography is the diagnostic modality of choice when evaluating a painful scrotum. In

BOX 1: Bedside ultrasonography of the scrotum.

Positioning the patient: Use a sheet or towel under the scrotum to support the testicles. Have the patient hold the penis or position it superior laterally. Cover the penis for more privacy

Transducer: Use a linear high-frequency 6- to 15-MHz probe. Start the examination by asking where it hurts:

- First obtain a midline transverse view with both testicles, also known as the saddle view, with the indicator to the right of the patient. Look for decreased flow in the symptomatic testicle compared with the asymptomatic side:
  - Take transverse static color Doppler images of both testicles
  - Take a color Doppler clip to demonstrate flow
- Scan each testicle in the long axis (longitudinal plane) with the indicator to the head of the patient. The epididymis should be on the left of the screen and the testicle on the right
- Rotate the probe 90° with the indicator to the right of the patient for the transverse plane. Scan through the entire testicle. Make sure to scan both testicles
- Scan the spermatic cord in the longitudinal plane. Follow the cord from the testicle to the inguinal canal. Image the spermatic cord in the longitudinal and transverse planes; again, repeating on both sides. Look for the whirlpool or snail sign

TABLE 3: Testicular Workup for Ischemia and Suspected Torsion (TWIST) score.

History and physical presentation	*Points*
Testicular swelling	2
Hard testicle	2
Absent cremasteric reflex	1
Nausea or vomiting	1
High-riding testicle	1
High risk—7 points. 100% sensitive and specific for testicular torsion	

TABLE 4: Scrotal ultrasonography findings.

Scrotal conditions	*Ultrasonographic findings*
Testicular torsion	Absent or decreased flow in testicle, kink in spermatic cord (whirlpool, snail, or spiral sign)
Appendage torsion	Normal flow of the testicle with a hyperechoic area near the superior pole
Epididymitis	Increased or normal blood flow of testicle, sometimes a reactive hydrocele, enlarged epididymis with increased flow
Scrotal edema	Thickening of the scrotal wall, hypervascularity of the scrotum with normal appearance of the testicle and epididymis, i.e., Fountain sign
Fournier gangrene	Multiple echogenic foci (representing gas) with areas of dirty shadowing may be identified within the scrotal wall
Varicocele	Single vein diameter above 3 mm and/or >1 mm increase in diameter during the Valsalva maneuver or prominence of venous plexus
Hydrocele	Fluid collection separating the two layers of the tunica vaginalis
Testicular fracture	Hypoechoic, linear stripe without disruption of the tunica albuginea
Testicular rupture	Disruption of the homogeneous echogenic tunica albuginea

general, laboratory work and urinalysis are not helpful in the diagnosis of testicular torsion but may help with ruling in epididymitis. Ultrasonography findings consistent with testicular torsion include absent or diminished intratesticular blood flow in the symptomatic testicle when compared with the asymptomatic testicle, or evidence of spermatic cord torsion with a *"whirlpool or snail sign"*. Comparison of flow between both testicles is an important step in assessing for torsion. Imaging the spermatic cord to find a kink in the cord is more sensitive than color Doppler alone in adults and children.

More recently, researchers have been looking at a clinical scoring system to help diagnosis of testicular torsion. The Testicular Workup for Ischemia and Suspected Torsion (TWIST) score (**Table 3**) may help guide younger clinicians to the diagnosis of testicular torsion. In a validation study using the TWIST score among pediatric emergency physicians, a high TWIST score of 7 had a 100% specificity and 100% positive predictive value for testicular torsion.

Epididymitis and appendage torsion may be hard to differentiate on ultrasonography. Epididymitis generally appears with increased or normal color Doppler flow with an enlarged epididymis and sometimes a reactive hydrocele. Appendage torsion will appear to have normal flow, with an area of hyperechoic material near the superior portion of the testicle. Urinalysis may show pyuria in the setting of epididymitis.

The diagnosis of Fournier gangrene is primarily clinical. However, advanced imaging can be helpful if the diagnosis is not clear clinically. A computed tomography (CT) scan can play an important role in evaluating the extent of disease for surgical planning. CT findings may include fascial thickening, fluid collections, fat stranding, or subcutaneous emphysema. Ultrasonography may also be used in the early diagnosis of Fournier gangrene. On gray-scale ultrasonogram, the scrotal wall appears with multiple echogenic foci and areas of shadowing representing gas. Differentiating painless scrotal swelling is primarily clinical. However, ultrasonography can help confirm the diagnosis by identifying fluid-filled, vascular, or solid structures (**Table 4**).

TREATMENT

Painful Scrotum

As mentioned earlier in this chapter, testicular torsion is time sensitive. Manual detorsion can be attempted before surgical intervention but should not delay surgical intervention. *Trials of manual detorsion* have been found to decrease ischemia time. Even if the testicle is manually detorsed, surgery is still required. Surgical exploration is the definitive management for testicular torsion. Before performing manual detorsion, it must

be explained that the procedure is painful but, if successful, it will alleviate the pain. Analgesic medication, local analgesia injection (i.e., local lidocaine), or procedural sedation should be administered. Stand at the foot of the bed or to the right of the patient. Holding the testicle between the thumb and index finger, rotate it in an outward direction (like opening a book) from medial to lateral. The initial attempt should be with one and a half full rotations (540°). Relief of pain is a positive endpoint. You can also reassess with bedside ultrasonography. If the pain worsened with detorsion in the medial to lateral rotation, detorse in the lateral to medial direction, because a third of testicular torsions occur with medial-to-lateral rotation. After manual detorsion, patients still require emergent surgical intervention. The urologist will expose the scrotum in the operating room and examine the testicle for viability after detorsion of the spermatic cord. If viable, the testicle is sutured into the inner scrotal lining (also known as an orchiopexy). The noninvolved testicle is also sutured into the lining to prevent torsion. If the testicle is found to be nonviable, the patient will undergo unilateral orchiectomy.

Epididymitis treatment is based on age at presentation. For patients under the age of 14 years, treatment varies. If urine cultures are positive, some clinicians cover for urinary bacteria, whereas others conservatively manage without antibiotics. There should be follow-up with a pediatric urologist for evaluation of congenital genitourinary anomalies. For sexually active patients over the age of 14 years and younger than 35 years, antibiotics are the mainstay of therapy. The preferred treatment is ceftriaxone 250 mg intramuscularly plus doxycycline 100 mg daily for 10 days. If the patient practices anal penetration, use fluoroquinolone instead of doxycycline. The Centers for Disease Control and Prevention suggest levofloxacin 500 mg daily for 10 days or ofloxacin 300 mg twice daily for 10 days. For patients >35 years of age, single coverage with fluoroquinolone is appropriate. Adjuvants, including bed rest, ice, scrotal elevation, and nonsteroidal anti-inflammatory drugs (NSAIDs), can be helpful for symptom relief. Treatment of epididymo-orchitis is the same as described above. Isolated orchitis management is determined by the cause of the orchitis. If the patient seems to be suffering from toxicity, they may require admission; otherwise patients can have urologic follow-up in 5–7 days. Finally, management of appendage torsion solely consists of symptom relief. The same adjuvants used to treat epididymitis can be used with appendage torsion. The pain usually resides when the appendage degenerates in 1–2 weeks. It can recur depending on the number of appendages and their positions.

Painless Scrotal Swelling

After diagnosis of a hydrocele, varicocele, or spermatocele, the management is primarily with nonemergent urologic follow-up. With pediatric patients, the parents can be counseled that most hydroceles resolve by 18–24 months of age. With suspected testicular malignancy, the emergency clinician can start the workup with laboratory tests, including α-fetoprotein and β-human chorionic gonadotropin. These patients will need urgent urologic follow-up or even consultation while in the emergency department.

Erythematous Scrotum

Idiopathic scrotal edema is self-limiting. Episodes resolve in 1–4 days with symptom management: Scrotal elevation, rest, and NSAIDs. Scrotal abscesses can be treated similarly to abscesses on other areas of the body with drainage and antibiotic treatment. Depending on abscess location and clinical picture, surgical consultation may be necessary.

Fournier gangrene needs aggressive antibiotic therapy and surgical debridement. Like testicular torsion, Fournier gangrene is a true surgical emergency. Broad-spectrum antibiotics are recommended, but specific coverage for Fournier varies. Most articles, primarily case reviews and retrospective data, recommend broad-spectrum antibiotics, empirical coverage with piperacillin/tazobactam, and vancomycin. Ultimately, these patients need wide surgical debridement. Surgery is the definitive treatment. There is mixed evidence on hyperbaric oxygen as adjuvant therapy; most evidence comes from small retrospective studies or case reports, but they demonstrate some benefit or decreased mortality. All patients should be admitted to an intensive care unit because of the high mortality risk.

Traumatic Scrotum

Minor testicular trauma, such as contusions or zipper injuries, are managed conservatively with supportive care (ice, NSAIDs, scrotal support, and elevation), whereas major trauma is typically managed surgically (**Table 5**). If there is suspicion of testicular rupture recommendation is for scrotal exploration. Early exploration is associated with higher rates of testicular

TABLE 5: Scrotal trauma.

Condition	*Etiology/Presentation*	*Treatment*
Testicular dislocation	Significant blunt-force mechanism (dislocation to the abdomen or to subcutaneous tissues surrounding the external inguinal ring)	Surgical intervention
Testicular rupture	Disruption of the tunica albuginea	Surgical intervention
Testicular contusion	Intratesticular hematoma; intact tunica albuginea	*Typically, conservative*: Ice, rest, and elevation
Hematocele	Blood accumulation in the tunica vaginalis	Surgical drainage for large hematocele; conservative otherwise
Penetrating injury	Varies depending on cause	Typically, surgical exploration/intervention
Traumatic testicular torsion	Traumatically induced torsion has been reported	Surgical exploration/intervention

salvage. For penetrating injuries, surgical exploration is also recommended. More than half of all penetrating scrotal injuries have testicular involvement. For zipper injuries, there are several options for management. One technique is to use mineral oil. After local anesthesia, the clinician can use mineral oil on the zipper and surrounding skin to gently untangle the zipper from the skin. The clinician may also try using a wire cutter or bone-cutting pliers. Cut the diamond (or the median bar) of the zipper, which will cause the zipper to fall apart, freeing the skin.

SUMMARY

Although scrotal emergencies are rare within the emergency department, they can be life and fertility threatening. It is important to differentiate the surgical emergencies (testicular torsion, Fournier gangrene, and testicular trauma) from the less-urgent diagnoses of acute scrotal pain. Among the wide differential, it is imperative that the emergency physician identify the more concerning causes early to save lives and preserve fertility.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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Renal Transplant Related Complications

115 CHAPTER

Vishal Saxena, Yogeshman Anand

INTRODUCTION

Organ transplantation is one of the most common modalities of treatment in patients with end-stage organ failure. With increasing success, more and more numbers of patients are coming in the emergency departments (EDs) for transplantation-related complications. Solid organ transplant patients regarded as a special population in the ED. In this chapter, brief description on common problem following the kidney transplant and principles for the management of patients with renal transplantation in the ED has been discussed. Every complaint from a transplant patient should be carefully evaluated. When major complaints are present, knowledge of the initial physiological condition of the allograft can help to rule in or rule out possible organ failure. Even minor changes in allograft functioning can indicate organ failure. The duration of time since the organ transplantation should always be considered when evaluating the patient's condition. Complications related to organ transplantation can be categorized into four groups: (1) Anatomical, (2) Infection, (3) Rejection, and (4) Drug toxicity. All these categories should be considered in the differential diagnosis. However, the exact etiology may not be known until admission to the hospital for further evaluation. Therefore, every complaint from a transplant patient should be carefully evaluated.

HYPERTENSION FOLLOWING KIDNEY TRANSPLANT

Hypertension (HTN) occurs in 60–80% of renal transplant recipients. It is associated with increased risk of graft failure, all-cause mortality, and cardiovascular disease (CVD). Risk factors are: Transplant renal artery stenosis (TRAS), calcineurin inhibitors (CNIs) and steroids, delayed and/or chronic allograft dysfunction, presence of native kidney, obesity, and diabetes mellitus (DM).

Transplant Renal Artery Stenosis

It is presents as worsening or refractory HTN and/or unexplained graft dysfunction, heart failure (HF), and flash pulmonary edema. Risk factors are operative trauma, atherosclerosis of transplant renal artery or iliac artery, cytomegalovirus (CMV) infection, and delayed graft function (DGF). Diagnosis includes Doppler ultrasound (US) which has 87–94% sensitivity and 86–100% specificity; spiral computed tomography (CT); magnetic resonance angiography (MRA); and arteriography [risk of acute kidney injury (AKI) due to contrast or thromboembolism]. Treatment includes conservative therapy with angiotensin-converting enzyme (ACE) inhibitor; percutaneous transluminal angioplasty (PTA) ± stenting (can restore perfusion in 70–90% but may recur in up to 10%); and surgery, if PTA unsuccessful or stenosis inaccessible to PTA (successful in 63–92% but recurrence rate up to 12% and high risk of complications, should be reserved for refractory HTN).

The kidney disease: Improving Global Outcomes (KDIGO) suggests a blood pressure target of <130/80 mm Hg irrespective of level of albuminuria (**Table 1**). Reduced dietary sodium chloride intake should the first step.

SURGICAL AND UROLOGIC COMPLICATION

Background

Occurs in approximately 6% of renal transplants, most occur within first 6 months after surgery. Ureteral stents reduce incidence of urine leaks and obstruction, but may increase cost of transplant and require cystoscopy for removal 3–6-week post-transplant.

Urinoma/Urine Leaks: 1–3% of Transplants

Most common site of leak is ureter—bladder anastomosis, though leaks from midureter and renal pelvis also seen. It presents as renal failure accompanied by enlarging fluid collection (usually adjacent to allograft and bladder), chemical peritonitis and ileus are frequent, occasionally leakage from wound. It may only manifest as DGF or immediately after ureteral stent removal.

Diagnosis

- Sample of fluid collection is sent for electrolytes and creatinine. If urine leak, then creatinine and potassium will be higher than serum.

TABLE 1: Choices of antihypertensive drugs for postrenal transplant.	
Diuretics	• Low dose thiazide diuretic (12.5–25 mg) is reasonable for patients with CrCl > 25–30 mL/min • *Advantages are*: Inexpensive, reduces edema, do not alter glucose or lipid levels, decreases risk of hyperkalemia, and potentiates the effect of ACE and ARBs
Beta blocker	• Especially attractive for patients with ischemic heart disease (IHD) • *Relative contraindication*: Peripheral vascular disease (PVD), reactive airway disease, and hypoglycemic reactions
ACE/ARBs	• Reduces proteinuria, stabilizes the deterioration in renal function in chronic allograft nephropathy (CAN), cardiovascular benefit, reduces insulin resistance, and useful in post-transplant erythrocytosis • Causes decrease in GFR which may interfere with dx of acute rejection (especially in first 6 months post-Tx); can exacerbate hyperkalemia especially in patients on CNIs; and can exacerbate anemia • Wait 3–6 months post-Tx before starting ACE inhibitor or ARB, if indicated • Despite beneficial effects on proteinuria and HTN, no long-term benefit on graft, patient survival has been shown in RCTs
Calcium channel blockers (CCBs)	• May ameliorate vasoconstriction induced by CNIs • *Non-DHP CCBs (diltiazem and verapamil)*: Potent inhibitors of CYP3A4, cause ↑ plasma levels of TAC, CsA, and sirolimus; effect occurs in 48–72 hours; close monitoring of CNI or mTOR inhibitor levels is required
Vasodilator and alpha blockers	Also effective, may cause reflex tachycardia. Excessive hair growth with minoxidil

(ACE: angiotensin converting enzyme; ARBs: angiotensin-receptor blockers; CsA: cyclosporine; CNIs: calcineurin inhibitors; CrCl: creatinine clearance; GFR: glomerular filtration rate; HTN: hypertension; mTOR: mammalian target of rapamycin; non-DHP CCBs: nondihydropyridine calcium channel blockers; RCTs: randomized controlled trials; TAC: tacrolimus)

- Nuclear medicine renal scan can also be diagnostic in cases where fluid is inaccessible.

Treatment

The majority of urinary leaks require surgical correction. Distal leaks with minimal extravasation and clinical stability may respond to Foley insertion for 5–7 days.

Lymphocele: 1–16% of Transplants

It occurs due to inadequate ligation of lymph vessels near iliac vessels or hilum which leads to lymph collection. It accumulates between the transplanted kidney and bladder. Small lymphoceles are frequent, but usually asymptomatic. Larger collections present few weeks to months after transplantation. A bulge near the surgical wound sometimes with extravasation of lymph and edema of lower limb ipsilateral to the graft may be seen. Rarely, compressive symptoms such as urinary urgency or hydronephrosis and allograft dysfunction may occur.

Diagnosis

Renal US shows the collection with associated compressive effects. Fluid sampling is done to rule out urinoma (serum creatinine/potassium are similar to serum).

Treatment

- Expectant treatment for small lymphoceles
- Drainage or laparoscopic/open surgery (marsupialization) for larger and recurrent collections

Ureteral Stricture: 3–6% of Transplants

It is usually due to ischemia because of inadequate distal blood flow in ureter, though fibrosis from local BK virus replication and rejection is also a possibility. Risk factors are donor age, DGF, and abnormal vasculature. It also presents as renal insufficiency with hydronephrosis on US despite decompressed bladder. Diagnosis is made by renal US or CT urogram. If the diagnosis is uncertain, antegrade pyelogram needs to be performed. Treatment is decompression of collecting system with nephrostomy to reverse renal insufficiency and perform pyelogram. Stent placement can temporize, dilatation with stents or balloons are frequently ineffective with success rate of 28–80%. Most patients need surgical reimplantation.

Allograft Pyelonephritis: 10–15% of Transplants in First Year

It results due to reflux from surgical bladder anastomosis. Risk factors are female sex, diabetes, urinary tract infections (UTIs) prior to transplant, immunosuppression (IS), ureteral stent AKI, fever, pain over allograft, frequently history of UTI symptoms preceding allograft pain. Occasionally it is asymptomatic and is found on biopsy done for graft dysfunction. Diagnosis is made clinically and confirmed with urine culture. CT anteroposterior (AP) can suggest diagnosis but not specific as perinephric stranding is common after all renal transplant surgeries. Treatment is intravenous (IV) antibiotics and treatment is continued for 2–3 weeks. Patients with two episodes in 6 months or three episodes in 1 year should be investigated further by urology. Such patients may benefit from suppressive antibacterials, such as methenamine 1 g BID plus vitamin C. Pyelonephritis may predispose to subsequent rejection and recurrent episodes can lead to allograft failure.

Asymptomatic Bacteriuria: 35–40% of Transplants

Urinary tract infections and episodes of pyelonephritis frequently preceded by periods of asymptomatic bacteriuria but most do not progress to symptomatic disease. Randomized trials of treating asymptomatic bacteriuria have not been associated with reduction in UTIs, hospitalizations, or pyelonephritis.

INFECTION AFTER KIDNEY TRANSPLANTATION

Infectious complications occur in more than two-thirds of patients in the 1st year with UTIs and viral infections being the most common causes (**Table 2**). Infections are the second leading cause of death in transplant recipients. Risk factors for infection after transplant are donor-derived infections, prior and recent recipient exposures, prior and current IS regimens, and recent treatment for rejection.

CYTOMEGALOVIRUS INFECTION

Risk of CMV disease is related to donor/recipient serologic match: High-risk: D+/R–; intermediate risk: D+/R+, and D–/R+; low-risk: D–/R–. It is associated with increased risk of acute/chronic rejection, graft failure, Epstein–Barr virus (EBV)-associated post-transplant lymphoproliferative disorder (PTLD) and other opportunistic infections.

It presents as:

- *CMV syndrome*: Fevers, malaise, weight loss, diarrhea, arthralgias, leukopenia, thrombocytopenia, and transaminitis
- *Tissue-invasive disease*: Gastrointestinal (GI) [most common tissue-invasive disease in kidney transplant recipient (KTR); colitis > gastritis; CMV viral load may be negative; if clinical suspicion is high, need biopsy with staining for CMV], pneumonitis, nephritis, hepatitis, and retinitis

Prophylaxis

Valganciclovir (900 mg QD, adjusted for CrCl) significantly reduces risk of CMV post-transplant. Duration is minimum 6 months if high risk; 3 months if intermediate risk, consider 3 months if low risk.

Treatment

PO valganciclovir (900 mg BID, adjusted for CrCl) and IV ganciclovir (5 mg/kg q12, adjusted for CrCl) equivalent; consider IV if tissue-invasive disease or significant GI symptoms. Treat until viral load undetectable × 2 weeks, then start secondary prophylaxis. Consider dose reduction of antimetabolite during/after treatment of CMV.

TABLE 2: Timeline of common infections after kidney transplantation (KT).

<1 month	*1–12 months*	*>12 months*
• Wound infection • UTI • Dialysis access infection • *Clostridium difficile* colitis • Multidrug-resistant organisms: MRSA, VRE, and ESBL • Donor-derived infections (uncommon)	• BK polyomavirus • Herpes viruses: CMV, EBV, HSV, and VZV • PJP • *Cryptococcus*	• Community-acquired pneumonia • UTI • Fungal infections • Late reactivation of herpes viruses

(CMV: cytomegalovirus; EBV: Epstein–Barr virus; ESBL: extended spectrum beta-lactamase; HSV: herpes simplex virus; MRSA: methicillin-resistant *Staphylococcus aureus;* PJP: *Pneumocystis jirovecii* pneumonia; UTI: urinary tract infection; VRE: vancomycin-resistant enterococci; VZV: varicella-zoster virus)

Resistant Cytomegalovirus Infection

It occurs in 1–2% of KTRs. Risk factors for resistant CMV include D+/R– and longer duration of antiviral exposure.

Treatment

Cidofovir and foscarnet; mortality rate up to 11% in resistant CMV.

BK POLYOMAVIRUS INFECTION

Ubiquitous polyomavirus establishes latency in genito-urinary (GU) tract and can reactivate in setting of IS. BK viruria occurs in approximately 30%, BK viremia in 15–20%, and BK nephropathy in 1–10%. BK viruria can cause hemorrhagic cystitis [more common after hematopoietic stem cell transplantation (HSCT)] or irritative voiding symptoms. Only sign of BK viremia/nephropathy typically is increasing creatinine. Viral replication in urine and blood is most common in 1st year post-transplant. Risk factors are degree of IS (most important), old age, male gender, diabetes, Caucasian, ureteral stent, and donor/recipient serologic mismatch. Kidney biopsy shows intranuclear viral inclusions, interstitial infiltrates, and lymphocytic tubulitis (may be difficult to distinguish from acute rejection); immune staining is positive for SV40. Screening is done by BK virus polymerase chain reaction (PCR) in blood. It is done at minimum of 3 months interval in first 2 years, then annually through till 5th year. Screening should be resumed after treatment for rejection. Decrease in IS particularly antimetabolites, e.g., mycophenolate mofetil (MMF) and azathioprine (AZA) decreases risk of nephropathy and graft loss.

FUNGAL INFECTIONS POST-TRANSPLANT

Fungal infections in KTRs can prove fatal. *Aspergillus* and mucormycosis historically have been associated with high morbidity and mortality risk. The mainstay of treatment is marked reduction in IS. Survival has improved slightly when this is combined with newer antifungal agents. Given regional variations in endemic fungal prevalence, patient residence, and travel history need to be considered in the evaluation of a patient. Lifelong prophylactic fluconazole therapy is used by some transplantation centers to prevent coccidioidomycosis infections for patients residing in endemic areas. The presentation of coccidioidomycosis (valley fever) can be respiratory symptoms, joint infections, or disseminated disease with a characteristic rash.

ALLOGRAFT REJECTION

Acute renal allograft rejection is a major cause of allograft dysfunction. There are two principal histologic forms of acute rejection:

1. Acute T cell-mediated (cellular) rejection (TCMR), which is characterized by lymphocytic infiltration of the tubules, interstitium, and, in some cases, the arterial intima.

2. Active (acute) antibody-mediated rejection (ABMR), the diagnosis of which requires morphologic evidence of acute tissue injury, evidence of circulating donor-specific alloantibodies, and evidence of antibody-endothelial cell interaction (such as C4d deposition in the allograft).

Antibody-mediated rejection and acute TCMR may coexist at the same time in the allograft. Subclinical rejection is defined as the presence of histologic evidence of acute rejection on biopsy without an elevation in the serum creatinine concentration. Subclinical rejection is detected by a protocol, or surveillance, biopsy, which is obtained at a protocol-driven, prespecified time after transplantation or on detection of de novo donor-specific antibodies (DSAs) rather than for an indication such as allograft dysfunction. Most of the reports of subclinical rejection involve TCMR. However, there are reports of allografts with histologic manifestations of ABMR in the absence of functional deterioration of kidney function.

Calcineurin Inhibitor Nephrotoxicity

The CNIs, tacrolimus and cyclosporine, are used as part of a maintenance IS regimen in >90% of KTRs. While these agents are used to prevent acute rejection, they are associated with nephrotoxicity and are a common cause of acute and chronic allograft dysfunction. CNI nephrotoxicity can manifest as either acute azotemia, which typically occurs within the first 3 months post-transplant and is largely reversible after reducing the dose, or as chronic progressive renal disease, which generally occurs after 3 months post-transplant and is usually irreversible. Other renal effects of the CNIs include tubular dysfunction and, rarely, a thrombotic microangiopathy that can lead to acute graft loss.

Thrombotic Microangiopathy

Thrombotic microangiopathy in the KTR may be the result of recurrent disease [e.g., in patients with a prior history of thrombotic thrombocytopenic purpura or complement-mediated hemolytic uremic syndrome (HUS)], CNI nephrotoxicity, active (acute) ABMR, or a hypercoagulable disorder (such as antiphospholipid syndrome). In addition to acute allograft dysfunction, common clinical features include microangiopathic hemolytic anemia, thrombocytopenia, and increased lactate dehydrogenase levels.

Recurrent Primary Disease

In patients whose primary renal disease was glomerulonephritis, disease recurrence must be considered as a possible cause of allograft dysfunction. Recurrence rates vary depending upon the specific glomerular disease. Glomerular diseases that commonly recur post-transplant include primary focal segmental glomerulosclerosis (FSGS), primary membranous nephropathy, membranoproliferative glomerulonephritis, complement-mediated HUS, and C3 glomerulopathy. Late recurrence (i.e., >1 year post-transplant) may be seen in many diseases, including FSGS, membranoproliferative glomerulonephritis, immunoglobulin A (IgA) nephropathy, and diabetic nephropathy. Biopsy of the renal allograft is required for diagnosis.

NEW-ONSET DIABETES AFTER TRANSPLANT

Tacrolimus, more than cyclosporine, is toxic to pancreatic islet cells. New-onset diabetes after transplantation (NODAT) affects up to 40% of transplant recipients, though the accuracy of this statistic is limited by controversy about the definition of NODAT. Risk factors for the development of NODAT are obesity, African American and Hispanic ethnicities, family history of diabetes, and hepatitis C virus (HCV) infection. Those with known diabetes before the development of ESRD are likely to require more intensive therapy.

Electrolyte Abnormalities

Electrolyte abnormalities are common post-transplantation. Hyperkalemia can be associated with CNIs, sulfamethoxazole, ACE inhibitors, and angiotensin-receptor blockers (ARBs) and with reduced glomerular filtration rate (GFR). CNIs can cause hyperkalemia with hyperchloremic metabolic acidosis due to downregulation of specific tubular transport proteins. Hypomagnesemia (magnesium, 1.2–1.7 mg/dL) is seen in most transplant recipients as a result of renal magnesium wasting due to tacrolimus. In addition, proton pump inhibitors may also contribute to hypomagnesemia. Oral magnesium replacement should target a level > 1.5 mg/dL because levels > 2.2 mg/dL are rarely achieved and usually result in magnesium-induced diarrhea.

POST-TRANSPLANT MALIGNANCY

The most common post-transplantation malignancy is nonmelanotic skin cancer. Squamous cell skin cancer risk is 100-fold increased among transplant recipients, especially in Latinos and whites as compared to the general population. All transplant recipients should wear sunscreen and be screened annually by a dermatologist. Though squamous cell skin cancers do not typically metastasize, if untreated, metastasis can occur. Recurrent skin cancers should prompt consideration of conversion to a mammalian target of rapamycin (mTOR) inhibitor, which has better efficacy in control of epithelial cell-derived skin cancers.

Post-transplant lymphoproliferative disorder is seen in 0.8% of adult and 2.6% of pediatric recipients. The majority of PTLD cases are driven by an EBV infection. The higher prevalence in children is due to a lack of acquired immunity to EBV. EBV infection or reactivation results in clonal expansion of B lymphocytes, resulting in lymphoma. PTLD often presents with infiltration of the internal organs, central nervous system, or intrathoracic or intra-abdominal lymph nodes. Palpable lymphadenopathy is uncommon. Presenting symptoms include low-grade fevers, shortness of breath, headaches, or abdominal discomfort. Physicians should have a low threshold for CT in patients presenting with these symptoms. Initial treatment is reduction in IS, followed by chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Renal cell cancers are seen more frequently in the transplantation population, likely related to malignant degeneration of cysts in patients with underlying polycystic or acquired cystic disease. There are no accepted

guidelines for screening transplant recipients for renal cell cancer. However, hematuria in a transplant recipient warrants urologic evaluation that includes ultrasonography or CT of both the native and transplanted kidney.

SUMMARY

Emergency department physician must be aware about the solid organ transplant-related complication because organ transplant nowadays is a common modality of treatment for end-organ damage. When dealing with the clinical findings of solid organ transplant patients, ED professionals should remember that symptoms may be vague and nonspecific. Furthermore, signs and symptoms related to infectious complications vary with the source of infection, pathogenic organism, and level of immunosuppression. It is important to continue appropriate immunosuppression while managing transplantation-related complications. Transplant patients require extensive laboratory and radiological evaluations to rule out an infectious etiology, evaluate the allograft function, and determine drug toxicity. With an increased awareness regarding transplantation, ED physician can offer accurate and effective management.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Headache

Devendra Richhariya

INTRODUCTION

Headache is one of the most prevalent patients' complaints, whether as chief or ancillary, in emergency departments (ED), consist of millions of ED yearly visits. Despite of uncertainty and major knowledge gaps, it was estimated that percentage of the adult population with an active headache disorder is almost 50% in general, with minor difference in various societies. It is a functionally disabling disorder leading to considerable years living with disability (YLDS), and has been experienced at least once by almost everyone. Therefore, it has taken into consideration by World Health Organization (WHO) as a public-health priority, in 2000. Although most of the cases are benign in nature, but needs some special attention regarding various aspects including primary pain management, diagnostic approach, disposition, and outpatient follow-up.

Headache is one of the common presentations in ED. About 2–5% of patients in various ED are due to headache, apart from these most of the patients with headache do not visit ED also. Important aspect of management of headache in emergency is identification of life-threatening causes of headache such as subarachnoid hemorrhage (SAH) and meningitis and early initiation of the treatment in these life-threatening causes. It is frequent scenario that patient with acute headache immediately sent to nearest computed tomography (CT) scan center by general physician in view of attendant anxiety and in hope that this will identify some cause. But this will delay in receiving the appropriate treatment while taking care full history alone differentiate the fatal (need further investigation and immediate intervention) from nonfatal causes (need only reassurance and discharge) in other word approach should be to classify the patient into two groups: Primary headache such as migraine, tension or cluster and secondary headache such as SAH, CVA, meningitis, temporal arteritis, carotid dissection, and sinus thrombosis. Educating the patient about probable causes and various treatment options are really helpful in headache management in ED. The main objectives for emergency physician while evaluating acute headache patients:

- Identify causes of secondary headache
- Rule out life-threatening causes
- Pain management
- Investigate and manage appropriately
- Follow-up

ETIOLOGY

When it comes to etiology, most acceptable categorization for headache is primary versus secondary causes, based on presence or absence of a pathologic structure justifying the symptoms (**Table 1**). The first recorded classification system was published by "Aretaeus", the ancient Greek physician, active during 1st century CE. Today, the 3rd edition of the International Classification of Headache Disorders is available that has been released by classification committee of International Headache Society (IHS) in 2018 (was published in 2013 in a beta version ahead of the final version) showed in **Box 1**.

PATHOPHYSIOLOGY

The brain parenchyma has no pain receptors, so is not sensitive to pain itself. But, some other components, adjunct to it such as meninges, blood vessels, skin, etc. have nociceptors that could stimulated from traction or by irritation. It usually defines the

TABLE 1: Categories of headache.

Primary headache	*Secondary headache*
• Tension • Cluster • Migraine • Febrile headache • Dental headache • Trigeminal neuralgias • Postlumber puncture headache • Others such as exertional, sex headache, and cough headache	• Subarachnoid hemorrhage • Stroke • Traumatic/nontraumatic EDH, SDH, and intracranial hemorrhage • Carotid or intracerebral arteries dissection • Head trauma • Brain infection • Intracranial space occupying lesion • Metabolic or toxic causes

(EDH: epidural hematoma; SDH: subdural hematoma)

BOX 1: The International Classification of Headache Disorders 3rd Edition.

Part one: The primary headaches

- Migraine
- Tension-type headache (TTH)
- Trigeminal autonomic cephalalgias (TACs)
- Other primary headache disorders

Part two: The secondary headaches

- Headache attributed to trauma or injury to the head and/or neck
- Headache attributed to cranial or cervical vascular disorder
- Headache attributed to nonvascular intracranial disorder
- Headache attributed to a substance or its withdrawal
- Headache attributed to infection
- Headache attributed to disorder of homoeostasis
- Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
- Headache attributed to psychiatric disorder

Part three: Painful cranial neuropathies, other facial pains, and other headaches

- Painful lesions of the cranial nerves and other facial pain
- Other headache disorders

pathophysiology of secondary type's headache. But, unlike secondary causes, the pathophysiology of primary headache disorders is not well understood and proposed theories were changed during the time. For example, it was long assumed that some vascular involvement is explaining the migraine pathophysiology. This vascular theory, which was settled and progressed in the 20th century, is no longer accepted. It seems that the literatures are yet nonconclusive in this era and more studies are still required to understanding the pathophysiology of primary headache disorders.

CLINICAL PRESENTATION

Headache is the sensation of pain anywhere in the region of the head or neck. Depend on the type, it could present with various manifestations. The presentation process is so important for the in-charge physicians. Some may present with new onset rapid progressive headache raise the attention to critically important underlying cause; on the other hand, some present with chronic pain not responded to their regular treatment. The details were discussed in the following sections.

Concerning features-red flags: Although most of headaches are benign, but there are still some life-threatening causes. Red flags are highly important points that careful attention to them by rapid reviewing in dealing with each patient, help the physician to differentiate the serious cause require further emergent investigations. Overall, complaining of first or worst headache, progressively worsening headache, headache triggered by exertion or started while engaged in sexual intercourse or after a recent traumatic event, presence of focal neurological findings or papilledema on physical examination, and any alteration in mental status warrant further work up in ED. To remember of the red flags for recognizing a secondary type headache, the American Headache Society recommends using of "*SSNOOP*" mnemonic abbreviated for the items below:

- ***S***ystemic symptoms (fever or weight loss)
- ***S***ystemic disease [human immunodeficiency virus (HIV) infection and malignancy]
- ***N***eurologic symptoms or signs
- ***O***nset sudden (thunderclap headache)
- ***O***nset after age of 40 years
- ***P***revious headache history (first, worst, or different headache)

EVALUATION

As obviate from the mentioned points in previous section, all the red flags were assessed through a detailed history taking and focused physical examination.

For a confident history taking, patient should ask for 10 important points about the pain including location, pattern and onset, activity at the onset (during marked exertion or coitus), characteristics (throbbing, steady, or tension), exacerbating or alleviating factors, history of trauma, risk factors (HIV or another immunocompromised state), prior history of headache, intensity, and associated symptoms (blurred vision, fever, nausea, vomiting, or syncope).

Physical examination also including of general appearance assessment, checking the vital signs, head and neck evaluation (acute red eye, poorly reactive or nonreactive pupils, or 3rd nerve palsy), and precise neurological examination (even the least change in mental status, any focal neurologic deficit or alteration in cerebellar tests). Ophthalmoscopy is also necessary for demonstrating or ruling out the possible loss of venous spontaneous pulsation or presence of papilledema.

Interpretation of Finding

It is expected that the primary evaluations reveal some findings that their interpretation leads to suggesting appropriate differential diagnosis which will be the basis for the next steps of patient evaluation process and proper decision-making in fact. Those life-threatening diagnoses which need treatment interactions right after confirming the diagnosis or even before are called as critical diagnosis **Table 2**. SAH, carbon monoxide (CO) poisoning, temporal arthritis, meningitis or encephalitis are among the most important critical diagnosis of a patient presenting with headache. Space occupying lesions including brain abscess and hemorrhagic events, cerebral vein thrombosis (CVT), glaucoma, hypertensive crisis, and mountain sickness are also considered as emergent diagnosis.

INVESTIGATIONS

Considering the suggested differential diagnosis, the patient may undergo some paraclinical procedures including laboratory and/or imaging. Complete blood count (CBC), and a coagulation profile may all required laboratory tests. Cerebrospinal fluid (CSF) analysis in those with impression of meningitis/encephalitis following lumbar puncture (LP) and erythrocyte sedimentation rate (ESR) in those suspected as giant cell arteritis are also required. Requesting for common biochemical profile is usually unnecessary. Most of the patients, who are suspected for secondary causes almost always need

TABLE 2: Interpretation of findings—most likely cause of secondary headache.

Presenting symptoms in emergency	*Most likely cause of headache*
Severe, sudden onset headache, altered mental status, history of hypertension, smoking, SAH, cerebral aneurysm, arteriovenous malformation/trauma, and coagulopathy	Subarachnoid hemorrhage/ intracerebral hemorrhage/subdural hematoma
Fever, neck stiffness, altered behavior, seizures, photophobia, history of ear infection, brain surgery, trauma, and immunocompromised status	CNS infections/ meningitis
Jaw pain, changes in vision polymyalgia, gradual onset, and severe throbbing pain	Temporal arteritis
Dizziness, fatigue, weakness, nausea, vomiting, confusion, syncope, headache in winters, and dull frontotemporal pain	Carbon monoxide poisoning
Sudden, moderately, severe, pain around eye unilateral vision change, and redness	Acute glaucoma
Neck pain, vertigo, history of trauma, stroke symptoms, Horner syndrome, and upper extremities weakness	Cervical artery dissection
Associated with nausea, vomiting, seizures, ocular nerve palsies, chemosis, proptosis, papilledema, pregnancy, postpartum, hypercoagulable, and oral contraceptive use	Venous sinus thrombosis
Chronic progressive headaches, papilledema, and history of malignancy	Intracerebral tumor/ space occupying lesion/increased ICP/ idiopathic intracranial hypertension
Headache associated with vertigo, vomiting, ataxia, and dysmetria,	Cerebellar infarction

(CNS: central nervous system; SAH: subarachnoid hemorrhage; ICP: intracranial pressure)

to perform a nonenhanced head CT scan as soon as possible. Almost all the hemorrhagic causes are diagnosed by this imaging. It also may revealed some findings pointing to other intracranial lesions such as brain abscess or tumors, that may require contrast enhanced magnetic resonance imaging (MRI) in next step. Advanced imaging techniques including magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) are also may necessitate in suspicion of vascular disorders including intracranial aneurism and cerebral venous thrombosis (CVT) respectively.

TREATMENT

Along with diagnostic approach, pain management is always necessary in all patients; since benign primary disorders are the most frequent diagnosis that is the only intervention in most cases as well. There are frequent guidelines for

TABLE 3: Parenteral pain control medications in ED.

Agent	*Dosage*
Acetaminophen	• <50 kg: 12.5 mg/kg IV q4h OR 15 mg/kg IV q6h; not to exceed 750 mg/dose or 3.75 g/day infuse IV over at least 15 min • ≥50 kg: 650 mg IV q4h OR 1,000 mg IV q6h; not to exceed 4 g/day infuse IV over at least 15 min
Ketorolac	• IV: 30 mg as single dose or 30 mg q6h; not to exceed 120 mg/day • IM: 60 mg as single dose or 30 mg q6h; not to exceed 120 mg/day
Ibuprofen	400–800 mg IV infused over 30 min q6h PRN; not to exceed 4,200 mg/day
Morphine	• SC/IM (opioid-naïve patients): 5–10 mg q4h PRN; dose range, 5–20 mg • IV (opioid-naïve patients): 2.5–5 mg q3–4h PRN, infused over 4–5 min; dose range, 4–10 mg

(ED: emergency department; IV: intravenous; IM: intramuscularly; SC: subcutaneously)

management of acute headaches that generally recommended several different agents. Intravenous (IV) acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), and opioids are common first choice. Corticosteroids, magnesium sulfate, caffeine, ergotamine, and sumatriptan may also be required. Serotonin antagonist (granisetron), intranasal lidocaine, and high-flow oxygen were also studied in this regard but have reported conflicting results. There is an interest about using IV ketamine as a treatment option for acute pain but does not provide significant relief. Despite of huge number of randomized clinical trials (RCTs), there is not an agreement on a single approved guideline. Overall, it is likely that investigators have tried to reduce using opioids and replace them by nonopioid agents that assumed have less side-effects, but opioids administration remains still prevalent in the ED. **Table 3** shows the dosage of some more frequent agents used as parenteral pain control medications in ED. All secondary type headaches are required specific intervention depend on the exact diagnosis, whether surgical or nonsurgical. Surgical interventions are usually conducted in cases of intracranial hemorrhagic insults, brain mass, and abscess. Nonsurgical treatments are also including antibiotic therapy in meningitis, antiviral in encephalitis, corticosteroid in temporal arteritis, oxygen therapy in CO poisoning, topical treatment to lower intraocular pressure (IOP) in glaucoma, and anticoagulation in CVT (even hemorrhagic ones).

Tension Headache

Most common type of headache presentation in ED. Tight or compression type sensation usually bilateral nonpulsatile type associated with stress and occurs daily not aggravated by exertion. Compliant of feeling constant pressure or weight on shoulders neck and head. Headache start gradually but increase in severity at the end of the day. Once the secondary headache is excluded tension headache can be treated with NSAID, chlorpromazine, metoclopramide, and sumatriptan.

Treatment of tension headache: Reassurance, anxiety and depression assessment, minor tranquilizers, tricyclic antidepressant, treatment with diazepam, chlordiazepoxide, and aspirin is helpful. Alprazolam: Antianxiety and antidepressant action. If severe depression suicidal ideation, or refractory to treatment then psychiatrist consultation.

Cluster Headache

As compared to migraine and tension headache cluster headache is uncommon. Cluster headache usually unilateral, short duration and associated with parasympathetic autonomic features such as lacrimation, rhinorrhea, warm, and redness of face. Headache is so severe that it awakens the patient from sleep. Objective of treatment in ED is control the pain and abort the cluster headache. Start oxygen inhalation by face mask at the rate of 7–10 L/min for 15 minutes. Subcutaneous sumatriptan 6 mg helpful in aborting the cluster headache attack. Subcutaneous sumatriptan is fast acting. Antiemetics should also be given to cluster headache patient. As recurrence is common after discharge from ED so adequate maintenance therapy should be prescribed to the patient.

Treatment of cluster headache: Subcutaneous injection of sumatriptan 6 mg abort cluster headache within 15-minutes, inhalation of 100% oxygen, ergotamine 1 mg at bed time total weekly dose not >14 mg, lithium 600–900 mg in chronic form, and prophylactic drugs are prednisolone, lithium, methyleserzide, ergotamine, and verapamil.

Migraine

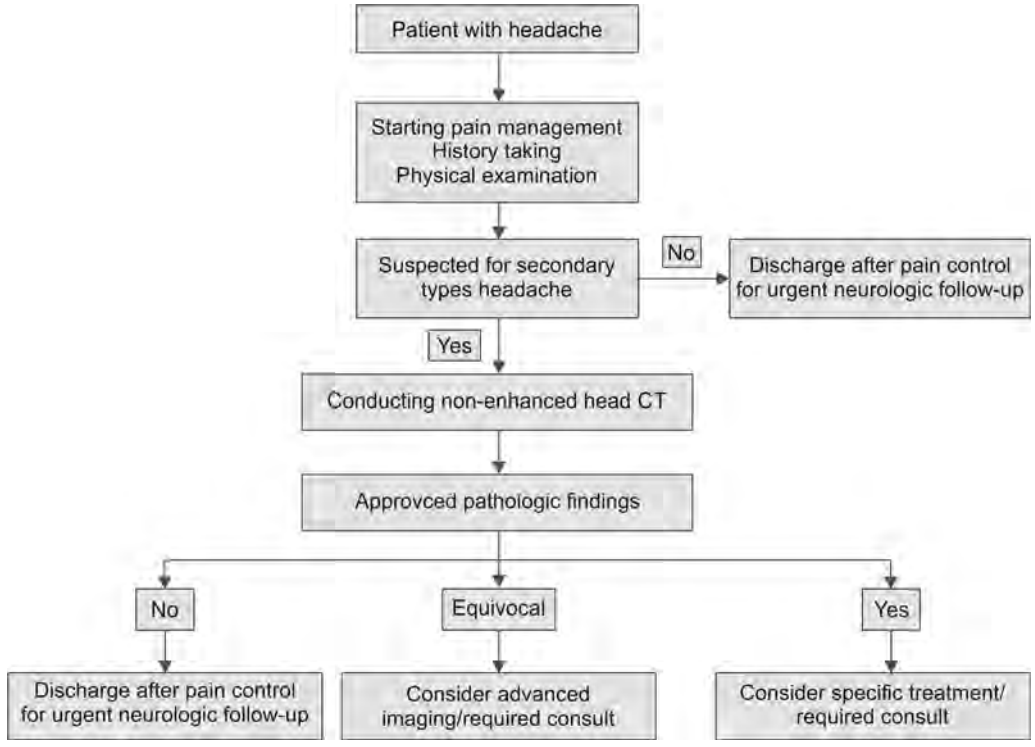
Migraine is common headache disorder after tension headache. Migraine is typically unilateral recurrent throbbing associated with nausea, photophobia, and phonophobia either associated with aura or without aura. Medications used to treat in ED are summarized in **Table 4**.

SUMMARY

In dealing with a patient complaining of headache, ruling out the critical and emergent diagnosis in ED is far more important than ruling in an exact benign diagnosis. Therefore, the physician should make his/her effort in this regard. Pain management should consider for all types of headache whether primary or secondary. Further investigation in ED should also be considered for those suspected for secondary types based on history and physical examination findings. If secondary cause of headache is identified after detailed examination and neuroimaging, patient should be admitted and manage appropriately (**Flowchart 1**). If workup is normal patient should be discharged with follow-up with neurologist.

TABLE 4: Drug therapy for migraine in ED.

	Abortive medication for migraine		
Preventive medications for migraine	***Analgesics***	***NSAIDs***	***Antiemetics***
Propranolol: 40–120 mg BD	Aspirin 500–650 mg	Ibuprofen 200–300 mg	Metoclopramide 5–10 mg
Metoprolol: 100–200 mg/day	Paracetamol 500 mg	Diclofenac 50–100 mg	Chlorpromazine 10–25 mg
Amitriptyline: 25–75 mg HS	Propoxyphene 65 mg	Naproxen 500–700 mg	Promethazine 50–100 mg
Valproate: 400–600 mg BD	Codeine 60 mg	Flurbiprofen 50–100 mg	Diphenhydramine 50 mg
Flunarizine: 5–15 mg/day	***Ergot derivatives*** *are low-cost medication and with vasoconstriction effect. Main adverse effects are nausea, vomiting angina, cramps, numbness, and tingling. Contraindicated in hepatic, renal failure, coronary artery disease, peripheral vascular disease, pregnancy, and hypertension*		
Serotonin antagonists Pizotifen: 0.3–3 mg/day Methyleserzide: 1–6 mg/day	***Triptans*** efficacy and safety are established by well-designed trials triptans are 5HT 1B/1D receptor antagonist. Adverse effects are skin reaction, dizziness, hypertension, and chest discomfort Contraindicated in angina and coronary artery disease. Sumatriptan, naratriptan, rizatriptan, and zolmitriptan are in use. ***Parenteral sumatriptan***: 6 mg of subcutaneous sumatriptan is highly effective in acute attack		



(CT: computed tomography)

FLOWCHART 1: Summary: Managing acute headache in emergency department.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Acute Dizziness and Vertigo

Ramyajit Lahiri, Subhra Choudhury

INTRODUCTION

Dizziness is a common presentation in an emergency department (ED) with varying underlying pathology. The diagnosis is complex. Studies suggest 3.5% patients presents with complaints of dizziness in ED. This is really a challenge for emergency medicine department to determine the exact cause of this dizziness and then provide treatment. Those found to have life-threatening causes arranging a proper disposition for them. Very little Indian literature is available stating the prevalence of this symptom in the Indian population. A study done by Raman et al. on prevalence and etiology of vertigo in adult rural population. There they have done survey on 10,000 adult patients between ages of 20 and 79 years. This study highlighted that 0.71% population having vertigo. Among multifarious causes cardiovascular cause is 0.32%, and neurologic dizziness account for 0.14%. Metabolic disease resulted in dizziness to 0.09% and 0.08% results of otologic disease. Miscellaneous disease 0.08%. To properly determine the exact cause in busy ED is tough. Many life-threatening diseases presents with dizziness. This results in multiple testing, imaging, and longer duration of ED stay. As per a study done in the United States of America (USA) on 2013, the approximate expense was 4 billion for patients presenting in ED. The 12% of that cost was on computed tomography (CT) scan of brain.

Dizziness is a nonspecific term used by patients to denote a variety of symptoms including vertigo, light-headedness, unsteadiness of gait, and disorientation. While dizziness and vertigo are often used interchangeably, they differ phenomenologically. While dizziness can be a manifestation of different causes, vertigo is necessarily a disorder of the vestibular system, or its central connections in the brainstem or rarely the temporal lobe resulting in an illusion of movement occurring horizontally and rarely vertically or obliquely.

DEFINITION

Dizziness is an impairment in spatial perception and stability and can range from fleeting faintness to a severe balance disorder that makes normal functioning impossible.

Accordingly, dizziness can be classified into four groups:

1. Vertigo
2. Disequilibrium without vertigo
3. Presyncope or near faint
4. Psychological dizziness (associated with panic attacks and anxiety disorders)

Vertigo is a symptom where a person feels as if they or the objects around them are moving when they are not. Often, they describe it like a spinning or swaying movement. It is an illusory sensation of movement in space.

Disequilibrium refers to imbalance or unsteadiness in the absence of vertigo. It can occur secondary to dysfunction in vestibular, somatosensory, visual systems, frontal lobes, cerebellum, and basal ganglia.

Presyncope is the sensation of light-headedness, which occurs just before fainting and is due to a transient impairment in cerebral circulation. The distinguishing feature from vertigo is the lack of an illusion of motion. It is often accompanied by pallor and weakness.

Psychological dizziness includes a combination of floating, swimming or rocking sensation, with giddiness which are usually accompanying features of stress, anxiety or fatigue, and an occasionally accompany labyrinthine disorders.

ETIOLOGY

It is commonly taught in old textbooks to diagnose a dizzy patient based on asking the patients "what actually they mean by dizzy". Current approach gives more emphasis on history and clinical examination. This helps in making more specific diagnosis. Multiple diseases can represent with dizziness. Many of them are benign but few are life-threatening. The main goal for emergency physician is to identify correctly the life-threatening causes. A 2008 study on 9,472 patients by National Hospital Ambulatory Medical Care Survey (NHAMCS) shows 50% of patients are having medical condition which includes cardiovascular pathology. Approximately 11% patients having neurological problems and 33% having otovestibular cause. In this prospective study they classified cardiovascular, cerebrovascular, infection, toxin, and metabolic causes as dangerous (**Table 1**). If timely treatment is not given, they can produce devastating results. They found 15% of the study population is having this dangerous disease where age >50 years are

more prone (21% compared to 9.35% in <50 years) with $p < 0.001$. Aortic dissection, carbon monoxide toxicity, and pulmonary embolus are all treatable causes which can presents as giddiness but rarely.

One institutional prospective study shows 30% has dangerous disease compared to 43% having peripheral vestibular disease. One retrospective study with 475 cohort done in Germany ED where a neurologist saw dizzy patients coming to ED. He diagnosed 73% as benign disease and only 23% as dangerous disease. This was blinded by a follow-up with another neurologist (not aware of previous diagnosis) showed almost 44% diagnosis got changed. Among that 6 patients initially diagnosed as benign found to have stroke in follow-up. This can actually results in catastrophe. Multiple studies have done to determine the cause of dizziness in patients presenting in ED. One study highlighted that subtle neurological abnormality with abnormal gait points toward cerebrovascular cause.

TABLE 1: Causes of vertigo.

Peripheral	*Central*	*Systemic/Vertigo mimics*
• BPPV • Labyrinthitis • Meniere's disease • Vestibular neuritis • Perilymph fistula • Acute otitis media • Schwannoma	• Stroke/TIA • Epilepsy • Migraine • Brain tumors • Multiple sclerosis • Familial ataxia syndrome • Postconcussion syndrome • Meningitis/ Encephalitis	• Ototoxic drugs • Anemia • Hypoglycemia • Dyselectrolytemia • Cardiac arrhythmias • Aortic dissection • Carbon monoxide poisoning • Adrenal insufficiency • Pulmonary embolism • Anxiety and panic attacks • Hyperventilation syndrome • Thiamine deficiency

(BPPV: benign paroxysmal positional vertigo; TIA: transient ischemic attack)

PHYSIOLOGY

The brainstem control centers integrate the information received from the specialized sensory receptors of the inner ear along with signals from vision and proprioception to determine the three-dimensional orientation of a person. The linear and angular acceleration receptors are present in the otolithic macula and the semicircular canals (SSCs) respectively. Electrical activities from these receptors travel along the vestibular nerve to reach the vestibular nuclei in the brainstem, where it forms vestibule-ocular reflex, vestibule-spinal tracts, and its connections with the cerebellum and emetic centers. Disruption of these pathways leads to the patient experiencing a disturbance in orientation.

Peripheral Vestibular System

The peripheral vestibular system consists of the paired vestibular sensory end organs of the SSCs and the otolithic organs (**Fig. 1**). These are present within the fluid filled bony channels of the otic capsule and are responsible for perception of both the sense of position and motion. The vestibular nerve is the afferent connection to the brainstem nuclei for the peripheral vestibular system. Within the ampulla of the SSCs are the end organs of cristae, which contain specialized hair cells that transduce mechanical shearing forces into neural impulses. The hair cells or the cilia extend into a gelatinous matrix better known as the cupula, which acts like a hinged gate between the vestibule and the canal itself.

The otolithic organs of the utricle and saccule are found within the vestibule, and are responsible for the perception of linear acceleration. Here also, the end organs consist of a flattened, hair cell rich macular area whose cilia project into a similar gelatinous matrix. The matrix here is however different, and contains a blanket of calcium carbonate crystals, better known as otoliths, with a mean thickness of around 50 μm.

Central Vestibular System

The main brainstem nuclei that receive afferents through vestibular nerve are the superior (Bechterew's nucleus), lateral (Deiter's nucleus), medial (Schwalbe's nucleus), and descending (spinal vestibular nucleus) nuclei (**Fig. 2**). The superior vestibular nucleus is apparently the major relay station

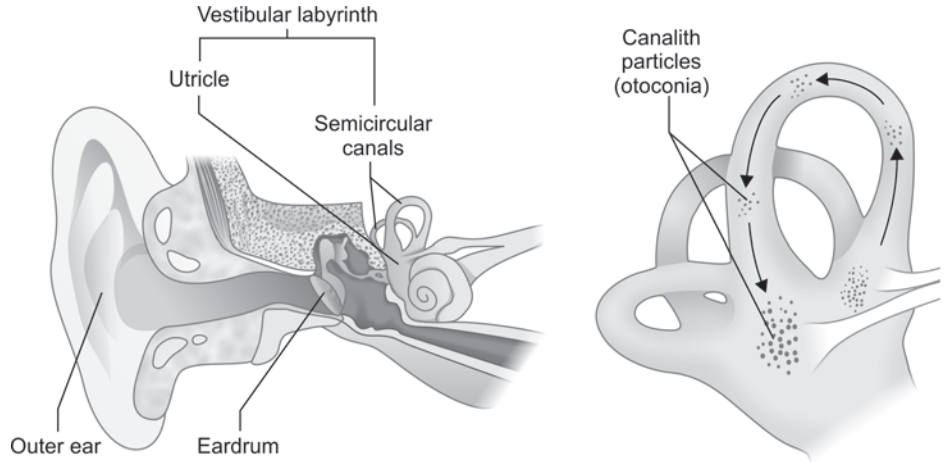


FIG. 1: Peripheral vestibular system.

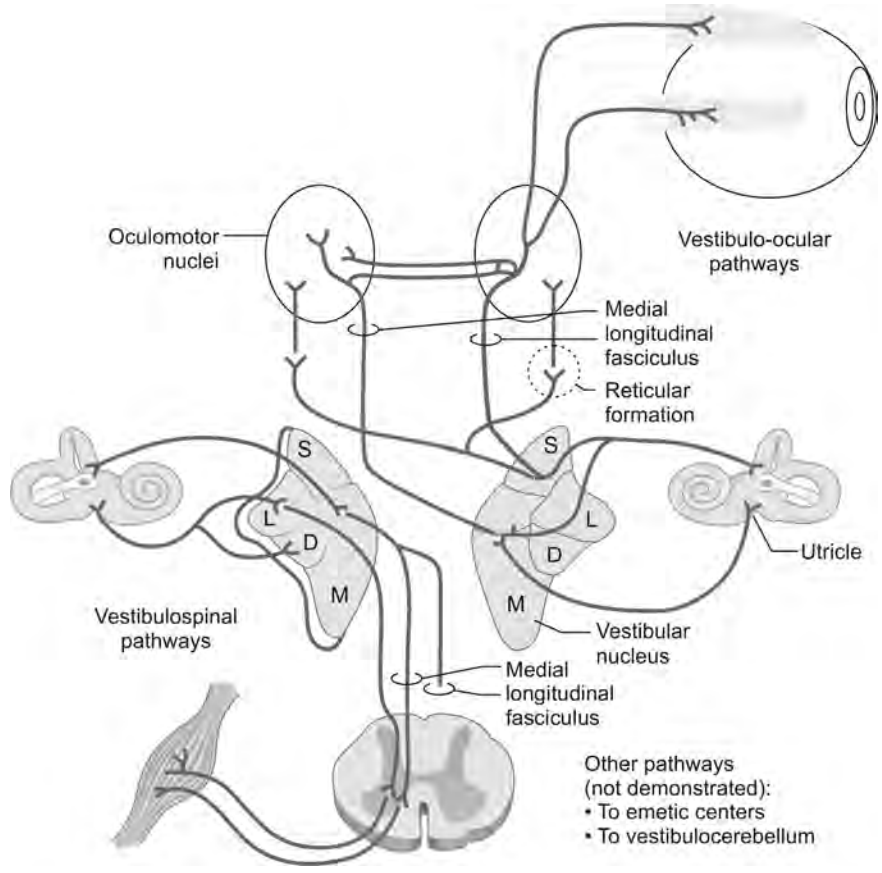


FIG. 2: Central vestibular system.

for conjugate vestibulo-ocular reflex (VOR) mediated by the SCCs. The lateral vestibular nucleus appears to be important for the control of ipsilateral vestibulospinal reflexes. The medial vestibular nucleus, because of it connections with the medial longitudinal fasciculus, appears to be responsible for coordinating eye, head, and neck movements. The descending vestibular nucleus apparently has an integrative function with respect to signals from the vestibular nuclei, the cerebellum, and an amorphous area in the reticular formation postulated to be a region of neural integration. The vestibular nerve in part also directly projects to the phylogenetically oldest parts of the cerebellum—the flocculus, nodulus, ventral uvula, and the ventral paraflocculus, thereby, facilitating smooth pursuits and VOR.

PATHOPHYSIOLOGY

Acute benign paroxysmal positional vertigo (BPPV) patients occasionally complain of persistent symptoms that may be due to repeated triggering symptoms with small, inadvertent head movements or anticipatory anxiety about moving. The main pathophysiology lies in the otolith debris degeneration within the utricle, and the migration of the debris into the SSCs—predominately the posterior canal that causes the manifestation of symptoms.

Meniere's disease is characterized by symptom triad of episodic vertigo and tinnitus with fluctuation in hearing, followed by a symptom-free period. Controversy exists regarding pathophysiology of Meniere's disease. The underlying mechanism is believed to be distortion of the membranous labyrinth resulting from over accumulation of endolymph mainly due to malabsorption, or due to endolymphatic hydrops. Many patients usually have endolymphatic hydrops, the reverse is not always true.

Few reversible causes include noise, toxins such as salicylates, viral infections, and immune mediated mechanism. Most of these does not show morphological changes unless they become permanent.

Vestibular neuritis is believed to be an inflammatory disorder selectively affecting the vestibular portion of the 8th cranial nerve. The cause is presumed to be of viral origin [e.g., the reactivation of latent herpes simplex virus (HSV) infection], although other causes of vascular etiology and immunologic in origin have been proposed. The typical presentation of vestibular neuritis is usually with the acute onset of vertigo, nausea, vomiting, and balance problems.

Labyrinthitis is an inflammatory response within the membranous inner ear structures, response to infection. It is generally a short-lived minor illness that has the potential to cause temporary or permanent hearing loss. Other symptoms include nausea and vomiting, pain in the affected ear, vertigo, and fever.

Posterior circulation stroke is another reason for acute onset vertigo along with nystagmus, gait disturbance or imbalance, and other neurological deficits. The main reason is compromised blood flow to brainstem or cerebellar vermis leading to the dizziness.

While epilepsy is commonly accompanied by dizziness or vertigo, vertigo is only rarely caused by epilepsy (Bladin et al. 1998). This arises primarily because vertigo is much more commonly caused by ear conditions.

Epileptic vertigo is thought to be cause by abnormal stimulation of parts of the cortex that represent the vestibular system—parietal, temporal, and frontal cortex. Specific areas include the superior lip of the intraparietal sulcus, the posterior superior temporal lobe, the posteromedial parietal lobe (Wiest et al., 2004), the temporal parietal border regions (Penfield, 1954; Blanke et al., 2000; Kahane et al., 2003), V5 (Laff et al., 2003), and frontal cortex—left middle frontal gyrus (Kluge et al., 2000).

CONCERNING CLINICAL FEATURES

Red flags: Persistent vertigo, progressively worsening symptoms, vertical nystagmus, associated severe headache, diplopia, dysarthria, dysphasia, ataxia, cerebellar signs, cranial nerve palsies, papilledema, fever, vomiting, and skew deviation.

EVALUATION-HISTORY AND PHYSICAL EXAMINATION

A useful strategy may be is to ask the patient to describe their symptoms without using the word "dizzy." As described earlier the first step would be to determine whether the symptom refers to a true vertigo, disequilibrium or unsteadiness, presyncope or light-headedness or psychogenic dizziness.

Rotatory or true vertigo: If the patient describes his dizziness as a clear spinning or rotator sensation, which is precipitated or worsened by head movements or changes in posture, it can be reasonably ascertained to be a true vertigo. It is inconsequential whether the sensation is of oneself spinning or the surroundings spinning. The patient may also complain of a feeling of being pushed backward or being tilted to one side. The sensation of spinning is also aggravated by turning the head or neck, e.g., looking up or down or turning to one side while lying in bed. Most of these symptoms are likely to be due to a disorder of the vestibular lesion, either peripheral or one of its central connections.

Disequilibrium or imbalance or unsteadiness: This is a feeling of loss of balance, or being unsteady on one's feet. It is typically noticed when a person walks or attempts to walk, and is aggravated by walking on uneven ground or in the dark. There is no spinning sensation, just a feeling that the person will fall or lose balance. Various causes include, bilateral vestibular failure, cerebellar disorders, Parkinsonian disorders, myelopathies, and neuropathies. A diagnosis of the cause of balance disorder can be made by enquiring carefully into certain specific issues, such as worsening of unsteadiness on closing eyes or walking into a dark room, or on keeping feet on different steps or a slowness of activities or a shooting pain down the back on flexing the neck. Also, evidence of oscillopsia when walking (bilateral vestibulopathy), oscillopsia when looking to either side (typical of downbeat nystagmus), slurred speech, slowness of activities, and numbness over the extremities, can also give a clue to the underlying condition that has resulted in imbalance.

Presyncope/Light-headedness/Faintness: A syncope will result in loss of consciousness. However, if a patient has a milder form, namely a presyncope, he usually experiences dizziness. This is an effect of compromised cerebral circulation usually secondary to cardiovascular causes. Typical symptoms include a sensation of feeling faint as if he may pass out, a curtain like darkness falling in front of the eyes or voices and sounds coming from a distance and usually occurs when the patient suddenly stands after he has been sitting or squatting for a long time. On occasions similar symptoms can be noticed on excessive emotional stress, cough, and micturition known as vasovagal syncope. In such situations, it is prudent to record the blood pressure in both, supine and standing posture, to rule out orthostatic drop in blood pressure.

Psychogenic dizziness: As described earlier, it may be due to psychogenic factors, such as stress, depression or anxiety. The symptoms usually are nonspecific, such as tingling or numbness or an inability to think clearly. However, on occasions there may be a tendency on the part of the physician to miss the above three categories and state a diagnosis of psychogenic dizziness. One must remember this is a diagnosis of exclusion and other causes must be adequately ruled out, before calling dizziness "psychogenic."

For the sake of brevity, we will restrict ourselves to the history that pertains to true vertigo. Once a diagnosis of rotator or true vertigo has been made it is imperative to distinguish between peripheral and central causes (**Table 2**) and also to narrow down the differential diagnosis based on the duration of the episode of vertigo. **Table 3**. History also be asked about whether acute onset of vertigo (**Table 4**) or recurrent vertigo (**Table 5**) and further causes can be narrowed down.

Accompanying central symptoms: Central symptoms if present, such as diplopia, dysarthria, dysphonia, dysphagia, dysesthesia, and limb ataxia or weakness would unequivocally point to a central disorder. Significant headache could herald the presence of a central cause like vestibular migraine or sometimes even more sinister cause like dissection of the vertebral artery.

TABLE 2: Distinguishing features of between peripheral and central causes.

Feature	*Peripheral*	*Central*
Nystagmus	Commonly combined (horizontal and torsional), Inhibited by fixation of eyes on to object, does not change direction with gaze to other side	Purely vertical, horizontal or torsional, and not inhibited by fixation of eyes on object, may change direction with gaze toward fast phase of nystagmus
Imbalance	Mild-to-moderate, generally able to walk	Severe, not able to walk or stand sometimes
Nausea and vomiting	Commonly severe	Varies
Hearing loss and tinnitus	Common	Rare
Neurological (no auditory)	Rare	Common
Latency followed by provocative maneuver	Up to few seconds	Up to 5 seconds

TABLE 3: Typical duration of symptoms for different causes of vertigo.	
Duration	***Suggested diagnosis***
A few seconds	*Peripheral cause*: Unilateral loss of vestibular function, vestibular neuronitis—late stage, and Meniere's disease—late stage
Seconds to minutes	BPPV and perilymphatic fistula
Minutes to hours	Posterior circulation TIA and perilymphatic fistula
Hours	Meniere's disease, perilymphatic fistula, migraine, and acoustic neuroma
Days	Acute vestibular neuronitis, stroke, migraine, and multiple sclerosis
Weeks	*Psychogenic*: Persist for weeks without improvement

(BPPV: benign paroxysmal positional vertigo; TIA: transient ischemic attack)

TABLE 4: Common causes of acute onset and prolonged vertigo.			
	Clinical history	***Examination***	***Management***
Vestibular neuritis	Acute or subacute onset of rotatory vertigo	Peripheral vestibular spontaneous nystagmus and pathological head impulse test	• Brief course of high dose steroids • Vestibular rehabilitation
Labyrinthine concussion	Onset after blow to head, hearing loss and tinnitus, symptoms of brain concussion	Hearing loss, possible blood or cerebrospinal fluid in ear canal	Vestibular rehabilitation
Lateral medullary infarction	Vascular risk factors, sudden onset, facial numbness and weakness, diplopia, dysphagia, and lateropulsion	Ipsilateral Horner's syndrome, facial numbness, lack of coordination, decreased gag reflex, and contralateral numbness in limbs	• Thrombolysis • General management of stroke • Control of vascular risk factors • Gait and balance training
Cerebellar infarction	Cardiac disease, vascular risk factors, sudden onset profound imbalance, and possible lack of limb coordination	Central ocular motor disturbance, gait and/or limb ataxia	• Thrombolysis • Secondary prophylaxis of stroke • Control of vascular risk factors • Gait and balance training

TABLE 5: Common causes of recurrent vertigo.			
	Clinical history (in addition to nausea, vertigo, and vomiting)	***Examination (between attacks)***	***Management (in addition to treatment of symptoms)***
Meniere's disease	Fluctuating hearing loss, ear fullness, roaring tinnitus, and possible sudden falling spells (otolithic crises)	Hearing loss (unilateral in most cases) and impaired vestibular function	• Betahistine in a high dosage and long-term treatment • Rarely transtympanic gentamicin or steroids
Autoimmune inner-ear disease	Fluctuating and slowly progressive hearing loss, may be systemic symptoms of autoimmune disease	Hearing loss (bilateral in many cases), interstitial keratitis, arthritis, and rash	High dose steroids
Perilymph fistula	"Popping" sound, hearing loss, or tinnitus after head trauma, barotrauma, cough, sneeze, straining, etc.	Possible positive fistula sign (nystagmus induced by pressure change in external ear canal)	• Avoidance of straining • Explore ear if symptoms persist
Vestibular migraine	Headache, other aura, numbness, motion sensitivity, dysphagia, and lateropulsion	Minor ocular motor dysfunction	• Beta blocker • Topiramate • Valproic acid

Triggers, aggravating, and relieving factors: It is important to take cognizance of what triggers an attack, what worsens it, and what relieves it. Dizziness precipitated by positional changes, looking up or down, or turning sideways in bed is usually due to BPPV. Loud noise or pressure changes may suggest superior canal dehiscence or labyrinthine fistula or sometimes even Meniere's disease. Recent viral infection may precede viral neuritis and a history of anxiety may suggest hyperventilation as a cause for vertigo.

Drug history: Certain drugs such as aminoglycoside antibiotics, diuretics, antidepressants, alcohol, and antipsychotics can all cause vertigo and a careful history should be taken to rule out an iatrogenic cause.

Clinical Examination

- Check for nystagmus
- Check skew deviation
- Head impulse test (HIT)
- Cranial nerve examination
- Cerebellar function testing
- Gait
- Some special tests

HiNTS examination: The HiNTs examination is a screening tool for distinguishing a central cause of vertigo from an acute peripheral vestibulopathy (APV), such as BPPV or vestibular neuritis and is particularly useful in an ED setting.

Nystagmus: The clinical examination for giddiness starts with, checking for nystagmus in each eye separately. By covering the nontesting eye, or shining a pen light on the testing eyes intermittently nullify visual fixation. Absence of nystagmus in a patient with no visual fixation essentially rules out a vestibular cause for the dizziness. Note, if it is present in primary gaze (i.e., looking straight ahead) and or in lateral gaze. What direction is the fast component? If the nystagmus is worse looking in one direction, with the fast component present in that same direction on contralateral gaze, it is unidirectional and reassuring for peripheral vertigo. If, for example, a patient has right-beating (fast direction to the right) nystagmus with rightward gaze and leftward gaze, this is unidirectional right-beating nystagmus. The most common peripheral nystagmus, BPPV, in the posterior SSC consists of a unidirectional horizontal nystagmus with a torsional component. Bidirectional nystagmus, i.e., fast component to the right with rightward gaze and to the left with leftward gaze, is concerning for a central process, as is vertical nystagmus or pure torsional nystagmus.

Skew deviation: Once nystagmus is tested look for skew deviation. Skew deviation (a vertical misalignment of the eyes due to imbalance in the gravity sensing pathways) is not sensitive (30%) but is specific (98%) for a brainstem lesion. To test this the patient has to look directly at the examiner's nose, while the physician alternately covers the right and left eye, alternately back and forth, approximately every 2 seconds. In patients with skew deviation, each time the covered eye is uncovered, there is a slight vertical correction (1 side corrects upward and the other corrects downward). The amplitude of correction is small—1–2 mm, therefore, it is key for the examiner to focus on one eye, rather than following the both eye. A normal response is no vertical correction, and an abnormal response should be considered a stroke in patients with an acute vestibular syndrome (AVS). This can be best appreciated by slow motion video recording with smart phone.

Head impulse test: If nystagmus is truly absent, then this is unlikely to be a vestibular process therefore, HIT is probably not useful and may yield false information.

For testing HIT, ask the patient to sit facing the examiner at the same level. Ensure that the patient does not have any neck issues such as vertebrobasilar insufficiency and neck range of motion is adequate. Ask the patient to keep their eyes focused on a distant target or the tip of the nose of the examiner during the testing procedure and avoid premature eye closure. Now move the head quickly and unpredictably to 10–15° to one side and then rapidly bring back to neutral position, care needs to be ensured to avoid cervical spine injury during the testing. In a normal person, the eyes remain on the target after the examiners movement of the head to one side. In an abnormal response, the eyes are dragged off the target by the turning of the head, called corrective saccade. The corrective saccade indicates a deficient VOR on the same side of the head turn and indicating a peripheral vestibular lesion on the same side. *In other words, the HIT is positive (consistent with peripheral vertigo) if there is a significant lag with corrective saccades*. If you can see the correction, it is abnormal. Compare this to the contralateral side; a difference in the speed of correction should be noted. The horizontal HIT is consistent with peripheral vertigo if it is positive in one direction only. *If there is a lag in corrective saccades in both directions, it may be concerning for central vertigo*. This test can also be performed in the vertical plane. *A lag in corrective saccades in the vertical plane is always suspicious for a central etiology for vertigo*.

Use of video nystagmography can help in the interpretation and accuracy of this test. This test is reported to have a higher specificity (82–100%) than sensitivity (34–39%) In one report, flexing the head forward by 30° during the test increased sensitivity to as high as 71–84%. The absence of a corrective saccade in AVS is consistent with a stroke, and that's why HIT is only useful in patients with the AVS and nystagmus. Occasionally, patients with posterior circulation stroke have a falsely positive (abnormal) HIT, usually from a lateral brainstem infarct involving the location where the vestibular nerve enters the brainstem. These strokes are uncommon and involve the anterior inferior cerebellar artery (AICA) stroke territory or an infarction directly involving the inner ear (labyrinthine stroke) itself. In both situations, hearing is usually acutely lost.

Interpretation of HiNTS Examination

If the HiNTs examination is entirely consistent with peripheral vertigo (positive HIT, unidirectional and horizontal nystagmus, negative test of skew), then, it is 100% sensitive and 96% specific for a peripheral cause of vertigo. However, it must be kept in mind that *all* findings must be present for the HiNTs examination to be invoked. If, for example, the patient has horizontal rightward nystagmus with right gaze and no skew, but has no findings on impulse test, you cannot invoke the HiNTs examination to clear the patient.

Next comes the examination of the cranial nerves and cerebellar function, which targets cranial nerve findings that localize the pathology to the brainstem. This key examination includes testing for pupillary function, facial motor and sensory symmetry, and dysarthria. Specifically, lateral medullary stroke (Wallenberg syndrome), an important cause of the AVS, merits special attention. These patients complain of dysarthria, dysphagia, or hoarseness due to lower cranial neuropathy and may have Horner syndrome with subtle ptosis and anisocoria that may only be evident in dim light (so that the normal larger pupil fully dilates, making the difference in pupil size more apparent). A common physical examination finding is ipsilateral hemifacial with decreased pain and temperature sensation with contralateral hemianesthesia. Routine testing of only light touch can miss this finding.

Cerebellar testing in addition to noting the presence of a scanning speech, also comprises ascertaining the presence of nystagmus (discussed above), along with evaluation of limb/appendicular ataxia, brought out by Finger-Nose or Finger-Finger—nose test and, the heel shin test. If abnormal and unilateral usually indicates an acute and possibly vascular

lesion of the ipsilateral cerebellar hemisphere. Also, truncal, stance, and gait ataxia should be looked into to rule out cerebellar vermian lesions as described below.

While testing for gait ideally, the patient should walk unassisted, but for patients who are too symptomatic to walk, test for truncal ataxia by asking the patient to sit upright in the stretcher without holding onto the side rails. Patient who cannot walk or sit up unassisted is unsafe for discharge. Additionally, an AVS patient who is unable to walk is more likely to have a stroke opposed to vestibular neuritis. Imaging is not infallible in patients with AVS. CT is a poor choice of investigation for posterior circulation stroke. Magnetic resonance imaging (MRI), even with diffusion-weighted imaging (DWI), misses 10–20% of strokes in spontaneous AVS during the first 24–48 hours. In small brainstem strokes, MRI (with DWI) can still miss 50% of the cases when tested within 48 hours. Importantly, 50% of those small strokes were not due to small vessel disease but due to vertebral artery atherosclerosis or dissection. Therefore, in patients with the AVS, the physical examination leads to a correct diagnosis as frequently than imaging.

Dix-Hallpike Test

If BPPV is suspected, it can be safely diagnosed by clinical examination—the Dix-Hallpike test (**Fig. 3**).

The patient is made to sit up straight with the head turned 45° on the side of the ear to be tested. The clinician then lies the patient down quickly with their head hanging past the end of the bed and extending their neck 20°, maintaining the initial rotation of the head. The clinician then watches the patient's eyes for torsional and up-beating nystagmus, which should start after a brief delay and persist for no >1 minute.

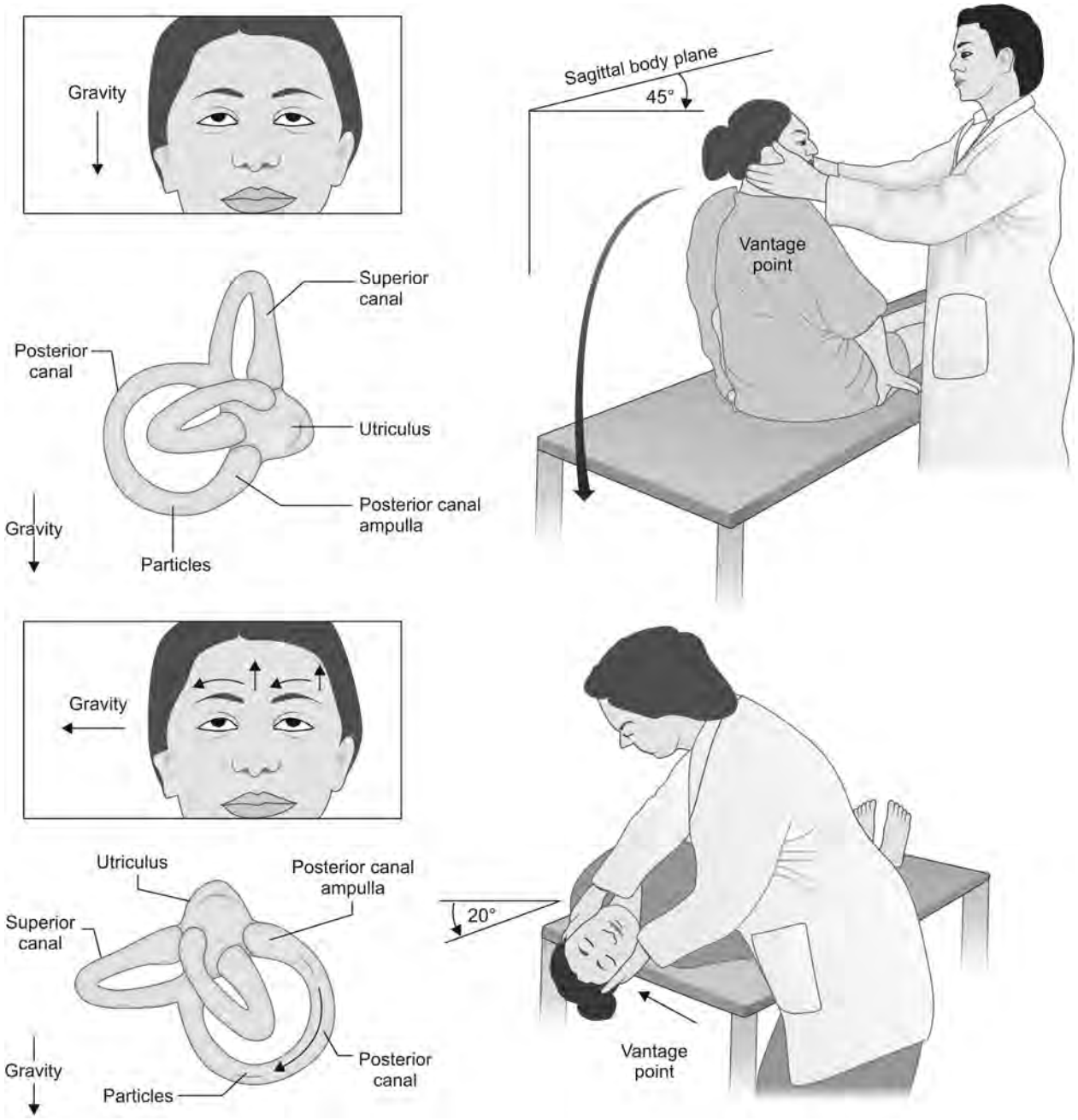


FIG. 3: Dix-Hallpike test.

This would indicate a positive test. If the test is negative but clinical suspicion remains high, the patient should be given a chance to recover for at least 1 minute, and then testing of the other ear can be undertaken. Lateral canal pathology may not be detected by this method, and a supine roll test may be done if this is suspected. Nausea and vomiting are common side-effects and can be avoided by administering prior antiemetics. A down beating nystagmus, nystagmus in different directions on multiple testing, presence of headache, diplopia, and abnormal cranial nerve or cerebellar functions are mostly suggestive of a central pathology. *If Dix-Hallpike test is inconclusive and there is still high degree of clinical suspicion of BPPV, supine roll test can be done.*

Supine Roll Test (Pagnini-McClure Maneuver)

It is done for horizontal canal BPPV. The ideal head position is with the horizontal SSCs in a plane perpendicular to the floor (parallel to gravity). This can be accomplished by tucking the chin 30° forward (either by elevating the back of the head manually, or by placing a supporting pillow under the head) or by inclining the examining table 30° (reverse Trendelenburg position, i.e., with head above feet) (**Fig. 4**). In patients with horizontal canal BPPV, a brisk horizontal nystagmus will develop within a few seconds after turning the head to one or both sides. If the positioning is correct and the BPPV is restricted to the horizontal canal, the nystagmus vector should be purely horizontal. The direction of the nystagmus will differ depending on the location of the pathological otoliths in the horizontal canal (long arm vs. short arm) and the side being tested. Note, that the nystagmus may occur while testing one or both sides, even if the disease is unilateral.

Unterberger's test: Vestibulospinal reflexes can be assessed while standing with eyes closed or on one's toes, and during tandem walking with eyes open and eyes closed as well as during the stepping tests (Unterberger's) eyes close, marching in place for 30 seconds, in which case an imbalance is reflected in excessive turning.

OTHER TEST

Video nystagmography: Any standard procedure for testing for vestibular function should comprise testing for pathological nystagmus, VOR, saccades, and smooth pursuit. A video camera, is used to directly record eye movements, which then interfaces with a digital computer. Saccadic and smooth pursuit eye movements can be digitally and quantitatively evaluated. Ocular pursuit is assessed by asking the patient to follow a moving laser target smoothly. The laser target is moved in sinusoidal pattern. The advantages of video nystagmography, is that it is inexpensive, and does not interfere with vision and does not require head restraint.

Caloric testing: It uses a nonphysiological stimulus to induce endolymphatic flow in the horizontal SCC. The chief advantage of this test is to stimulate each ear individually. This produces a horizontal nystagmus, by creating a temperature gradient from one side of the canal to the other. Each ear is irrigated with water which is 7° lower and 7° higher than body temperature, i.e., 30°C and 44°C respectively. The patient lies in a supine position with head tilted upward to 30°, bringing the horizontal SCC into a vertical plane. Recordings are made with the patient's eyes open behind Frenzel's goggles or in total darkness.

Posturography: The easiest method to record human postural sway uses a so-called force plate, which records the position of a subject's center of mass when upright. With such a device the platform on which the subject stands can be moved simultaneously with the visual surround. A constant angle between the foot and lower leg is maintained by coupling the platform to the sway of the subject, thereby, reducing a major source of somatosensory input to the postural control system. If the subject closes his eyes, or if the movement of the visual enclosure is coupled to body sway, the subject is also deprived of visual information, about postural sway. With this method the influence of the labyrinth on the upright posture through the vestibulospinal system can be studied in an isolated manner.

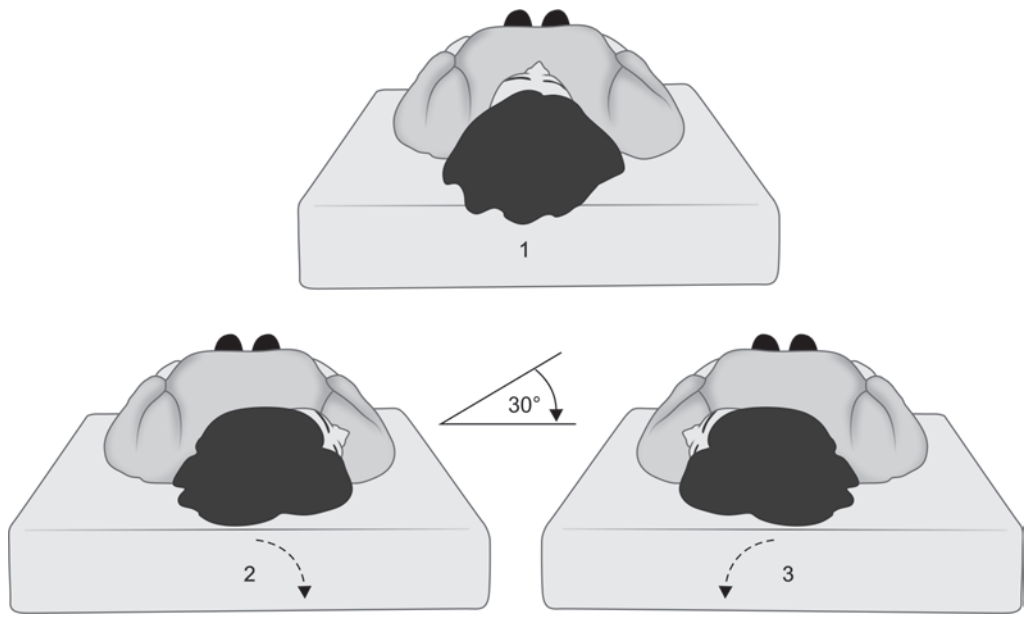


FIG. 4: Supine roll test (Pagnini-McClure maneuver).

It can be used to:

- Differentiate between vestibular, visual, and somatosensory impairments to postural control.
- Differentiate between peripheral sensory and central nervous system (CNS) postural control abnormalities.
- To isolate sensory and motor components of postural instability associated with neurological diseases.
- To document age related changes in balance function, and to differentiate between organic balance problems and a physiologic postural sway.

INVESTIGATIONS

- *Arterial blood gas (ABG):* To look for metabolic, as well as electrolyte abnormalities bedside.
- *Electrocardiogram (ECG):* To rule out cardiac arrhythmia and myocardiac ischemia/infarction.
- *Two-dimensional (2D) echocardiography*: To look for cardiac contractility, wall motion abnormality, and to guide fluid in hypotensive patients.
- *Diffusion weighted (DW) MRI brain:* To rule out stroke.
- *Focused assessment with sonography for trauma (FAST) and extended (eFAST):*
- Complete blood count, C-reactive protein, Liver function test, Blood culture, cerebrospinal fluid studies, 24 holter monitoring

MANAGEMENT

The management begins with supportive care. If stroke is suspected then a neuroimaging study could help in establishing the diagnosis. But as discussed earlier there is certain percentage of chance MRI might miss. While performing MRI patients should be closely observed. If stroke is confirmed to be the cause and the patient presents within 3 hours of onset, thrombolytic treatment can be considered depending upon National institutes of health stroke scale (NIHSS).

A short course of corticosteroids should be considered for patients with vestibular neuritis. After the initial severe symptomatic time period, it is important that patients resume activities because this helps the brain to compensate for the asymmetry of vestibular signals. A formal vestibular therapy program has been shown in a randomized trial to improve outcomes in patients with vestibular neuritis.

Recurrent Positional Dizziness

In case of recurrent positional dizziness, positional testing and particle repositioning improves symptoms. When the patient with posterior canal BPPV is placed in the head-hanging position (Dix-Hallpike test) with the head turned toward the affected side, a burst of upbeat and torsional nystagmus is seen. To reposition the debris Epley maneuver can be done bedside. Success of the maneuver can be confirmed by retesting. If nystagmus continues to be triggered by the Dix-Hallpike test, the Epley maneuver can be repeated.

When the particles are in the horizontal canal, the nystagmus triggered by head movement is a horizontal nystagmus rather than the vertical-torsional nystagmus seen with BPPV of the posterior canal. The nystagmus of horizontal canal BPPV typically lasts longer than posterior canal BPPV. Horizontal canal BPPV can be more difficult to treat than posterior canal BPPV. The repositioning strategy to have the patient roll toward the unaffected side (360°) in 90° increments. Another approach is simply to instruct the patient to lie on the unaffected side for hours, which can be done at home rather than in the ED. *BPPV of the anterior canal* is quite rare. *This cause will also respond to the Epley maneuver. If lateral canal BPPV is diagnosed, it can be managed by Lempert roll maneuver or Gufoni maneuver.*

Epley Maneuver

To begin with, the patient is made to sit up straight with the head turned 45° on the side of the affected ear. Then the patient is made to lie down flat maintaining the position of the head for about 30 seconds. Then the head is suddenly turned by 90° so that the patient is now looking 45° toward the side of the healthy ear. Maintain this position for about 30 seconds, and then roll over to the side of the healthy ear before sitting up (**Fig. 5**).

Gufoni Maneuver

Geotropic type: The patient is taken from the sitting position to the straight side-lying position on the unaffected side for about 30 seconds. Then the patient's head is quickly turned toward the ground at about 45–60° and held in position for 1–2 minutes. After that the patient then sits up again with the head held toward the shoulder on the unaffected side until fully upright and then may be straightened.

Apogeotropic type: The patient is taken from the sitting position to the straight side-lying position on the affected side for about 30 seconds. From this point there are *two variations* of this maneuver that can be done, based on the possibility that debris can be on either the utricular or the canal side of the cupula (or just lodged in the anterior arm of the lateral SSC) (**Figs. 6A** and **B**).

In one variation, the patient's head is then quickly turned toward the ground 45–60° and held in position for 1–2 minutes, which would free the debris from the utricular side of the cupula. The patient then sits up again with the head held toward the shoulder on the unaffected side until fully upright and then may be straightened. In the other variation, the patient's head is turned nose up, 45–60° and held in that position for 1–2 minutes, which would free the debris from the canal side of the cupula (or from being lodged in the anterior arm of the lateral SSC).

Lempert Roll Maneuver

Start from the supine position or from lying on the involved side. Now roll his or her head (or full body) to the unaffected side, and keep rolling in the same direction until his or her head is completely nose down or prone. Some recommend ending the maneuver here and returning to sit (270° roll) as anatomically the debris is repositioned. However, as originally published, complete the final roll (full 360°), and return to sitting position. Hold each position for 15–30 seconds or until nystagmus stops (**Fig. 7**).

Symptomatic Treatment

Patients who present with severe nausea and vomiting typically require intravenous fluids during the ED stay. When drug therapy is necessary to reduce symptoms in the acute setting, generally two different categories of drugs are used: Vestibular suppressants and antiemetics medicines. They

help to symptomatically reduce dizziness in acute attacks, but are generally not effective as prophylactic agents. When taken on a daily basis, the medicines are more likely to result in side-effects or reduce the brain's ability to compensate (as with vestibular neuritis). The major classes of vestibular suppressants include antihistamines, benzodiazepines, and anticholinergics. Most of the vestibular suppressants have anticholinergics or antihistamine qualities, giving them antiemetic properties in addition to the effects on vertigo. A major side-effect of both medicine categories is drowsiness, although this effect probably contributes to the therapeutic effect as well.

Pharmacological Treatment

Benign paroxysmal positional vertigo should not be routinely treated with vestibular suppressant medications such as antihistamines and/or benzodiazepines as there is no evidence in the literature to suggest that any of these vestibular suppressant medications are effective as a definitive, *primary treatment for BPPV or effective as a substitute for repositioning maneuvers*. Benzodiazepines have anxiolytic, sedative, muscle-relaxant, and anticonvulsant properties derived from potentiating the inhibitory effect of the gamma-amino butyric acid system. In prolonged dizziness, these medications can reduce the subjective sensation of spinning but also can interfere with central compensation in peripheral vestibular conditions.

Antihistamines, however, appear to have a suppressive effect on the central emetic center to relieve the nausea and vomiting associated with motion sickness. Other medications that are often used for motion sickness include promethazine, which is a phenothiazine with antihistamine properties, and ondansetron, which is a serotonin-5HT3 antagonist. Last, anticholinergic medications, such as scopolamine, block acetylcholine, and a widespread CNS transmitter, can help with motion sickness by reducing neural mismatching.

Conversely, vestibular suppressant medications have the potential for significant harm as they may produce drowsiness, cognitive deficits, and interference with driving or operating machinery. Benzodiazepines significantly increase the risk for falls. The risk of falls increases in patients taking multiple medications. Benzodiazepines and antihistamines interfere with central compensation for a vestibular injury. The use of vestibular suppressants may obscure the findings on the Dix-Hallpike maneuvers. In addition, there is evidence of additional potential harm from the antihistamine class of medications on gastrointestinal motility, urinary retention, vision, and dry mouth in the elderly.

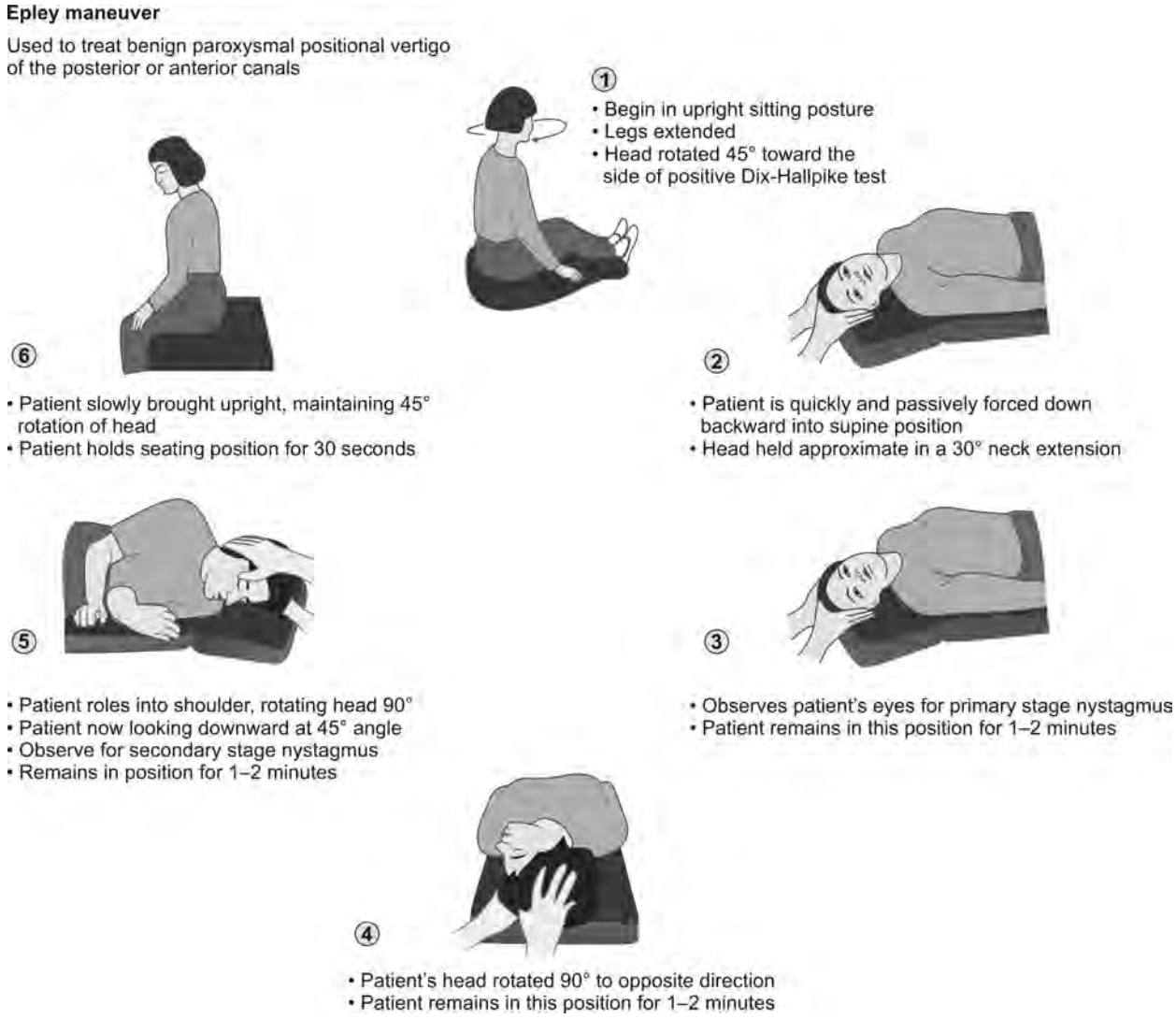

Epley maneuver
Used to treat benign paroxysmal positional vertigo of the posterior or anterior canals
1
• Begin in upright sitting posture
• Legs extended
• Head rotated 45° toward the side of positive Dix-Hallpike test
2
• Patient is quickly and passively forced down backward into supine position
• Head held approximate in a 30° neck extension
3
• Observes patient's eyes for primary stage nystagmus
• Patient remains in this position for 1–2 minutes
4
• Patient's head rotated 90° to opposite direction
• Patient remains in this position for 1–2 minutes
5
• Patient roles into shoulder, rotating head 90°
• Patient now looking downward at 45° angle
• Observe for secondary stage nystagmus
• Remains in position for 1–2 minutes
6
• Patient slowly brought upright, maintaining 45° rotation of head
• Patient holds seating position for 30 seconds

FIG. 5: *Continued*

Continued

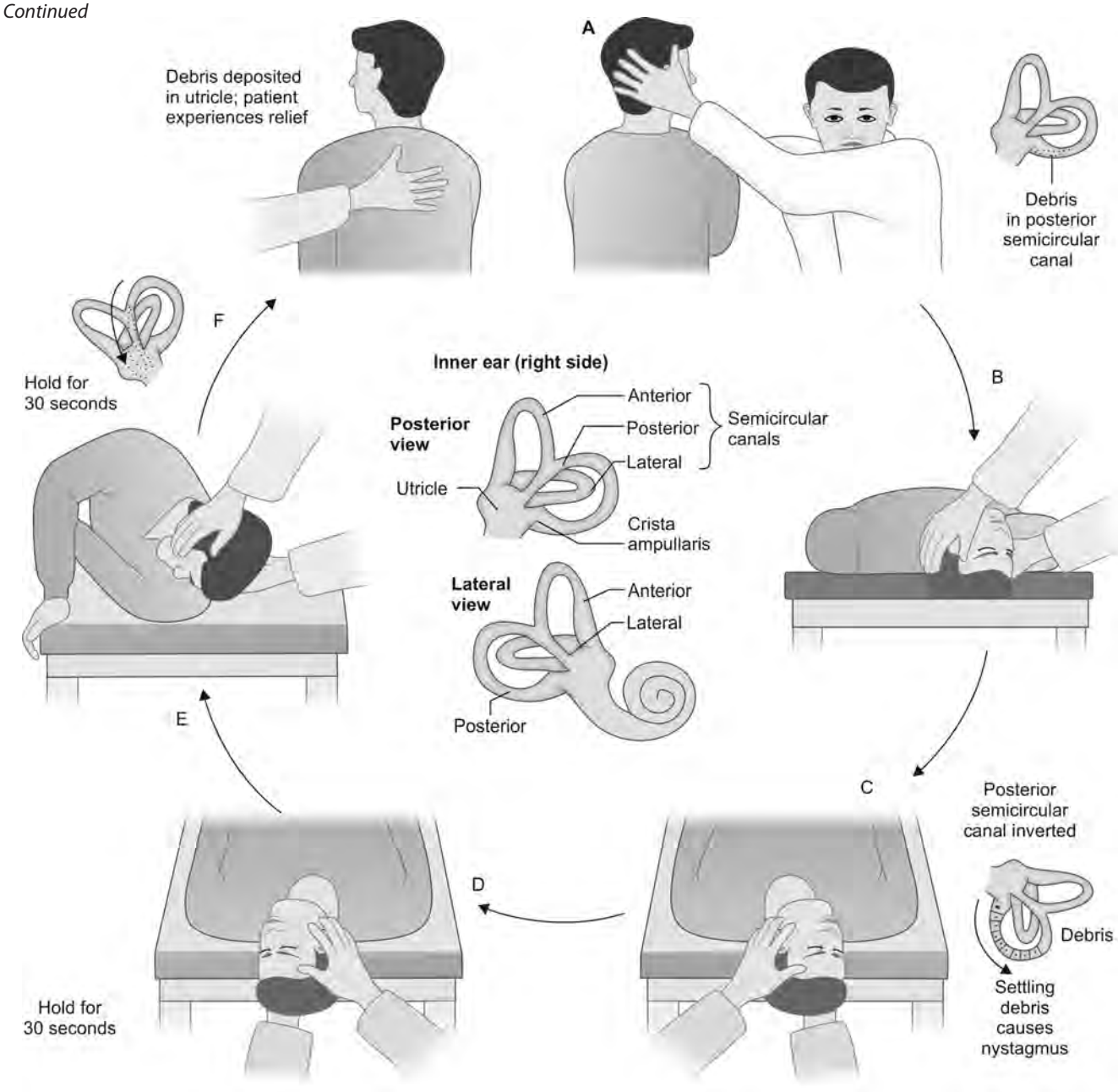
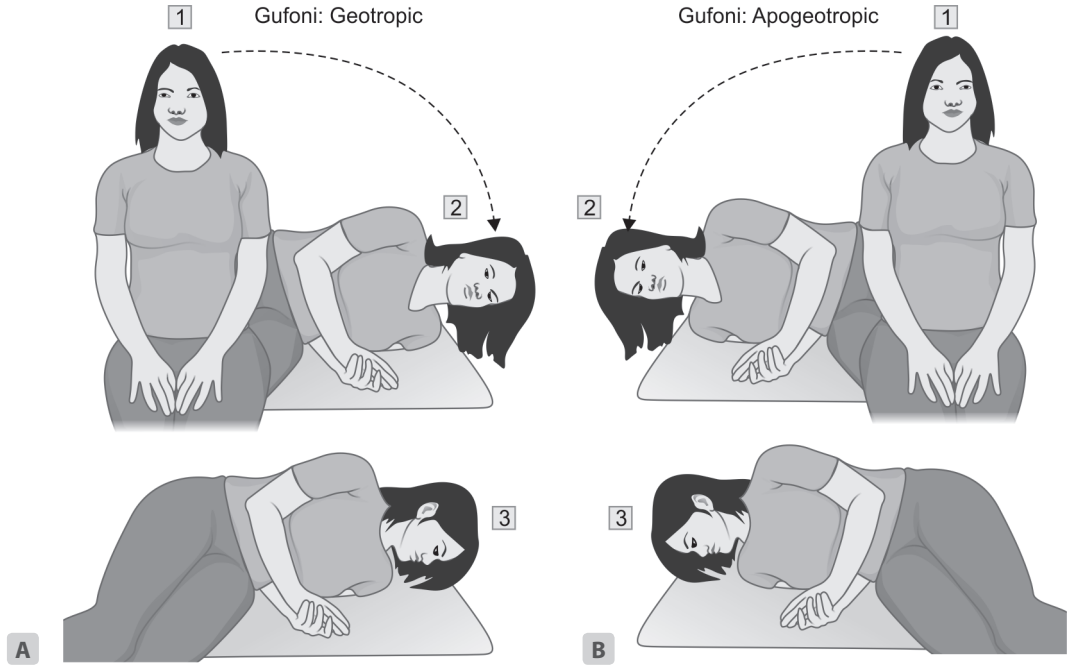


FIG. 5: Epley maneuver.

Particle repositioning maneuvers should be done for BPPV. In patients with severe symptoms, drugs should be prescribed for short durations. Patients should be counseled regarding the disease process, reassured, and encouraged to go back to regular work as soon as possible so as the central compensation can take place. For the central and systemic causes of dizziness and vertigo, treatment should be aimed at the specific cause. Patients should be adequately followed up for assessing response to therapy or treatment failure.

SUMMARY

Dizziness, vertigo, and unsteadiness are common complaints caused by numerous diseases. Therefore, diagnosis can be difficult, leading to overutilization of resources and misdiagnosis. Dizziness can be a problematic presentation in the emergency department, both from a diagnostic and a management point of view. Dizziness is one of the most common reasons for presentation in emergency department for an evaluation. Symptoms can be vague, inconsistent, or unreliable and overlapping among the many potential causes. Accurate and efficient, history, and physical examination more likely to result in a specific diagnosis. The ability of emergency physician to identify the key features of the most common benign peripheral vestibular disorders as well as red flags allows to sort through the most common types of dizziness presentations in the emergency department. Approach to patient with acute dizziness vertigo is summarized in **Flowchart 1**.



FIGS. 6A AND B: Gufoni maneuver. (A) Geotropic; (B) Apogeotropic type.

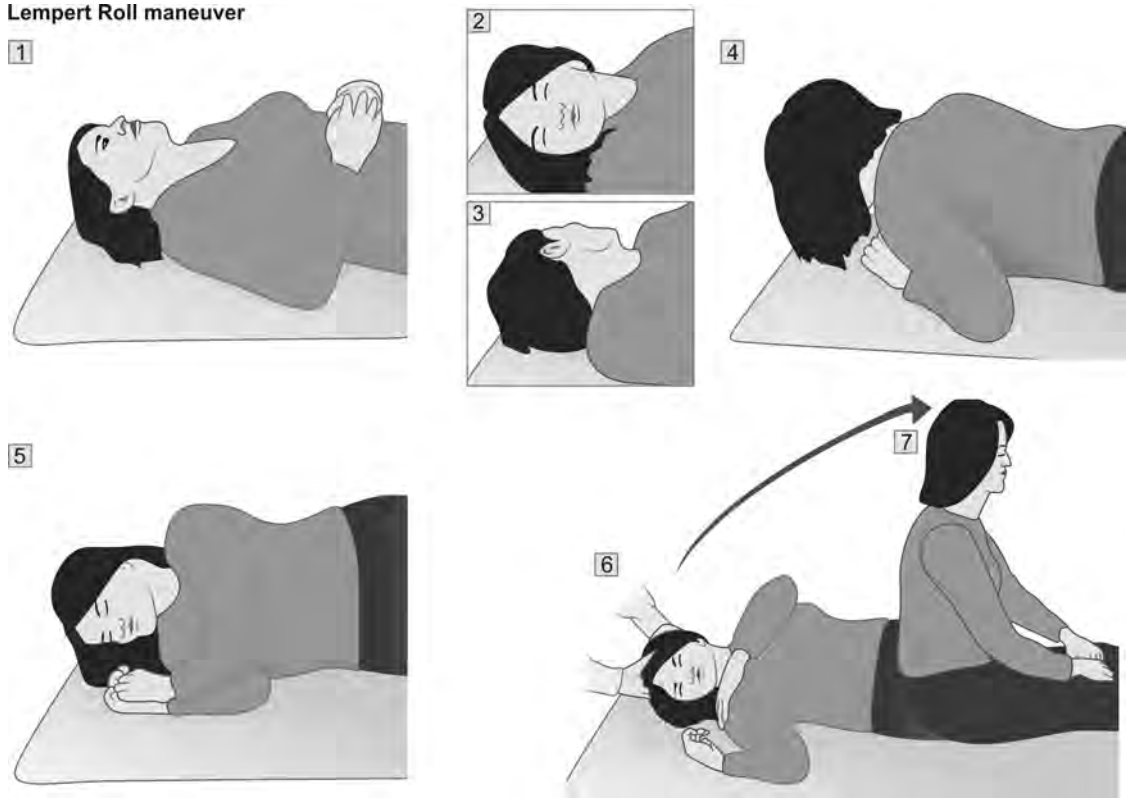
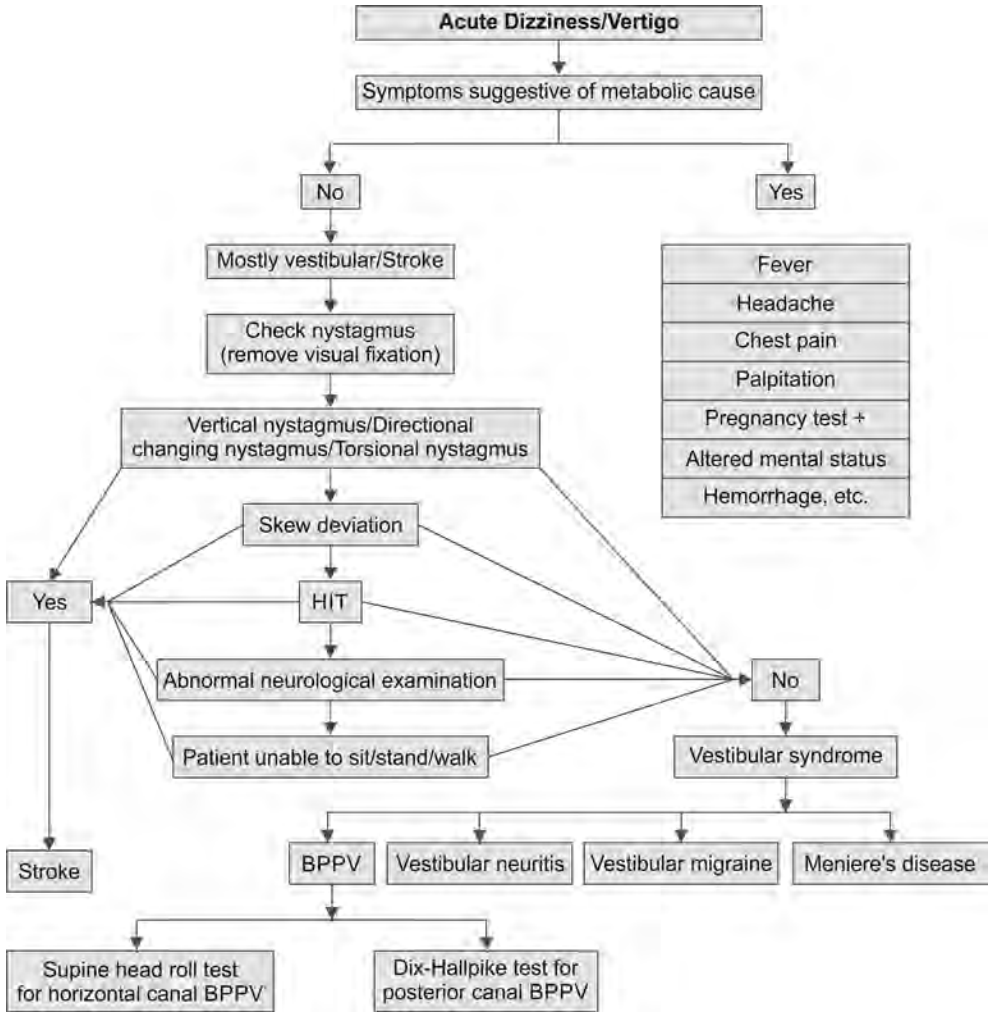


FIG. 7: Lempert roll maneuver.



(HIT: head impulse test; BPPV: benign paroxysmal positional vertigo)

FLOWCHART 1: Approach to patient with acute dizziness/vertigo.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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118 CHAPTER

Altered Mental Status: Delirium

Devendra Richhariya

INTRODUCTION

Synonym: Acute confusion state, acute brain failure, acute organic reaction, and acute encephalopathy.

Altered mental status is common and challenging presentation for emergency physician. Altered mental status can present in all age (pediatric to geriatric) group but more in elderly age group and in about 5–12% of total emergency patient. Altered mental status is considered as disorder of arousal (basic alert and wakefulness) with disturbance in consciousness (awareness, memory, attention, thought perception, and psychomotor behavior). Altered mental status is a nonspecific term used to describe spectrum of brain dysfunction such as delirium, dementia, and psychiatric disorder. Altered mental status clinically present as abnormal behavior, confusion, agitation, hyper alertness, obtundation, stupor and coma. Early differentiation in all three entity and management in emergency department is important. This is very important task of emergency physician to identify acute or chronic changes of mental status.

Delirium is acute onset fluctuation of symptoms, changes in attention, cognitions, and awareness (**Fig. 1**). Delirium associated with highest morbidity and mortality if missed in emergency department. Dementia is chronic deterioration of cognition with or without behavioral disturbances. If chronic changes and impairment of dementia are not identified it adversely affect the outcome because patient unable to follow the discharge instruction and their histories are also unreliable. Hallucination and delusion may be the common features in altered mental status and psychiatric disorder. This chapter discuss the risk factors etiology approach to managing the altered mental status.

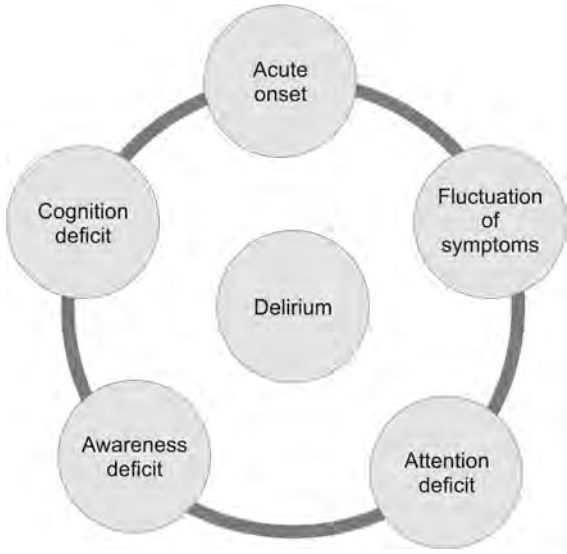

FIG. 1: Clinical components of delirium.

DEFINITION

Delirium is defined as acute onset fluctuating changes in cognition, attention, and awareness, changes are rapid in onset within hours or day and usually reversible. Patient of delirium typically present as inattention, disorganized thinking, perception disturbance, and altered conscious level (somnolent or agitated). Elderly group are increased risk (**Box 1**) of mortality if delirium is missed in emergency department.

BOX 1: Risk factors for acute confusional state.

- Elderly male
- Multiple comorbidities
- Advance form of comorbidities
- Previous episode of delirium
- Advance dementia
- Chronic kidney disease
- End-stage liver disease
- Postoperative status such as recent hip fracture
- Conditions like burn hypoalbuminemia dehydration
- Malnutrition infection AIDS
- Multiple medications and dependence such as benzodiazepine
- Alcohol abuse or withdrawal
- Socially neglected stressful people
- Visual or hearing problem
- Poor mobility terminally ill
- Prolong intensive care unit admission

(AIDS: acquired immunodeficiency syndrome)

About 70–80% of delirium are missed in emergency department due to time pressure or not recognized due to subtle nature and if admitted also be missed in hospital setting. It is very crucial to avoid missed diagnosis in understanding about subtype of delirium in hyperactive, mixed, and hypoactive form.

SUBTYPE OF DELIRIUM

In its *hypoactive form* patient present with lethargic condition while in *hyperactive form* patient will be agitated, restless, anxious, and in *mixed* variety fluctuation of symptoms occurs. Morbidity and mortality are high, if this condition remain untreated or missed in emergency department either due to its subclinical nature of the disease or due to work load and also raises serious issue related to quality of the care. Patient with hypoactive symptoms like lethargy and elderly people are prone for "missed diagnosis" in emergency department. Patients with delirium are vulnerable and may not cooperate with the staff so emergency physician should focus on maintaining airway, breathing, circulation vitals, and normal blood sugar level.

RECOGNIZING THE DELIRUM

In view of high morbidity and mortality in missed cases of delirium and varied and fluctuation clinical presentation it is important to understand the disease course and various assessment as well as diagnostic tools for delirium.

Clinical Presentation

Delirium is acute or subacute onset with fluctuation of symptoms and start with irritability and disturbance in sleep cycle (day time sleep), bizarre behavior, hyperalertness, and confusion. Most of the time family members are the first one who notice the confusion. Other clinical features are clouding of consciousness, reduced level of alertness and arousal, deficit in attention and awareness and concentration, disorientation for time and place, short-term memory deficit, hallucination, illusion, agitation, asterixis, unsteady gait, and tremors.

There are several tools available for assessment of confusion in emergency department. AVPU simplest scale which stands for alertness response to verbal and painful stimuli and unresponsiveness. There is no assessment of "response to painful stimuli" so limited usefulness of this scale. *Richmond agitation sedation scale (RASS) and Glasgow coma scale (GCS)* described 40 years ago and are most familiar among physicians.

Confusion assessment methods: First described by Inouye and colleagues in 1990 based on the *diagnostic and statistical manual of mental disorders revised 3rd edition* (DSMIIIR) criteria, helpful for nonpsychiatric trained physician to diagnose delirium quickly and accurately. Confusion assessment methods (CAM) consists of four components: (1) acute onset mental status changes fluctuating course; (2) Inattention; (3) disorganized thinking and; (4) altered level of consciousness. First two components are mandatory and either of two from rest of two necessary for diagnosis of delirium.

Differentiating Delirium from Psychiatric Illness

Another important concern is to differentiate delirium from psychiatric illnesses as most of the causes of delirium are reversible if identify and treated urgently. One should not be confused with the presence of history of psychiatric illness because many medical conditions exacerbate the underlying psychiatric illness and make the situation more complex and here effective management depends on the high index of suspicion. Some differentiating points of delirium from dementia and psychiatric illness are shown in **Table 1**.

PATHOPHYSIOLOGY OF DELIRIUM

Pathophysiological mechanism of the delirium is complex and related to various neuronal connectivity and trigger factors. Various triggers such as stroke, major surgery, and medications substance abuse or withdrawal can activates/inhibits various neuronal transmitters in response and give rise to various symptoms (**Fig. 2**).

ETIOLOGY

Very important for the emergency physician to identify the systemic and life-threatening cause of acute confusional state and manage urgently. Emergency physician should be able to identify life-threatening causes such as hypoxia, hypoglycemia stroke, hypertensive encephalopathy, Wernicke

TABLE 1: Differentiating delirium from dementia and psychiatric illness.

Features	*Delirium*	*Dementia*	*Psychiatric illness*
Onset and course	Acute (hours-to-days) fluctuating	Insidious (months-to-years) progressive	Acute or insidious progressive/chronic
Vitals	Abnormal	Normal	Normal
Attention	Abnormal	Normal (except in severe dementia)	Normal
Cognition	Abnormal	Abnormal	May be abnormal
Orientation	Abnormal	Often abnormal	May be abnormal
Reversibility	In most of cases	Irreversible	Usually not
Hallucination	Visual ± auditory	Absent	Auditory
Delusion	Transient	Absent	Continuous
Movements	Asterixis tremor may present	Absent	Absent

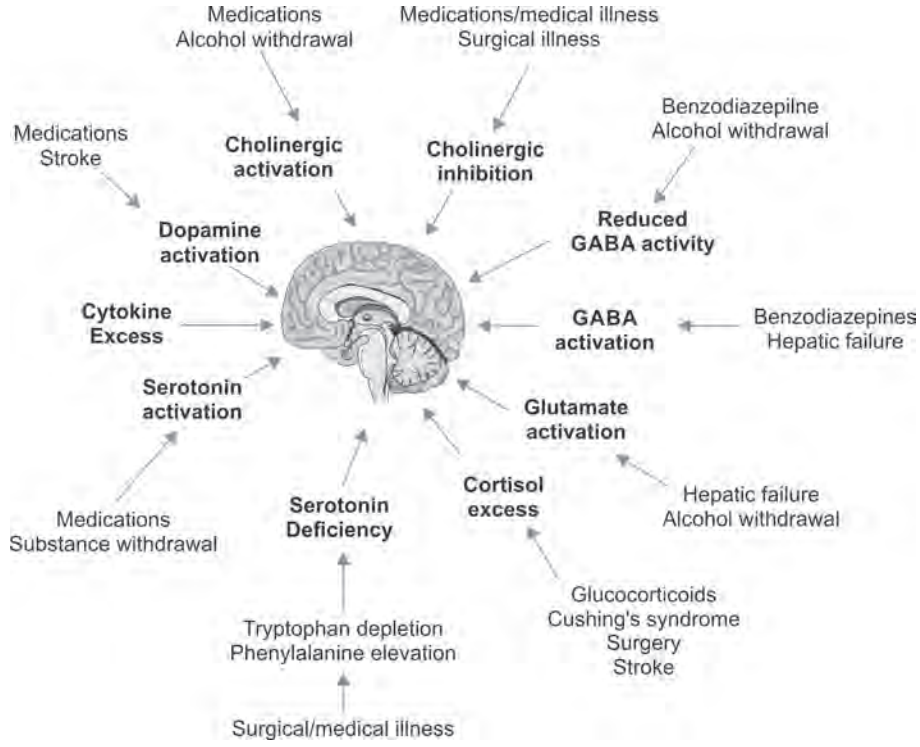

FIG. 2: Pathophysiology of delirium.
(GABA: gamma-aminobutyric acid)

encephalopathy, meningitis/encephalitis, status epilepticus, and poisoning and treat them on priority basis. Other systemic causes should also be ruled out (**Table 2**).

TABLE 2: Etiology of delirium.

Systemic	Infections including urinary tract infection, malaria, pneumonia, sepsis, inadequate pain management, trauma (head injury) dehydration, hypothermia, and hyperthermia
Metabolic	Hypoxia, hyponatremia, hypoglycemia, hyperglycemia, renal, hepatic, thyroid dysfunction, thiamine B_{12}, and nicotine deficiency
Central nervous system	*Stroke*: Ischemic/hemorrhagic, subarachnoid hemorrhage, subdural/ epidural hematoma, meningitis, encephalitis, seizure, and postictal state migraine space occupying lesion brain tumor brain abscess
Cardiac system	Acute myocardial infarction, heart failure, and cardiogenic shock
Medications	Benzodiazepine, morphine, steroid, antiepileptics, antiparkinsonism, and anticholinergics
Toxic substance	Alcohol intoxication or withdrawal, substance misuse or withdrawal, and carbon monoxide poisoning
Others	Postoperative state urinary retention, bladder catheterization and physical retrain

EVALUATION

Immediate Steps

Put the patient on monitoring device so that vital signs are recorded immediately and airway, breathing, and circulation can be assessed and ringer lactate can be started if poisoning is suspected for circulatory support. Abnormal vital signs in nonagitated patient is a dangerous sign and indicates systemic illness. Use the point of care testing to identify the life-threatening cause immediately such as random blood sugar, blood gases, and electrocardiogram (ECG).

History

Taking history in these patients are difficult as patients are often confused and disoriented. In most of the patients' history alone gives the diagnostic clues so emergency physician should obtain the information through previous medical records, family members, and friends. History of fever, headache, suicidal tendency fall or trauma, alcohol use or any substance abuse should be recorded.

Elderly are more vulnerable for acute confusional state/ delirium so emphasis should be given on their medication chart and recent changes done in medication doses. Important drugs that causes acute confusional state/delirium need screening are benzodiazepines, opiates, antidepressants, muscle relaxants, anticholinergics, and sympathomimetics. Anticholinergic group of medication, narcotic, and benzodiazepines are the drugs which commonly precipitate delirium especially in elderly group of population. Promethazine, diphenhydramine, hydroxyzine, lomotil, meclizine, amitriptyline, and doxepin are the drugs with anticholinergic properties and generally prescribed to elderly.

Generally, elderly population with comorbidities are on multiple drugs regimens so while evaluating the delirium in emergency department it is mandatory to check the medication

list regarding recent addition of any culprit medication or dose modification. Emergency physician should take help of **Table 3** to identify the medications/substances.

Physical Examination

Head, eyes, ears, nose, and throat examination, neck examination for stiffness, cardiovascular and respiratory examination for any murmurs or abnormal lung sounds, abdominal and genitourinary examination, and neurological examination: GCS score and asterixis can be seen in hepatic encephalopathy.

Laboratory and Radiology Tests

Appropriate laboratory and radiological tests should be carried out to confirm the suspected conditions. Complete hemogram, kidney function test, liver function test, thyroid function test, and arterial blood gases interpretation are the basic investigations. Electrocardiograph and cardiac enzyme should be performed urgently if any cardiac event is suspected. Chest X-ray will be helpful in identifying the lung pathology.

Computed tomography (CT) head is not indicated in all cases of acute confusional states but more helpful in elderly group of patients, and or on anticoagulation history of trauma immunocompromised patient noncontract CT head is usually sufficient. Lumbar puncture and cerebrospinal fluid (CSF) examination should be considered in patient with fever and confusion. Urine drug screen should be used cautiously due to false positive and negative results. Recommended laboratory and radiology tests are summarized in **Table 4**.

MANAGEMENT

Management of Agitation

Physical or chemical restrains of patient are required whenever there is possibility of "self-harm" and agitated behavior dangerous to hospital staff. Close observation of patient is required to record changes in tone, speech, irritability, clinched jaw, and fist for intervention at the right time. Physician must record the GCS before applying any measures for agitation control. Medications used for chemical restrain are haloperidol (antipsychotic agent)/lorazepam. Few characteristic features of commonly used haloperidol and lorazepam are described in **Table 5**.

Drug Therapy

Haloperidol is commonly used first line medication for delirium. *Haloperidol* given in 2–5 mg intramuscular. *Olanzapine*: 2.5–5 mg orally once a day. *Risperidone* 0.5 mg orally twice daily. *Quetiapine* 12.5–25 mg orally twice daily,

TABLE 4: Laboratory and radiological tests for evaluation of acute confusional state.

Laboratory and radiology investigations	*Clue about causes of acute confusional state/delirium*
Complete hemogram	Acute anemia, (hemorrhage), leukopenia, leukocytosis, (infection), thrombocytosis, and thrombocytopenia
Kidney functions and electrolytes	• Hyponatremia, hypoglycemia, and hyperglycemia, • Acute kidney injury and uremia
Liver functions test and ammonia levels lipase	Jaundice, hepatic failure, hepatic encephalopathy, and pancreatitis
Thyroid function test	Myxedema or thyroid storm
Arterial blood gases	Hypoxia, hypercarbia, and metabolic acidosis
ECG	Myocardial infarction, arrhythmias, and drug toxicity
Cardiac enzyme	Myocardial infarction
Chest X-ray	Pneumonia, pulmonary edema, and heart failure
CT abdomen	Appendicitis, pancreatitis, and obstructive uropathy
Noncontrast CT head	Stoke, mass, and lesion
Lumber puncture and CSF examination	Meningitis and encephalitis

(CT: computed tomography; CSF: cerebrospinal fluid; ECG: electrocardiogram)

TABLE 3: Medication/toxidrome and their systemic effects.

Drugs	*Effects*	*Clinical features*
Alcohol benzodiazepines	CNS depression	Decrease motor activity hypotension
Alcohol benzodiazepines withdrawal	Agitation, excitation, and hallucination	Sweating, tachycardia, and mydriasis
Opiates	Sedation	Hyperventilation and miosis
Opiates withdrawal	Anxiety	Nausea, vomiting, and tachycardia
Cholinergic	CNS depression	• Salivation, lacrimation, urination, bradycardia, and miosis are muscarinic effects • Hypertension, tachycardia, and fasciculations are nicotinic effects
Anticholinergics	Agitation and coma	Tachycardia, flushed and dry skin, dry mucus membranes, hyperthermia, decreased bowel sounds, urinary retention, and mydriasis
Sympathomimetics	Agitation, seizures, and coma	Hypertension, tachycardia, hyperthermia, diaphoresis, hyperpnea, and mydriasis

(CNS: central nervous system)

TABLE 5: Characteristic features of haloperidol and lorazepam.

	Haloperidol	***Lorazepam***
Qualities	High-potency antipsychotic, less sedative, and less chances of exacerbation of delirium	Short-acting
Dose	Mild/moderate cases 0.5–2 mg orally twice/thrice daily. Severe cases 2–5 mg IM every 8 hours	0.5–2 mg orally/IM/IV every 2–4 hours
Precautions	Monitor for extrapyramidal symptoms, hypotension, rise in temperature, and CNS depression	Can cause hypoxic cardiac arrest use cautiously in elderly severely ill and patient with low pulmonary reserve myasthenia gravis
Contraindication	Severe depression, comatose, hypersensitivity, and Parkinson's disease	Hypotension, sleep apnea, severe respiratory insufficiency, and CNS depression
Interaction	Raises tricyclic antidepressant, concentration, and hypotensive action of antihypertensive drugs	Raises toxicity when used with alcohol phenothiazine barbiturates

(CNS: central nervous system; IM: intramuscular; IV: intravenous)

is used for hypoactive form of delirium. *Benzodiazepine*: Lorazepam 2 mg intravenous is also used commonly alone or with haloperidol and diazepam is the drug of choice when delirium is suspected due to alcohol withdrawal.

Specific Treatment

Interpret the history, physical examination, laboratory and radiological investigations, and appropriate drug therapy should be started. Withdraw or reduce the drug causing confusion or delirium. Correct electrolyte abnormalities. Antibiotic to treat the infection. Adequate pain management to reduce the agitation.

Supportive Management

Team of doctor, nurse, social worker, and managers are required to give supportive care. These measures reduce the need of antipsychotics and benzodiazepines drugs. Important measures should be initiated are: Avoid long stay of patient in emergency department. Monitoring device that may irritate the patient should be avoided, vitals can be checked intermittently, and intravenous fluid can also be given intermittently as bolus instead of continuous infusion. False alarm of monitoring devices can also irritate and disorient the patient. Urinary catheters also increase agitation and risk of infection and increase length of hospitalization, there is always risk of traumatic self-removal of catheters. Physical restrain also increases agitation and delirium, use only for brief period if necessary. Arrange adequate lighting of surroundings and presence of family members and close friends. Placing white board/clock/calendar in room displaying date and time for orientation. Increase mobilization by avoiding physical restrain. Minimize sleep disruption provide calm environment. Handle gently. Avoid frequent ward transfers and multispecialty complexity. Provide glasses and hearing aids if necessary. Avoid sedation if possible, they increase confusion and risk of falls.

DISPOSITION

According to various studies acute confusional states/delirium is marker of severity of illness and multiple comorbidities, and also associated with in hospital and long-term mortality. Acute confusional state adversely affects the patient quality-of-life. These patients are more to develop hospital acquired infections, pressure, sore, malnutrition, fractures, and repeated hospitalization. Most of the patients of delirium need hospitalization once they are identified in emergency department. A very few patients can be discharged if closed supervision and monitoring can be arranged at home but frequent hospitalization are reported in these patients.

SUMMARY

Delirium is common in emergency department especially in elderly with comorbid conditions. This nonspecific type of presentation actual has serious underlying pathology. If there is missed diagnosis or delay in management, leads to poor outcome and high in hospital mortality. Confusion assessment method is best tool for emergency department for assessment of delirium. Delirium is acute change in mental status, fluctuation in attention, awareness, and cognition. Physical examination, trauma evaluation, and stroke scale evaluation. Diagnostic evaluation to confirm diagnosis. Treat the underlying cause. Apply supportive and nonpharmacological measures. Haloperidol for hyperactive delirium to control the agitation and quetiapine for hypoactive form of delirium. In view of high morbidity, mortality, and poor outcome, patient should be admitted and managed aggressively. Evaluation and management of delirium is summarized in **Figure 3**.

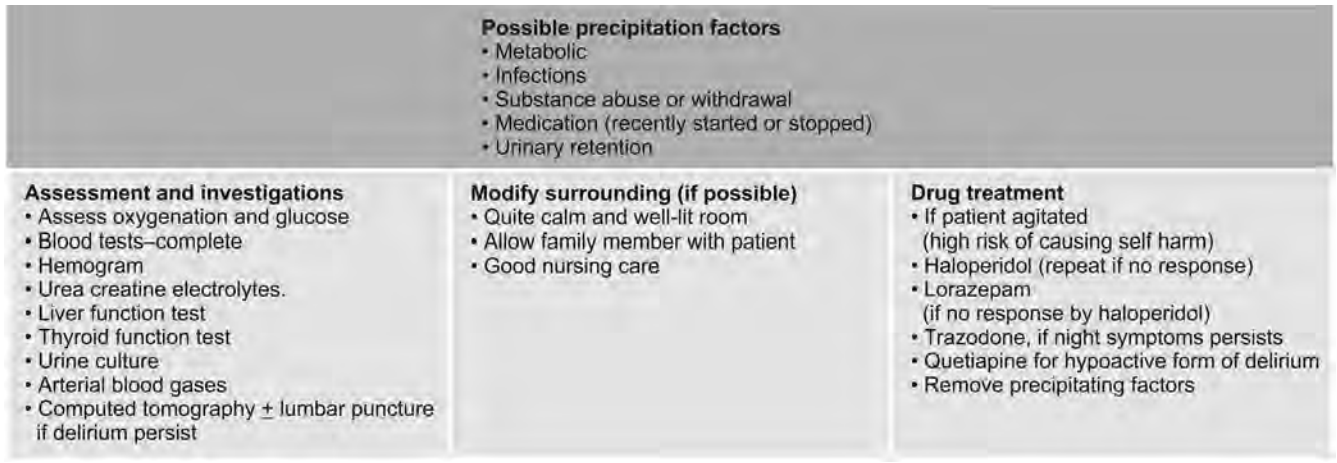
Possible precipitation factors
• Metabolic
• Infections
• Substance abuse or withdrawal
• Medication (recently started or stopped)
• Urinary retention
Assessment and investigations
• Assess oxygenation and glucose
• Blood tests–complete
• Hemogram
• Urea creatine electrolytes.
• Liver function test
• Thyroid function test
• Urine culture
• Arterial blood gases
• Computed tomography ± lumbar puncture if delirium persist
Modify surrounding (if possible)
• Quite calm and well-lit room
• Allow family member with patient
• Good nursing care
Drug treatment
• If patient agitated (high risk of causing self harm)
• Haloperidol (repeat if no response)
• Lorazepam (if no response by haloperidol)
• Trazodone, if night symptoms persists
• Quetiapine for hypoactive form of delirium
• Remove precipitating factors

FIG. 3: Summary evaluation and management: delirium.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Acute Ischemic Stroke

Chandril Chugh

INTRODUCTION

Stroke is considered as one of the leading causes of morbidity and mortality in the world. As per the World Health Organization (WHO), stroke is defined as rapidly progressing neurological deficits that is vascular in origin. Stroke is classified broadly into three categories; ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage. Ischemic stroke occurs due to blockage of blood vessel which limits the blood supply to the brain whereas hemorrhagic stroke occurs due to rupture of blood vessel leading spillage of blood in the intracranial cavity. Hemorrhagic stroke could be classified as intracerebral hemorrhage or subarachnoid hemorrhage depending on the site of blood spillage. Approximately 60–80% of all strokes are ischemic. Assessment and management of patients who have suffered a stroke includes testing to determine the precise etiology of the event so as to prevent recurrence and management of risk factors. Immediate intervention should be applied for minimizing brain injury, treating medical complications, and moving toward uncovering the pathophysiologic basis of the patient's symptoms.

EPIDEMIOLOGY AND RISK FACTORS

According to the WHO, 5 million die and another 5 million are left permanently disabled out of 15 million people who suffer stroke worldwide each year. Worldwide, 68% of all strokes are ischemic and 32% are hemorrhagic. Numbers from the United States of America (USA) differ a little with 87% of all strokes being ischemic, 10% hemorrhagic and about 3% being subarachnoid hemorrhage. Data regarding prevalence of stroke in India is lacking; however, it can extrapolate from the data available from the west. In 2001, crude prevalence rate of stroke in India was 147/100,000 and the annual incidence rate was 36/100,000 as per study done by Banerjee et al.

Men are at higher risk for stroke than women; one-third of strokes occur in persons younger than 65 years, although stroke often is considered a disease of elderly persons. Risk of stroke increases with age, especially in patients older than 64 years, in whom 75% of all strokes occur. Risk factors of stroke are categorized into modifiable and nonmodifiable group (**Box 1**). Patients with cardiovascular disease more prone for embolic ischemic strokes which may arise directly from the heart or the aorta. List of conditions that carry a high-risk for embolic strokes are shown in **Box 2**.

ISCHEMIC STROKE CLASSIFICATION

According to the multicenter trial of acute stroke treatment (TOAST) there are three kinds of ischemic stroke:

1. Large vessel stroke
2. Small vessel stroke or lacunar stroke
3. Cardioembolic stroke

Large artery strokes could be due to thrombotic or embolic occlusion of the major arteries of the brain such as the internal carotid artery (ICA), middle cerebral artery, anterior cerebral

BOX 1: Nonmodifiable and modifiable risk factors.

Nonmodifiable risk factors include:

- Age
- Race
- Sex
- Ethnicity
- History of migraine headaches
- Fibromuscular dysplasia
- *Heredity*: Family history of stroke or transient ischemic attacks (TIAs)

Modifiable risk factors include:

- Hypertension
- Diabetes mellitus
- Cardiac disease
- High cholesterol
- Previous stroke
- Carotid stenosis
- Hyperhomocysteinemia
- *Lifestyle issues*: Excessive alcohol intake, tobacco use, illicit drug use, and physical inactivity
- Obesity
- Oral contraceptive use/postmenopausal hormone use

BOX 2: Risk factors for embolic strokes.

Arrhythmias:
- Atrial fibrillation and paroxysmal atrial fibrillation
- Sick sinus syndrome
- Sustained atrial flutter

Valvular heart disease:
- Rheumatic mitral or aortic valve disease
- Bioprosthetic and mechanical heart valves
- Fibrous nonbacterial endocarditis (i.e., Libman–Sacks endocarditis), antiphospholipid syndrome, and cancer (marantic endocarditis), and systemic lupus erythematosus
- Infective endocarditis

Thrombus and structural lesion:
- Papillary fibroelastoma
- Left atrial myxoma
- Atrial or ventricular thrombus

Structural heart disease:
- Recent myocardial infarction (within 1 month)
- Chronic myocardial infarction together with ejection fraction <28%
- Congestive heart failure with ejection fraction <30%
- Dilated cardiomyopathy

Surgical:
- Coronary artery bypass graft (CABG) surgery

Conditions which have been associated with embolic stroke but lack definitive evidence are mitral annular calcification, patent foramen ovale, left atrial smoke on echocardiogram, atrial septal aneurysm, left ventricular aneurysm, and aortic arch atheroma. Genetic diseases, storage diseases, and traumatic vascular diseases are well known causes of stroke which are beyond the scope of this chapter.

artery or the vertebrobasilar system. Lacunar strokes are more often due to involvement of smaller or perforating blood vessels supplying the deeper structures of the brain.

CLINICAL PRESENTATION

Clinical signs of stroke depend upon the part of the brain involved. American heart association/American stroke association (AHA/ASA) have popularized the FAST algorithm to diagnose stroke in the *prehospital setting*. FAST acronym stands for **F**acial droop, **A**rm weakness, **S**lurred speech, and **T**ime of onset. Another easy way to remember to signs of stroke is the BEFAST method. This method also takes into account the symptoms of the posterior circulation.

BEFAST: **B**alance (loss of balance/dizziness), **E**yes (disturbance of vision in one or both eyes), **F**ace (facial droop), **A**rm (weakness), and **S**peech (slurred) **T**est.

All the symptoms *need not be* present to diagnose stroke. Any of the above-mentioned symptoms can be present and is helpful in diagnosing ischemic as well as hemorrhagic stroke.

For complete assessment of a stroke patient, it is recommended to use the National institutes of health (NIH) stroke scale. According to the latest stroke metrics a patient with acute stroke should be examined by a trained physician or a neurologist within 10 minutes of arrival to the emergency room. Common stroke syndrome and their symptoms are shown in **Table 1**. Common stroke mimics are shown in **Table 2**.

TABLE 1: Common stroke syndrome and their symptoms.

Anterior cerebral artery	• Contralateral motor deficits • Contralateral sensory deficits • Gait apraxia
Middle cerebral artery	• Aphasia (expressive and receptive) • Contralateral motor deficits • Contralateral sensory deficits • Homonymous hemianopia • Neglect
Posterior cerebral artery	• Alexia (inability to read) • Choreoathetosis • Cranial nerve III palsy • Motor deficits • Sensory deficits • Visual disturbances
Vertebrobasilar artery	Ataxia, cranial nerve palsies, coma, dizziness with nausea and vomiting Dysarthria, dysphagia, motor deficits with contralateral sensory deficits
Posterior inferior cerebellar artery (Lateral medullary (Wallenberg's) syndrome)	Ataxia—ipsilateral, contralateral limb with ipsilateral face pain, cranial nerve IX and X palsy, dysmetria, ipsilateral Horner syndrome, nystagmus, and vertigo
Anterior inferior cerebellar artery	Cranial nerves V and VII palsy, ipsilateral Horner syndrome, motor deficit of the face, nystagmus, and vertigo
The five classic lacunar syndromes result from occlusion of a single penetrating artery, which may be caused by small vessel vasculopathy, cardioembolism, or large artery atherosclerosis	• Pure motor—weakness of opposite side of face arm and leg • Pure sensory—sensory loss of opposite side of face arm leg • Sensorimotor—weakness and sensory loss of opposite side of face arm leg • Ataxic hemiparesis—contralateral ataxia out of proportion to mild weakness • Clumsy hand dysarthria—weak face and clumsy ipsilateral hand, dysarthria, and dysphagia

RADIOLOGICAL INVESTIGATIONS IN ACUTE STROKE

Computed tomography (CT): Urgent CT brain under stroke protocol with angiography of head and neck vessels. The most important early imaging test is noncontract CT of the brain. This helps with one of the first branch points of therapy, which is distinguishing hemorrhagic stroke from ischemic stroke. Some hospitals use emergent magnetic resonance imaging (MRI) to evaluate patients with possible stroke, but this is much less common. Rapidly obtaining a noncontract CT of the head should be a priority in working-up the patient with suspected CVA. Head CT is the first and most important test when evaluating for thrombolysis and helps in differentiating

hemorrhage, subdural hematoma, and tumor. On CT, most ischemic strokes eventually become visible as hypodensities of the brain parenchyma, but CT is largely normal for at least 6 hours. The earliest CT signs are loss of the cortical ribbon and gyral edema (**Figs. 1A** and **B**).

Magnetic resonance imaging: On MRI, strokes will appear hyperintense on T2-weighted sequences. Cytotoxic edema and accompanied ischemic cell death can be detected by diffusion-weighted imaging (DWI) and can appear very shortly after onset of ischemia. True diffusion positivity of DWI will appear dark may be delayed up to 48–72 hours, particularly in the brain stem, and typically lasts 10–14 days.

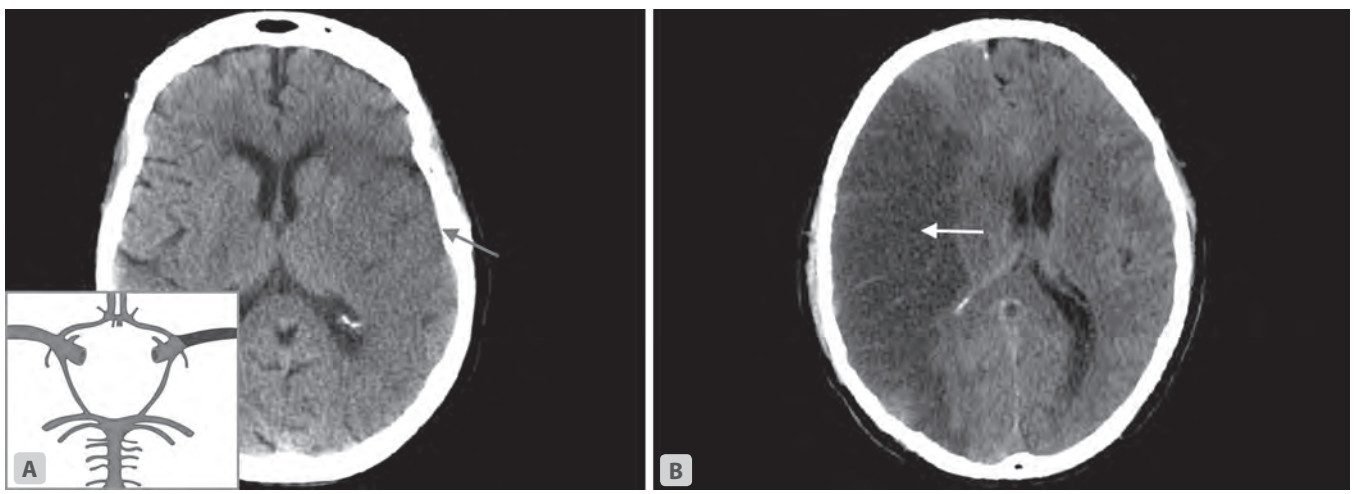
TABLE 2: Stroke mimics.

Toxic-metabolic	• Hypoglycemia or hyperglycemia • Hyponatremia or hypernatremia • Ingestion or overdose • Drug toxicity • Intoxication (alcohol and illicit drugs) • Hepatic encephalopathy
Intracranial hemorrhage	Intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hematoma
Infectious	• Sepsis • Encephalitis • Meningitis
Structural lesions	• Brain mass or tumor • Spinal cord lesion
Others	• Demyelinating disease (i.e., multiple sclerosis), seizure or Todd paralysis • Migraine • Idiopathic intracranial hypertension • Reversible cerebral vasoconstrictive syndrome • Central nervous system vasculitis • Vestibular dysfunction • Hypertensive encephalopathy • Peripheral neuropathy • Dementia • Conversion disorder

Perfusion imaging: Vascular occlusion of the brain causes three-compartment changes in the brain parenchyma and divided into three categories: (1) The infarct core, which represents nonviable brain tissue, which cannot be salvaged; (2) The penumbra, which represents tissue that has reduced blood flow, but the potential for survival if blood flow is restored; and (3) The outer zone, which survives regardless of treatment. Recent endovascular therapy trials utilized perfusion imaging techniques to identify patients with a mismatch between the volume of hypoperfused tissue and the volume of nonsalvageable infarct core.

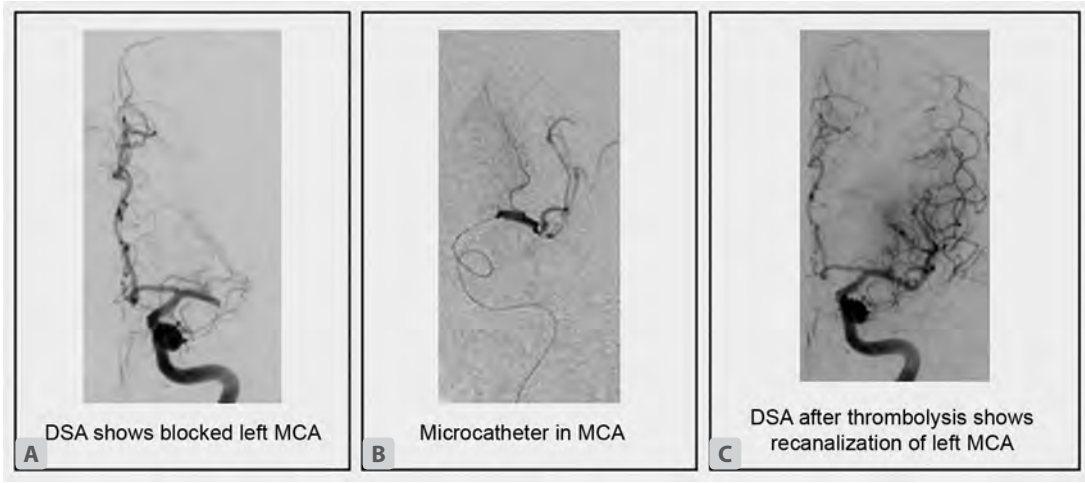
Computed tomography or MRI, both uses the same basic concepts for perfusion imaging. With the help of perfusion imaging we can measure the time for blood to reach brain tissue time to peak of the residual function (Tmax) and mean transit time (MTT) and the amount of blood flowing through the brain vasculature, including capillary and venular flow [cerebral blood volume (CBV) and cerebral blood flow (CBF)]. Tmax is the time it takes the contrast to reach maximum enhancement in the selected region of interest. Time between the arterial inflow and the venous outflow reflected by MTT. CBV is the volume of blood available per unit of brain tissue. CT perfusion uses iodinated contrast whereas magnetic resonance perfusion uses gadolinium to achieve these measurements. The acquisition and processing of perfusion images take time and expose patients to additional iodinated contrast and radiation.

Digital subtraction angiography (DSA): This is the most accurate investigation in diagnosing most of the diseases of blood vessel. A small tube (catheter) is guided from the leg blood vessel into the blood vessel we wish to study followed by dye (contrast) injections to obtain the images (**Figs. 2A** to **C**). CT/MR angiography is also an option in some cases.



(CT: computed tomography; MCA: middle cerebral artery)

FIGS. 1A AND B: (A) CT showing early sign of middle cerebral artery with loss of definition of gyri and grey white boundary; (B) CT scan of brain showing MCA infarct.



(MCA: middle cerebral artery)

FIGS. 2A TO C: Digital subtraction angiography in diagnosis of stroke.

MANAGEMENT OF ACUTE STROKE

Time is most important factor in the management of acute ischemic stroke. Patient with ischemic stroke loses 1,900,000 brain cells every minute, about 14,000,000,000 nerve connections are destroyed every minute, and 12 km (7.5 miles) of nerve fibers are lost every minute. The brain ages 3.6 years for every hour it is deprived of blood supply. Ischemic stroke therapies are cantered on restoring the blood flow in blocked vessels. *There are two modalities of treatment available for treatment of acute ischemic stroke. Intravenous thrombolysis and mechanical thrombectomy*. The only medication currently approved by the Food and Drug Administration (FDA) for acute ischemic stroke is intravenous tissue plasminogen activator (IV tPA), administered within 3–4.5 hours of onset of symptom. Only alteplase is approved for acute stroke thrombolysis.

Concept of thrombolysis: When the blood flow to the brain stops suddenly, brain cells start dying immediately, but few cell in "penumbra" area can survive for few hours with low oxygen or low energy state. If blood flow is restored in this area within window period then these cells can be salvaged and become functional (**Fig. 3**). Favorable outcomes are achieved in 30–50% of cases. Major risk of treatment is symptomatic brain hemorrhage.

Once the clinical diagnosis of an acute stroke is made the following steps need to be followed:

- Ensure that the patient is medically stable.
- Evaluate for reversible causes of neurological symptoms.
- Determine the nature of stroke (ischemic vs. hemorrhagic)
- Treatment of stroke
- Determine the causes of stroke (beyond the scope of this chapter).

Ensure the Patient is Medically Stable: Never Forget the Airway, Breathing, and Circulation

In the treatment of acute stroke time is of the essence. Medical stability of the patient should be established as soon as possible so that stroke management can proceed. Like in every medical emergency airway, breathing, and circulation need to be assessed. Hypoxia should be avoided and corrected

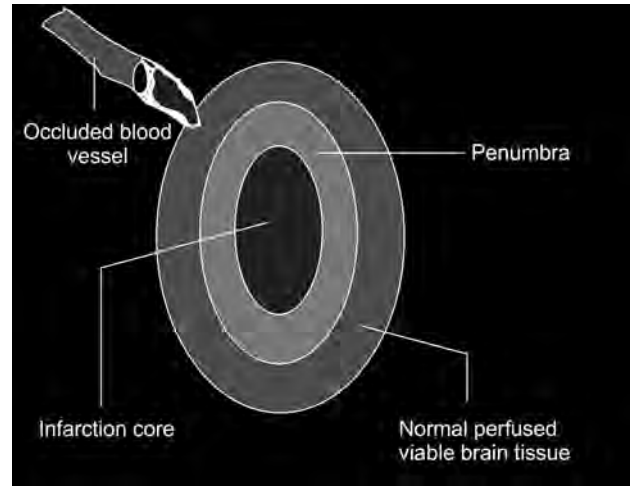


FIG. 3: Concept of thrombolysis (preservation of penumbra).

immediately and if the airway is not protected or the patient needs ventilator support intubation should be considered. Respiratory distress is prominent in large strokes, intracranial hemorrhage, and strokes affecting posterior circulation present with loss of consciousness and bulbar dysfunction.

Evaluation of Reversible Causes of Neurological Symptoms

As per the stroke guidelines of finger-stick glucose it is an essential test before thrombolysis is started. Following basic tests can be considered in special patient groups but the start of thrombolytic therapy if indicated should not be delayed unless the patient has a history of bleeding disorder, is taking anticoagulants or has history of thrombocytopenia. After completion of acute management of stroke other laboratory tests such as liver function, kidney function, etc. can be done.

- Electrocardiogram (this should not delay the noncontract brain CT)
- Complete blood count (CBC) including platelets
- Troponin
- Prothrombin time (PT) and international normalized ratio (INR)

- Activated partial thromboplastin time (aPTT)
- Ecarin clotting time (ECT), thrombin time, or appropriate direct factor Xa activity assay (if the patient is taking new oral anticoagulants)

Determine the Nature of Stroke (Ischemic vs. Hemorrhagic)

First test needed to start stroke treatment is a plain head CT. Head CT without contrast is sufficient to rule out hemorrhage and start stroke treatment. As per the guidelines, systems should be established so that brain imaging studies should be performed within 20 minutes of arrival in the emergency department (ED) in patients who may be candidates for intravenous alteplase and/or mechanical thrombectomy (door to imaging time). Further studies can be conducted depending on the time of onset of symptoms which will further aid in management.

- *If the patient presents within first 6 hours of symptoms onset:* CT scan should be combined with CT angiogram of the brain and the neck to rule out large vessel occlusion, should not wait for serum creatinine results. Whenever possible CT angiogram should be completed with the CT scan to save time for possible mechanical intervention.
  MRI or MR angiogram or MR perfusion is not indicated within the first 6 hours of symptom onset.
- *For patients presenting between 6 and 24 hours of symptom onset:* In selected patients with acute ischemic stroke within 6–24 hours of last known normal who have large vessel occlusion in the anterior circulation, obtaining CT perfusion, diffusion weighted-MRI, or MRI perfusion is recommended to aid in patient selection for mechanical thrombectomy.

INTRAVENOUS THROMBOLYSIS

As recommended by AHA/ASA intravenous tPA infusion is treatment modality of choice for patients presenting within first 3 hours of onset of symptoms. The treatment window can be extended to 4.5 hours for eligible patients. Use of intravenous alteplase is based on the landmark National Institute of Neurological Disorders and Stroke (NINDS) tPA trial which showed that patients who received tPA were at least 30% more likely to have minimal or no disability at 3 months on the assessment scales. Outcome measures were in favor of the group that received tPA [global odds ratio (OR) for a favorable outcome, 1.7; 95% confidence interval (CI), 1.2–2.6]. A pooled analysis of Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), European Cooperative Acute Stroke Study (ECASS), and NINDS was published in 2004 which showed that the tPA window could be extended to 4.5 hours with reasonable benefit to the patient. ECASS-III definitively established the efficacy of tPA within 3–4.5 hours window. ECASS-III showed that patients who received tPA within 3–4.5 hours window had a better chance to a favorable outcome with an OR of 1.42 (95% CI, 1.02–1.98, $p = 0.04$).

Intravenous tPA infusion can only be given to eligible patients and there are strict inclusion and exclusion criteria (**Box 3**) as per stroke guidelines published in 2018.

- The checklist includes some FDA-approved indications and contraindications for administration of intravenous recombinant (IV rtPA) for acute ischemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.
- Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.

BOX 3: Inclusion and exclusion criteria for intravenous tPA infusion.

Inclusion criteria:

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <3 hours before beginning treatment
- Aged ≥18 years

Exclusion criteria:

- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated blood pressure (systolic > 185 mm Hg or diastolic > 110 mm Hg)
- Active internal bleeding
- Acute bleeding diathesis
- Platelet count < 100 000/mm^3
- Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
- Current use of anticoagulant with INR >1.7 or PT > 15 seconds
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration <50 mg/dL (2.7 mmol/L)
- CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
- Relative exclusion criteria
- Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present.
- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Pregnancy
- Seizure at onset with postictal residual neurological impairments
- Major surgery or serious trauma within previous 14 days
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Recent acute myocardial infarction (within previous 3 months)

(aPTT: activated partial thromboplastin time; CT: computed tomography; ECT: ecarin clotting time; INR: international normalized ratio; PT: prothrombin time; TT: Thrombin time; IVrtPA: intravenous recombinant tissue plasminogen activator)

- In patients without recent use of oral anticoagulants or heparin, treatment with IV rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.
- In patients without history of thrombocytopenia, treatment with IV rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100,000/mm^3.

There are additional relative exclusion criteria for patients in 3–4.5 hours window that determine if the patients are eligible for tPA or not (**Box 4**).

A primary goal of achieving door to needle time (DTN) within 60 minutes in ≥50% of acute ischemic stroke patients treated with IV alteplase should be established. It may be reasonable to establish a secondary DTN time goal of achieving DTN times within 45 minutes in ≥50% of patients with acute ischemic stroke who were treated with IV alteplase.

Dose of tPA: As per the guidelines, infuse 0.9 mg/kg (maximum dose 90 mg) over 60 minutes, with 10% of the dose given as a bolus over 1 minute.

For treatment within 3 hours of stroke onset, alteplase led to a good outcome for 33% versus 23% for control (OR 1.75; 95%, CI 1.35–2.27). The number needed to treat (NNT) for one additional patient to achieve a good outcome was 10.

For treatment from 3 to 4.5 hours, the proportion with a good outcome in the alteplase and control groups was 35 and 30% (OR 1.26; 95%, CI 1.05–1.51, and NNT 20).

The benefit of IV defibrinogenating agents and of IV fibrinolytic agents other than alteplase and tenecteplase is unproven; therefore, their administration is not recommended outside a clinical trial. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.

BOX 4: Additional relative exclusion criteria.

- *Aged >80 years:* For patients >80 years of age presenting in the 3–4.5 hours window, IV alteplase is safe and can be as effective as in younger patients (New Recommendation)
- *Severe stroke (NIHSS > 25):* The benefit of IV alteplase between 3 and 4.5 hours from symptom onset for patients with very severe stroke symptoms (NIHSS > 25) is uncertain. (Class IIb; LOE C-LD) (New Recommendation)
- *Taking an oral anticoagulant regardless of INR:* For patients taking warfarin and with an INR ≤1.7 who present in the 3–4.5 hours window, IV alteplase appears safe and may be beneficial. (Class IIb; LOE B-NR) (New Recommendation)
- *History of both diabetes and prior ischemic stroke:* In patients with prior stroke and diabetes mellitus presenting in the 3–4.5 hours window, IV alteplase may be as effective as treatment in the 0–3 hours window and may be a reasonable option. (Class IIb; LOE B-NR) (new recommendation)

(IV: intravenous; INR: international normalized ratio; NIHSS: National institutes of health stroke scale)

Blood Pressure Management in Acute Ischemic Stroke

In thrombolytic candidate: *Labetalol* (if no bradycardia and bronchospasm) 5–10 mg IV every 5 minutes. If not controlled in <4 doses start infusion: *Nicardipine infusion* 5–15 mg/h: *Hydralazine* (if bradycardia and bronchospasm) 5–20 mg IV every 5 minutes. If not controlled in <4 doses change to nicardipine infusion

If not a candidate for thrombolysis: Ischemic stroke: Treat only blood pressure (BP) >230/120 mm Hg or end organ failure, and maximum reduction <20%.

Complications of Intravenous Thrombolysis

Complications related to IV rtPA include symptomatic intracranial hemorrhage, major systemic hemorrhage, and angioedema in approximately 6%, 2%, and 5% of patients, respectively. Guidelines recommend strict BP control and serial neurological exams to diagnose intracranial hemorrhage (15, 40). In the event that an intracranial hemorrhage is suspected it is recommended to stop alteplase infusion and perform stat laboratories which include a CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match. An emergent nonenhanced head CT should be performed to evaluate further. Intravenous cryoprecipitate (includes factor VIII), at a dose of 10 U infused over 10–30 minutes (onset in 1 hour, peaks in 12 hours) should be administered and may be repeated for fibrinogen level of <200 mg/dL. Tranexamic acid or ε-aminocaproic acid may also be used. Stat hematology and neurosurgery consultations should be sought. Supportive therapy should continue. Angioedema should be treated like an allergic reaction and emergent intubation may be needed if breathing difficulty is present. Use of antihistamines and steroids are recommended in managing angioedema.

ENDOVASCULAR TREATMENT FOR STROKE

For almost 20 years IV tPA has been the backbone of stroke treatment. Intravenous therapy (IVT) although effective has specific inclusion and exclusion criteria which limits its use in a large number of patients. Moreover, the IV tPA cannot be used after the 4.5 hours window and has limited efficacy in patients with large vessel occlusion. Riedel et al. showed that it is almost impossible to dissolve large clots with IVT. In another study by Alexandrov and Grotta up to onethird of patients had re-occlusion of blood vessels after initial recanalization.

Over the last two decades the field of endovascular stroke intervention has grown exponentially. From initial trials of intra-arterial tPA infusion to initial clot retrieval devices and now to stent retriever technology the field has come a long way indeed. Initial trials, Pro-Urokinase for Acute Cerebral Thromboembolism I (PROACT I) and II showed promise with intra-arterial pro-urokinase infusion with improved outcomes and recanalization rates, however, pro-urokinase was never approved by the FDA citing need for further confirmatory trials. Intra-arterial therapy theoretically sounds promising but has never been shown to improve outcomes or decrease mortality in randomized trials, thus is not the preferred approach today.

First generation device, the mechanical embolus removal in cerebral ischemia (MERCI) device (**Figs. 4A** and **B**), was approved for mechanical thrombectomy by the FDA and marked the beginning of era of endovascular stroke intervention. The MERCI device was tested in the MERCI and MULTI-MERCI trials both which had significantly high mortality (44% and 34% respectively), despite that the patients who had successful recanalization had a better chance at achieving good functional outcome. These trials laid the foundation for further research in the field of acute stroke intervention.

In 2013, three landmark trials SYNTHESIS, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and Interventional Management of Stroke (IMS III) were published and disappointingly all three trials ruled against endovascular stroke intervention. The SYNTHESIS trial compared treatment with IV tPA alone to intra-arterial thrombolysis with rtPA, mechanical clot disruption or retrieval or a combination of these approaches. There was no difference in good clinical outcome (42%) in the endovascular arm versus (46%) in the IV tPA arm. Mechanical device was used in only 56/181 patients and stent retrievers were only used in 23 patients. MR RESCUE trial compared patients receiving standard care versus endovascular therapy using the MERCI device and the PENUMBRA system. Patients with intracranial ICA or M1 occlusion, NIHSS ≥6 and within 8 hours of symptoms onset were enroled. This trial showed no difference in outcomes of patients in the two groups. Reperfusion, defined as modified thrombolysis in cerebral infarction score (mTICI) 2a/3 was 67% and defined as mTICI 2b/3 was only 27%. Good clinical outcome [modified Rankin scale (mRS 0–2)] was only demonstrated in 14%. IMS III trial showed a similar outcome with 41% good clinical outcome (mRS 0–2) in the combined IVT/endovascular therapy arm versus 39% in the IVT only arm. IMS III did not require demonstration of vascular occlusion until the trial was midway when CT angiogram was included in the study protocol. IMS III also did not standardize the endovascular therapy as a result; the methods were a mix of pharmacological thrombolysis, manipulation of clot with use of a guidewire or microcatheter, mechanical and aspiration thrombectomy, and stent-retriever technology. These trials failed to show any benefit of endovascular intervention over the IVT for a variety of reasons. These trials did not standardize the noninvasive vascular imaging thus in IMS III > 50% patients did not undergo vascular imaging. The endovascular therapy was performed using older devices and thus the results were often not promising. There were long delays from stroke onset to revascularization, in part due to lack of rapid workflow.

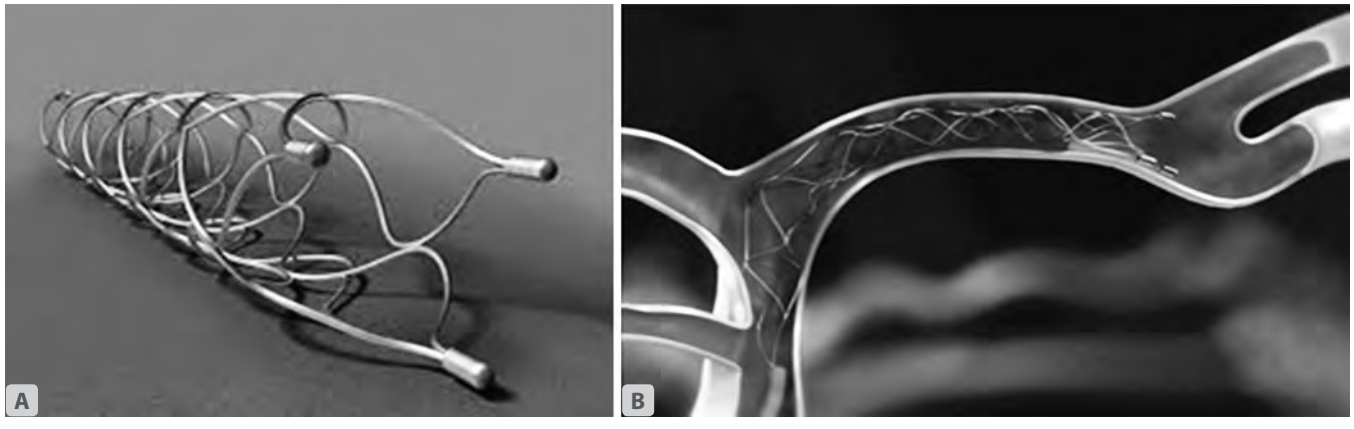
Learning from the shortcomings of the trials done in 2013, multiple trials were started using standardized endovascular and imaging approaches. Six trials published from 2014 to 2016 showed statistically significant benefit of patients with anterior circulation strokes who presented within 6 hours of onset of symptoms. These trials have established the efficacy of mechanical thrombectomy over IVT with patients doing considerably well in the endovascular arm. The meta-analysis of the trials including the three negative trials IMS III, SYNTHESIS, and MR Rescue trial have shown benefit of endovascular intervention. The adjusted combined OR for reduced disability at 90 days was 2.49, 95%, CI 1.76–3.53; $p < 0.0001$ and NNT to reduce the disability by at least one point was 2.6. The largest meta-analysis to date included the above eight trials and also preliminary data from THERAPY and THRACE trial, the rate of functional independence (i.e., a 90-day mRS score of 0–2) was significantly greater for the intervention group compared with the control group (46 vs. 27%; OR 2.35; 95%, CI 1.85–2.98).

Recent success of DAWN and DEFUSE 3 trials has further extended the window for mechanical thrombectomy from 6 to 24 hours. These trials have also made it easier to manage patients presenting with wake-up strokes or unknown time of onset in the preceding 24 hours (**Table 3**). DAWN trial enrolled 206 patients with stroke onset between 6 and 24 hours. There was a 33% adjusted difference in functional outcome in favor of the intervention arm. The NNT for one additional patient to achieve functional independence was 3. Likewise, in the DEFUSE 3 trial there was a 28% adjusted difference in functional outcome in favor of the intervention arm and therefore, the NNT for one additional patient to achieve functional independence was 3.6.

Mechanical thrombectomy—is now strongly recommended for patients in whom large arteries within the brain are blocked.

CRYPTOGENIC STROKE

Cryptogenic stroke can be defined as, if no probable cause is identified for ischemic stroke after complete standard diagnostic evaluation. Cryptogenic stroke is about 10–35% of



FIGS. 4A AND B: Mechanical embolus removal in cerebral ischemia (MERCI) device.

TABLE 3: Characteristics of DAWN and DEFUSE-3 trials.

DAWN	*DEFUSE-3 trials*
Clinical inclusion criteria age 18 years Baseline NIHSS score 10 Prestroke mRS <1	Clinical inclusion criteria age 18–90 years Baseline NIHSS score ≥6, Prestroke mRS ≤2
Eligible 6–24 hours after last seen well	Eligible 6–16 hours after last seen well
Occlusion of intracranial ICA or proximal MCA	Occlusion of extracranial or intracranial ICA or proximal MCA
• Group A: >80 years, NIHSS ≥10; infarct volume ≤21 • Group B: <80 years, NIHSS ≥10; infarct volume ≤31 • Group C: <80 years, NIHSS ≥20; infarct volume ≤51	Infarct volume <70 mL+ ratio of ischemic tissue to initial infarct volume of >1.8
CT or magnetic resonance–based imaging	CT or magnetic resonance–based imaging
Rapid software for image analysis	Rapid software for image analysis
Only Trevo (Stryker, Kalamazoo, and MI) device allowed for recanalization	All FDA-approved devices for recanalization allowed

(CT: computed tomography; ICA: internal carotid artery; FDA: Food and Drug Administration; MCA: middle cerebral artery; mRS: modified rankin scale)

all ischemic stroke but with availability of advanced testing in higher center, this percentage has declined to 10–15%. Cryptogenic strokes are mostly embolic in origin either from heart or right to left shunt. In young adult, patent foramen ovale and in elderly group occult paroxysmal atrial fibrillation is commonly found as a source of cryptogenic stroke.

SUMMARY

Management of acute ischemic stroke is time dependent. Efficient and effective stroke care depends on a well-functioning team from the emergency room to the neurologist and the interventional neurologist. Accurate diagnosis, emergent management to stabilize the patient, and correct choice of imaging can make a lot of difference in the outcome of a patient. Every minute lost in wrong imaging or laboratory test results in decrease in functional outcome and ultimately irreversible paralysis. Success of stroke treatment is dependent on the entire team working smoothly and efficiently. As the times evolve, more and more centers will come up with dedicated stroke teams just like cardiologists manage acute myocardial infarction. Although, future of stroke care is bright, two major roadblocks persist public awareness and hospital competence. Hopefully, this chapter will help with at least one of them.

MULTIPLE CHOICE QUESTIONS

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Subarachnoid and Intracerebral Hemorrhage

120 CHAPTER

Alireza Baratloo, Arash Safaie

INTRODUCTION

When blood goes out of the vessels, it can enter into the subarachnoid or intracerebral (whether intraparenchymal and/or intraventricular) space, depending on the position of the ruptured vessels, known as hemorrhagic strokes. Hemorrhagic strokes are count for almost 10–15% of all stroke cases, but accompanied with higher mortality rate than nonhemorrhagic ones, so need different management. Due to increasing the mean age of population, it is expected that the incidence going to be raised in near future.

ETIOLOGY/CAUSES

Spontaneous hemorrhage, as the name implies, is caused by the rupture of blood vessels and the withdrawal of blood from the vascular bed. These vessels are usually those that have been damaged or weakened for various reasons, frequently in form of aneurysms and vascular malformations. Also, some categorized the etiologies based on patient's age and type of hemorrhage. When it comes to subarachnoid hemorrhage (SAH), aneurysm is the most frequent known etiology in all age groups; On the other hand, hypertensive hemorrhage and cerebral amyloid angiopathy (CAA) are the most prevalent etiologies of elderly and brain vascular malformations in both pediatrics and young/middle aged adults affected by spontaneous intracerebral hemorrhage (ICH). Neoplasms, bleeding diathesis and coagulopathies, acute ischemic stroke hemorrhagic transformation, and cerebral venous thrombosis are all among other known etiologies of hemorrhagic stroke (**Table 1**).

PATHOPHYSIOLOGY OF THE CONDITION

Various pathophysiology has been proposed based on different etiologies. Lipohyalinosis of blood vessels and also deposition of amyloid in the layers of the vessel are the most important ones that has been defined in this regard, both of which weaken the vessel wall and lead to decreased tone and poor compliance. Lipohyalinosis may also lead to aneurysmal dilatations of some vessels. As well, aneurysms can form due to micro-injuries within the vessel wall that earlier affected by hyperplastic arteriolosclerosis.

TABLE 1: Etiologies and risk factors for subarachnoid hemorrhage and intracerebral hemorrhage.

	Subarachnoid hemorrhage	
Intracerebral hemorrhage	***Aneurysmal***	***Nonaneurysmal***
• Hypertension • Cerebral amyloid angiopathy • Vascular malformations • Hemorrhagic transformation of ischemic strokes (including venous sinus thrombosis) • Septic embolism and mycotic aneurysm • Brain tumors • Bleeding disorders and antithrombotic drugs • Central nervous system infection • Moyamoya • Vasculitis • Sympathomimetic drugs	• Vascular malformations • Intracranial arterial dissection • Cerebral venous thrombosis • Sickle cell disease • Bleeding disorders and anticoagulant therapy • Traumatic • Sympathomimetic drugs • Pituitary apoplexy • Cerebral amyloid angiopathy	• Cigarette smoking • Hypertension • Autosomal dominant polycystic kidney disease • Glucocorticoid-remediable aldosteronism • Ehlers–Danlos syndrome • Family history of subarachnoid hemorrhage • Alcohol consumption • Sympathomimetic drugs • Antithrombotic drugs • Hypocholesterolemia and statin drugs

CLINICAL PRESENTATION AND RED FLAGS

Subarachnoid hemorrhage is usually present with severe thunderclap headache but may also present with syncope, decreased level of consciousness, neck pain, nuchal rigidity, seizure, and other nonspecific symptoms. The range of symptoms of spontaneous ICH is even wider, and depending on the site of bleeding and the volume, may vary from a mild headache to a deep coma with/without focal neurologic deficits. An important point is that over first hours, the symptoms may worsen or rarely improve. Taking everything into account, there is no definite finding in terms of diagnosis of hemorrhagic stroke patients, and diagnostic certainty always needs brain imaging.

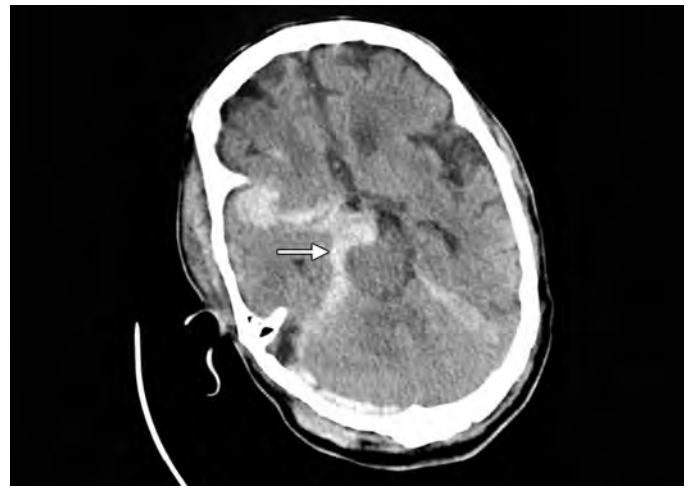
EVALUATION AND INTERPRETATION OF FINDINGS

Beside stabilization process considering airway and breathing, a brief oriented history should be taken from the patient, if possible, and his/her accompanies including: chief complaint, onset of symptom, duration of symptom, course of symptom, precipitating factors, and associated features; underline disease such as diabetes, hypertension, dysrhythmia, hypercholesterolemia, autosomal dominant polycystic kidney disease, glucocorticoid-remediable aldosteronism, and Ehlers–Danlos syndrome; recent or previous hospitalization, head trauma or any stroke event; drug history especially anti-coagulant agents; social habits such as recreational drug use (mainly sympathomimetic), smoking, and excessive alcohol intake. Apparently, measurement of all vital signs including bedside testing of blood glucose by glucometer is necessary. Thereafter, a detailed and complete neurological examination is required. These evaluations rise some differential diagnosis that needs further paraclinical investigations for rule in/out.

INVESTIGATIONS

In patients who do not need establishing a definite airway urgently, do not need respiratory support, and are not in shock state the only two recommended modalities before performing urgent brain imaging are bedside testing of blood glucose by glucometer in patients with a decreased level of consciousness and obtaining an electrocardiogram (ECG). Head computed tomography (CT) scanning is the modality of choice for detecting blood in the brain.

In most of the cases, both SAH and ICH are easily diagnosed due to hyperdense appearance of blood (density of 30–80 HU) in subarachnoid or intracerebral area (**Figs. 1** and **2**). The sensitivity of the CT scan for detecting blood in the subarachnoid space is nearly 100% in the first 6–12 hours after the bleeding. Nevertheless, the sensitivity gradually decreases over time and reaches about 90% and 50% in 24 hours and 5 days after bleeding, respectively. Therefore, when the history and the physical examination are suggestive of a SAH, the physician should perform a lumbar puncture to exclude it. This is particularly true when the imaging has been performed >6 hours after the symptoms developed. A normal head CT scan and absence of xanthochromia and zero or few red blood cells (RBCs) in cerebrospinal fluid (CSF) exclude the SAH (**Flowchart 1**). However, equivocal findings may require further evaluations or repeating the performed tests. More advanced brain imaging technique such as CT angiography, digital subtraction angiography (DSA), or magnetic resonance imaging (MRI) may be still required in further management steps but not as primary assessment.



(CT: computed tomography; SAH: subarachnoid hemorrhage)

FIG. 1: Axial view of head CT scan showing SAH (white arrow).

(CT: computed tomography; ICH: intracranial hemorrhage; IVH: intraventricular hemorrhage)

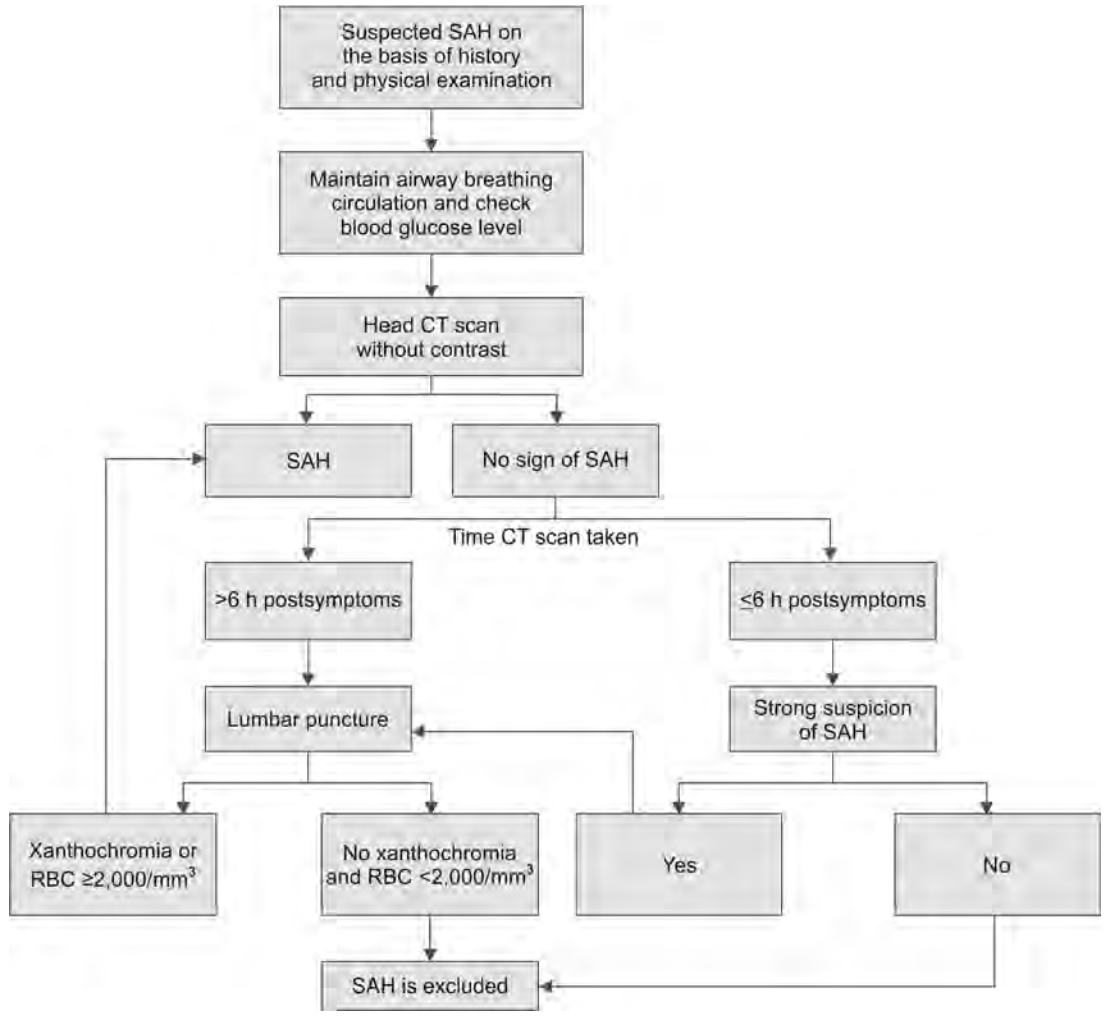
FIG. 2: Axial view of head CT scan showing ICH (white arrow) and IVH (arrowhead).

Other recommended laboratory tests for patients with SAH or ICH include complete blood count, basic biochemistry panel, coagulation profile, and cardiac troponin level.

TREATMENT

Subarachnoid hemorrhage and ICH have some same and also specific management in term of both surgical and nonsurgical interventions. All patients with SAH need neurological surgeon's consultation. Patients with ICH are generally managed medically by neurologists, though there are few indications for surgical intervention.

- *Airway management*: The physician should be warned of the risk of sudden airway compromise due to the deterioration of the neurologic status. Oral intratracheal intubation with rapid sequence induction is the method of choice



(CT: computed tomography; RBC: red blood cell; SAH: subarachnoid hemorrhage)

FLOWCHART 1: Diagnosing subarachnoid hemorrhage.

for securing the airway in these patients. The liberal use of opioids for the pretreatment is recommended to inhibit sympathetic response to laryngoscopy. Most intravenous inducting agents are safe in the setting of suspected raised intracranial pressure (ICP). Although ketamine does not rise the ICP, it is wise to avoid it in SAH and ICH patients due to the possibility of elevating blood pressure and rebleeding or hematoma growth. Either succinylcholine or nondepolarizing neuromuscular blocking agents can be used.

- *Blood pressure control*: The latest recommendation for the target point is systolic blood pressure (SBP) <140 mm Hg in ICH that should be achieved during the first hour using titratable agents to prevent the expansion of present hematoma. However, if elevated ICP presents based on signs, symptoms, and radiologic findings; the physician should decrease blood pressure to the point that cerebral perfusion pressure (CPP) remains in the range of 60–80 mm Hg. Intravenous labetalol and nicardipine are the first line agents. Angiotensin-converting enzyme (ACE) inhibitors like enalapril could be administered as the second line option. It seems that nitroprusside and nitroglycerine may increase ICP, so they should be avoided.

  In SAH the target point is SBP < 160 mm Hg that could be achieved by various titratable agents such as nicardipine or labetalol to prevent stroke and rebleeding, and also maintaining proper CPP. As mentioned in case of ICH, nitroprusside should be also avoided in SAH. Oral nimodipine improves neurological outcomes and should be administered to all patients with SAH.
- *Blood Sugar control*: Blood glucose level on admission affects the outcome of the hemorrhagic stroke patients, and it is claimed that hyperglycemia is associated with poorer prognosis, length of hospital stays, and increased risk of 30-days mortality. However, the target level is still unclear and the latest recommendation is to do not interfere unless the blood glucose level is above 180 mg/dL.
- *Reversal of anticoagulation*: The higher the international normalized ratio (INR), the higher the incidence of early neurological deterioration of hemorrhagic stroke patients. There is an agreement on that coagulopathy should be corrected, so in all hemorrhagic stroke patients who had impaired INR, early correction of coagulopathy is necessary and a combination of vitamin K, and fresh frozen plasma (FFP) or 4-factor prothrombin complex concentrates (PCC) or recombinant factor VII (rFVIIa) should be administered

with the aim of INR correction. Vitamin K should be administered intravenously (IV) that takes almost 6 hours to reach its therapeutic levels. Therefore, a rapid-acting agent should also be administered that can be chosen between FFP, 4-factor PCC or rFVIIa. Choosing either of these drugs has its advantages and disadvantages over the other that is beyond the scope of this chapter. The most serious adverse events have been associated with rFVIIa administration; therefore, it is the least recommended agent in this regard contrary to the agreement mentioned above on correction of warfarin induced coagulopathy, there is no consensus on antiplatelet medications. In general, no intervention is needed routinely in all antiplatelet users; but desmopressin (DDAVP) may have some benefits in patients with renal failure and platelet dysfunction, and also platelet transfusions in case of severe thrombocytopenia. For who are under treatment by intravenous heparin infusion, beside discontinuation of the infusion, protamine sulfate should be administered. Although reversal may be incomplete, but the same approach is also recommending for those who are receiving low-molecular-weight heparin.

- *Antifibrinolytic*: As much as there is agreement on administration of antifibrinolytic agents (e.g., tranexamic acid) in case of ICH, there are controversies in case of SAH. Early definitive obliteration of the aneurysm in SAH is generally superior to all other interventions; but in cases that neurosurgical interventions are not readily available, short-term antifibrinolytic may be beneficial. It was claimed that early administration of tranexamic acid to SAH patients lead to reduction of rebleeding rate.
- *Seizure management*: Although not frequent, but seizure can lead to rebleeding and increased ICP in SAH patients. Apparently, actual seizure should be immediately controlled, but prophylactic anticonvulsants are optional. There is no strong evidence against its use in SAH patients but may have no benefit. Overall, guidelines still recommend to administration of a short course of prophylactic anticonvulsants during immediate posthemorrhage period and before definitive aneurysm treatment in SAH patients, particularly in those with altered mental status. Routine long-term use is not recommended except in specific situation that is beyond the scope of current chapter. Newer anticonvulsants such as levetiracetam may be superior to phenytoin in terms of long-term side-effects. The role of prophylactic anticonvulsants administration in ICH cases also remains uncertain. Unlike SAH, clinical seizures have not been associated with worse outcome in ICH. Current guidelines do not recommend routine prophylactic anticonvulsants in ICH except in those who had seizures or in patients that nonconvulsive ictal activity cannot be excluded (i.e., deeply comatose patients) and continuous electroencephalography (EEG) monitoring may be valuable in the latter.
- *Intracranial pressure control*: The hematoma itself or the surrounding edema can result in elevated ICP, which can precipitate secondary brain injury and neurologic deterioration. Elevation of the head of the bed and providing the patient with adequate analgesia and sedation are the mainstay of preventing ICP elevation in ICH. The patients should be treated with normal saline and hypotonic fluids should be avoided.

  In case of elevated ICP, osmotic agents such as mannitol and hypertonic saline are the first line agents. Though the care should be taken while achieving a mild serum hyperosmolality (300–310 mOsmol/kg), maintain normovolemia and prevent marked hyperosmolality and hypernatremia. Using the barbiturate anesthesia is the next step in managing raised ICP. Nevertheless, the physician should be aware of its adverse effects including hypotension. Hyperventilation ($PaCO_2$: 25–30 mm Hg) decreases ICP markedly. However, its effect is temporarily and in the cost of decreasing CPP. Therefore, it should be avoided generally and only be used when the aforementioned steps failed to decrease ICP.

  Neuromuscular blockade can reduce ICP. However, due to its potential adverse effects including pneumonia, it is generally avoided. Glucocorticoids are ineffective in reducing or preventing increased ICP in ICH.
- *Surgical interventions*: Most patients with spontaneous ICH do not benefit from the surgical evacuation of the hematoma. The most accepted criteria for evacuating a hematoma in spontaneous ICH are cerebellar hematomas with >3 cm in diameter and lobar hematomas with >30 mL volume which are within 1 cm of the cortical surface. Aneurysmal or vascular malformation related SAH and ICH patients are treated by surgical or interventional radiology interventions. In patients with SAH or ICH who develop hydrocephalus, an external ventricular drain (EVD) may be placed.
- *Other managements*: In addition to all mentioned managements, control of pain, vomiting, fever and anxiety, and stress ulcer prophylaxis are also essential. Also, venous thromboembolism (VTE) prophylaxis with compression stockings and intermittent pneumatic compression is recommended in all hemorrhagic stroke patients as soon as possible.

DISPOSITION

All patients with diagnosis of SAH or ICH definitely need to be admitted in intensive unit care (ICU), whether candidate for neurosurgical intervention or not. If not available, close monitoring is still required.

SUMMARY

The ICH can be detected readily by head CT scan. However, detection of a SAH may need lumbar puncture and CSF analysis. There are various managements that can be considered for dealing with these patients, but all with either conditions need to be admitted in ICU and treated by neurologist and/or neurological surgeon.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Seizures and Status Epilepticus

Gouri A Ranade, Priyanka G Mahale

INTRODUCTION

Status epilepticus (SE) is the most extreme form of seizure in which aggressive approach can save many lives. Delay in treatment can lead to significant morbidity and mortality. SE is a very common medical emergency in day to day critical care and emergency care practice. Annual incidence rates for generalized SE range from 3.6 to 6.6/100,000 in European countries. The incidence rate is significantly high if all kinds of sporadic epileptiform discharges (SED) are included and is about 41/100,000 in United States. Reported mortality rate is 17–26% and significant morbidly including disabling neurological deficits range from 10–23% among the cases who survived SE. It is very important to recognize and treat SE at an early stage as longer the duration of seizures, higher the chances of landing it into refractory SE. In emergency settings, the treating physician is the first contact and should be familiar with various steps of management of SE. He or she should not wait for the specialist to start treatment for SE. An early and aggressive treatment can lead to early control of seizures and a state of refractory status can be avoided. For further management of SE especially refractory SE a team of neurologist with expertise in electrophysiology and critical care expert is required as such patients require continuous monitoring in intensive care unit (ICU) including continuous electroencephalogram (EEG). Status epilepticus is a common neurological emergency seen in prehospital setting and in emergency department. It is necessary for all emergency physicians to recognize and promptly treat SE, as they are associated with significantly high morbidity.

Status epilepticus was earlier defined as a continuous seizure lasting >30 minutes, or two or more seizures without full recovery of consciousness between any of them. Later the definition was modified as: Status epilepticus is defined as any seizure that is prolonged after initiation of mechanisms to terminate the seizure within 5 minutes. This rephrasing ensured early and aggressive treatment of SE.

Refractory/malignant status epilepticus: Refractory SE and the continuous or repetitive seizures are unresponsive to first- and/or second-line antiepileptic drug (AED) therapy with a benzodiazepine and other anticonvulsant in adequate loading dose.

Malignant status epilepticus: Malignant SE is a variant of refractory SE which fails to respond to anesthetic agents. It is commonly associated with encephalitis.

COMMON CAUSES OF STATUS EPILEPTICUS

- *Drug related*: Discontinuation of antiepileptic medications. Few drugs may lower the seizure threshold or increase clearance of antiepileptic medications, e.g., isoniazid, erythromycin, etc.
- *Drug withdrawal*: Alcohol, barbiturates or opioid withdrawal.
- *Infection*: Meningitis, encephalitis, and brain abscess
- Stroke
- *Metabolic causes*: Electrolyte disturbances and hypoglycemia
- Hypoxia
- Central nervous system (CNS) tumors
- Traumatic brain injury

CLASSIFICATION AND STAGES OF STATUS EPILEPTICUS

Based on electroclinical features it can be classified as: Nonconvulsive status epilepticus (NCSE) and convulsive SE. NCSE refers to continuous or near continuous electrical seizure activity without any obvious physical convulsions. It may be characterized by abnormal oculomotor movements, altered mental status, and unresponsiveness. NCSE may be categorized as absence SE and complex partial SE. Convulsive SE can be classified as tonic-clonic, tonic, clonic, and myoclonic. Generalized tonic-clonic is the most common form. It is hypothesized that ineffective recruitment of inhibitory neurons with excessive neuronal activation plays a key role in initiation and maintenance of SE.

Convulsive status epilepticus: Generalized convulsive SE in adults and children >5 years is operationally defined as "≥5 minutes of (1) Continuous seizure or (2) two or more discrete seizures between which there is incomplete recovery of consciousness." Though traditionally duration of 30 minutes

or more continuous seizures were taken as SE, the duration has been reduced considering the fact that majority of generalized seizures terminate spontaneously within 2–3 minutes and seizures that do not cease in 5–10 minutes will need aggressive intervention to get controlled.

Nonconvulsive status epilepticus: NCSE is defined as a state when in an obtunded or comatose patient there are no ongoing obvious clinical seizures but the seizure activity is well seen on the EEG. The duration required to label NCSE is still >30 minutes. It is important to rule out NCSE in any patient with unexplained altered sensorium especially with reasonably normal radiological and biochemical parameters. Subtle SE may be seen in patients treated for convulsive SE. If convulsions are no longer there but the patient is comatose then a possibility of NCSE should be considered. However, discrete (subtle) clinical manifestations like perioral twitching or nystagmus or fixed gaze may be present in such patients.

Stages of status epilepticus: First stage is characterized by generalized tonic-clonic seizure. It is associated with increased autonomic activities such as increased temperature, hypertension, salivation, and hyperglycemia. After approximately 30 minutes, second stage is noticed with failure of cerebral autoregulation. It can lead to hypoglycemia, acidosis, hypoxia, hypotension, etc. The five distinct electrographic stages: (1) Discrete electrographic seizures, (2) merging of electrographic seizures-waxing and waning of ictal discharges, (3) continuous ictal discharges, (4) continuous ictal discharges punctuated by flat periods, and (5) periodic epileptiform discharges against a relatively flat background.

Status epilepticus mimics: Symptoms such as tonic-clonic movements, frothing at mouth, and involuntary passage of urine help in diagnosis of seizure. However, it is important to differentiate from other conditions which may mimic SE. Few examples of them are: Tetanus, neuroleptic malignant syndrome, and tremor mimics of partial SE are: Tic disorder and focal dystonia myoclonic jerks. Mimics of NCSE are: Locked-in syndrome, cataplexy, and periodic paralysis encephalitis. Video EEG monitoring is the gold standard to differentiate SE from mimickers.

INITIAL EVALUATION AND MANAGEMENT

Prehospital Management

Obtain history: History of trauma, substance abuse, and history of seizure.

Secure airway, breathing, and circulation: Airway, breathing, and circulation should be assessed immediately. Patient should be positioned in left lateral decubitus which will help to reduce the risk of aspiration of gastric contents. Bite block or oropharyngeal airway application may be dangerous for healthcare providers; hence, it is not recommended. If any airway adjuvant device is necessary nasopharyngeal airway may be used during active seizure.

Breathing: Respiratory failure is a known complication of seizure. Bag mask ventilation must be done cautiously as it may increase the risk of aspiration. Decision of intubation must be taken by treating physician. Rapid sequence intubation is preferred method. Succinylcholine must be used cautiously as prolonged seizure may predispose the patient to hyperkalemia as a consequence of rhabdomyolysis.

Circulation: Intravenous access should be attempted. Maintenance of hydration will reduce the risk of myoglobin induced renal injury. Point of care for blood sugar levels must be measured and corrected if necessary. Hypoglycemia may be one of the precipitating factors of SE. Prolonged seizure or fall during the episode may result in trauma. Prompt correction of blood sugar levels if they are below 60 mg% is advised.

Medication: Intramuscular or buccal administration of midazolam is recommended if intravenous access is not achieved. If intravenous access is achieved lorazepam can be administered. Benzodiazepines act by postsynaptic gamma-aminobutyric acid-nergic (GABA-nergic) inhibition, reducing repetitive firing of action potential.

Emergency Department Treatment

Primary management should aim at stabilization of airway, breathing, circulation, and administration of medications to terminate the clinical and electrical seizure. Airway, breathing, and circulation management is as described above. After stabilization of airway, breathing, and circulation arterial blood gas analysis may be performed. Initial hyperpyrexia, acidosis, and hypertension may not be immediately treated as it usually subsides without any corrective measures. All the patients should get a blood glucose levels; serum calcium, magnesium, sodium, and potassium levels. If the patient is known epileptic on medication, then blood levels of antiepileptic medications must be performed. Based on history and clinical findings other investigations such as computed tomography (CT) scan, lumbar puncture, and blood toxicology panel may be performed.

PHASE WISE MANAGEMENT OF STATUS EPILEPTICUS

Stabilization Phase (0–5 Minutes Seizure Activity)

Airway: Consider nasopharyngeal airway and suction.

Breathing: Supplement oxygen.

Circulation: Secure intravenous access. Check blood glucose levels. If sugar levels <60 mg/dL, start intravenous dextrose (D50W) 50 mL.

Initial Therapy Phase (5–20 Minutes)

Benzodiazepines are the first therapy of choice:

- 10 mg for >40 kg, 5 mg for 13–40 kg of intramuscular midazolam single dose OR
- 0.1 mg/kg/dose, maximum: 4 mg/dose of intravenous lorazepam may repeat dose once, OR
- 0.15–0.2 mg/kg/dose, maximum: 10 mg/dose of intravenous diazepam may repeat dose once.

If none of the above benzodiazepines are available any one of the following may be administered:

- 15 mg/kg/dose of intravenous phenobarbital, single dose, OR
- Intranasal midazolam and buccal midazolam, OR
- 0.2–0.5 mg/kg, maximum: 20 mg/dose of rectal diazepam, single dose

Second Therapy Phase (20–40 Minutes)

At this point, a response to the therapy administered in the previous phase should be evident. If there is a lack of response, the following can be administered as a single dose:

- 20 mg PE/kg, maximum: 1,500 mg PE/dose of intravenous fosphenytoin, single dose, OR
- Intravenous levetiracetam 60 mg/kg, maximum: 4,500 mg/dose, single dose, OR
- 40 mg/kg, maximum: 3,000 mg/dose of intravenous valproic acid, single dose.

If none of the options are available, intravenous phenobarbital 15 mg/kg, single dose can be administered. Consider definitive airway protection by endotracheal intubation and mechanical ventilation.

Third Therapy Phase (40–60 Minutes)

If the seizure persists, any drug of the second-line therapy may be repeated or administer anesthetic doses of:

- Thiopental 100–250 mg bolus with repeat bolus of 50 mg every 2–3 minutes till seizures are controlled followed by infusion of 3–5 mg/kg/h, OR
- Propofol 2 mg/kg intravenous bolus followed by 5–10 mg/kg/h infusion, OR
- Midazolam 0.1–0.3 mg/kg bolus followed by infusion at 0.05–0.4 mg/kg//h.

If patient needs third-line therapy then the airway must be protected by endotracheal intubation and mechanical ventilation. The patient should undergo continuous EEG monitoring.

Refractory Status Epilepticus

If despite giving loading doses of AEDs the seizures are going on, then the patient is considered to be in refractory SE. At this stage, there are two options to treat. Such patients will need use of anesthetic agents such as midazolam, propofol or thiopentone sodium. Midazolam may be preferred with strict monitoring in cases where intubation is to be avoided. If ICU facility with ventilator support is available then stronger anesthetic drugs such as thiopentone sodium or propofol may be a better choice. If a patient with convulsive SE is having altered sensorium with no ongoing convulsions then it may be due to nonconvulsive status and an urgent EEG monitoring is required.

Malignant/Super-refractory Status Epilepticus

If the seizures are not controlled in 24 hours or recur 24 hours or more after the onset of anesthetic therapy then this is called super refractory SE. If seizures recur on stopping or reducing anesthetic agents then also it will be termed super refractory SE. This condition requires aggressive therapies such as ketamine, hypothermia, ketogenic diet, and immunotherapy like immunoglobulin. This will help in controlling seizures, preventing excitotoxicity, and providing neuroprotection.

Reasons for Failure of Treatment in Status Epilepticus

Treatment of SE can fail due to following reasons:

- *Underdosing of antiepileptics*: Treating SE half-heartedly by going half loading dose may frequently result in failure and should be avoided. A full loading dose is quite safe to give in a patient with SE.
- *Early stoppage of treatment*: If only emergency therapy or loading dose of AEDs is given then patient may develop recurrence of seizure as most of the AEDs work for about 12 hours after loading so maintenance of antiepileptic therapy should always be given.
- *Proper diagnosis*: It is very important to keep a high index of suspicion for NCSE in a patient with unexplained altered sensorium as early treatment can result in good outcome and delayed treatment may result in refractory status.

How to do Electroencephalogram Monitoring in a Patient with Status Epilepticus?

Electroencephalogram monitoring is helpful in all the patients with SE. It can be done for short period or as continuous monitoring to rule out electrographic seizures Continuous EEG monitoring is especially required in whom the patient has not recovered even after the control of convulsions to rule out electrographic seizures. In a patient with refractory SE EEG monitoring may help in optimizing the dose of anesthetic agent with a target to achieve burst suppression pattern (BSP) on EEG. A suppression period of >10 seconds of the electrical activities on EEG will indicate adequate doses of anesthetic agents. The tapering of these agents should be considered only after 24 hours of BSP and then also it should be slow withdrawal.

SPECIAL SITUATIONS IN STATUS EPILEPTICUS

Porphyria: Many antiepileptic agents are contraindicated in porphyria. SE can be treated by lorazepam or intravenous magnesium sulfate without risk of aggravating porphyria.

Isoniazid intoxication: Status epilepticus due to isoniazid intoxication can be treated with pyridoxine.

Hyponatremia: Intravenous administration of 3% NaCl solution when hyponatremia is known cause of SE.

Pregnancy: Consider eclampsia in a pregnant female with SE. Magnesium sulfate is superior to other AEDs in eclampsia and delivery of fetus is best definitive treatment. Immediate control of seizure is essential for good fetal outcome. Phenobarbitone, phenytoin, and sodium valproate are known to have teratogenic effects, particularly in first-trimester. Levetiracetam can be considered first line of drug in pregnant patient with SE. Pregnancy results in increased volume of distribution and affects the metabolism and clearance of drugs. These factors should be considered while calculating doses of drugs.

Status epilepticus in children: The definition and management of SE are more or less same as in adult population. The main difference is in the etiology. In pediatric population especially in neonates and early infant symptomatic causes such as metabolic, infections, and structural lesion in the brain are more common. The prognosis depends upon

the primary pathology but seems to be better. Every child with SE must undergo workup for metabolic causes such as hypocalcemia, hypoglycemia, and hypomagnesemia. Early identification of the etiology can result in aggressive specific management of cause. Other investigations may include complete blood count, renal function test, liver function test, serum calcium, serum magnesium, serum electrolyte, blood urea nitrogen, glucose, and AED levels, as well as a toxicology screening. Brain imaging is an important part of investigation especially in pediatric age group. Magnetic resonance imaging (MRI) is the ideal investigation but in emergent condition it may be more convenient to do CT head. Cerebrospinal fluid (CSF) should be done in cases of suspicion of brain infection.

SYSTEMIC COMPLICATIONS OF STATUS EPILEPTICUS

- Hyponatremia
- Hyperkalemia
- Hypercarbia
- Hypoglycemia
- Lactic acidosis
- Rhabdomyolysis
- Hyperpyrexia
- Aspiration pneumonia

SUMMARY

Treat fever aggressively as it can precipitate seizure recurrences especially in pediatric population. Always look for metabolic factors such as hypoglycemia, hyperglycemia, and hypocalcemia and correct it. In case of difficult intravenous access phenobarbitone, midazolam, and fosphenytoin can be given intramuscularly.

Antiepileptic drugs level monitoring during SE is useful to determine optimal doses. Oral AEDs the patient already taking should be continued during the management of SE. Oral route can changed to intravenous if drug is available. CSF pleocytosis can also be seen in SE without any CNS infection. Avoid phenytoin in patient with myoclonic epilepsy. In patients with chronic liver disease levetiracetam is a safer option. In renal disease phenytoin/fosphenytoin can be used safely. True morbidity and mortality from SE is unclear. Age >65years is one of the most important prognostic factors. Other factors which impact the prognosis are—underlying etiology and absence of prior seizure. Treatment for SE is summarized in **Table 1**.

TABLE 1: Treatment summary for status epilepticus.

Immediate treatment (first 5–10 minutes)	
Monitoring of vitals	Airway, oxygen, and cardiac monitor
Securing IV lines	Two lines for blood samples and starting treatment
To start IV fluids	• Fluid of choice is normal saline • To give 100 mg IV thiamine and 50 mL of 50% dextrose in patients with history of alcoholism
First antiepileptic	• To give lorazepam/midazolam/diazepam IV • 0.1 mg/kg bolus dose of IV lorazepam in equal volume of diluent by slow IV push at ~2 mg/min
Repeat dose if seizure persists	Repeat another half of the bolus dose if seizures are not controlled
Early treatment for next 10–60 minutes	
Loading antiepileptic second line IV agent	• *Phenytoin*: IV infusion 15 mg/kg @ 50 mg/min • (*Fosphenytoin*: IV infusion 15 mg PE/kg @ 100 mg PE/min) • *Valproate*: IV infusion 25 mg/kg at 3–6 mg/kg/min • *Phenobarbital*: IV infusion 10 mg/kg at a maximum rate of 100 mg/min • *Levetiracetam*: 20 mg/kg bolus of dose over 15 min
If seizure persists then two options	• Repeat half dose of any of the above-mentioned antiepileptic drugs • To load with any of the other antiepileptic drug
Refractory status epilepticus (>60 minutes ongoing convulsions)	
Midazolam infusion (Possible to avoid ventilator support)	• *Loading*: 0.2 mg/kg by slow IV bolus • *Maintenance IV dose*: 0.1–0.4 mg/kg/h • *Maximum IV dose*: 2.0–3.0 mg/kg/h
Thiopental sodium	• *Loading*: 3–5 mg/kg at 0.2–0.4 mg/kg/min • *Maintenance IV dose*: 3.0–5.0 mg/kg/h • *Maximum IV dose*: 5.0 mg/kg/h
Propofol infusion	• *Loading dose*: 1–2 mg/kg at 10 mg/min • *Maintenance IV dose*: 2–10 mg/kg/h • *Maximum IV dose*: 15 mg/kg/h

Continued

Continued

Malignant/Super-refractory status epilepticus (seizures >24 hours)	
Magnesium infusion	• *Loading*: 2–6 g/h • *Maintenance*: 3.5 mmol/L
Hypothermia	• 32–35°C for <48 h • Endovascular cooling versus external cooling
Immunotherapy	• IV methylprednisolone 1 g/day × 5 days • IV immunoglobulins 0.4 g/kg/day × 5 days • Plasma exchange
Ketogenic diet	1:1 or 1:4 ketogenic diet To avoid glucose containing fluids
Epilepsy surgery	Consider surgery in special circumstances with documented brain lesions responsible for status epilepticus

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Acute Flaccid Paralysis

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INTRODUCTION

Acute flaccid paralysis (AFP) is a complex clinical syndrome characterized by rapid onset of weakness of limbs, which may include muscles of respiration and swallowing, rapidly progressing to maximum severity within few days. The term flaccid indicates decreased tone of affected muscles. It includes broad spectrum of diseases which may vary with age and region. Poliomyelitis was one of the most common causes of AFP. However, because of global polio eradication initiative by World Health Organization (WHO), poliomyelitis has reached near eradication in world. Hence, other causes of AFP must be sought and evaluated. Early diagnosis in emergency department significantly improves the outcome of the patient. Etiology of AFP summarized in **Table 1**. AFP can occur in any age group and need urgent evaluation, prompt, and appropriate therapeutic intervention. Lesions at following sites explain the muscle weakness.

Muscle: Inflammatory myopathies.

Neuromuscular junction: Myasthenia gravis (MG) botulism Lambert–Eaton syndrome.

Peripheral nerves: Porphyria neuropathies and neuropathy due to metal toxicity.

Motor nerve root: Infectious polyradiculopathies and diabetic polyradiculopathies.

Anterior horn cell: Poliomyelitis.

Lower motor neurons: Antiganglioside antibody related neuropathy.

TABLE 1: Etiology of acute flaccid paralysis.

Metabolic causes	• Hypokalemia • Hyperkalemia • Hypophosphatemia • Thiamine deficiency
Muscle disorders	• Infection—viral myositis • Inflammatory myopathy—polymyositis, dermatomyositis
Disorder of neuromuscular junction	• Myasthenia gravis crisis • Lambert–Eaton syndrome • Botulism • Tick paralysis • Snake bite • Organophosphate poisoning
Neuropathy	• Guillain–Barré syndrome • Porphyria • Diphtheria • Vasculitis
Anterior horn cell disease	• Poliomyelitis • Paraneoplastic
Spinal cord diseases	• Trauma • Transverse myelitis • Anterior spinal artery syndrome

GUILLAIN–BARRÉ SYNDROME

Guillain–Barré syndrome (GBS) is acute inflammatory demyelinating polyneuropathy characterized by progressive sensory motor dysfunction. It is usually preceded by gastrointestinal dysfunction. It is commonly associated with areflexia. Characteristic features of GBS are:

- Progressive ascending symmetrical paralysis with symptoms reaching maximum intensity within 4 weeks of onset.
- Afebrile onset
- Involvement of sensory system
- Cerebrospinal fluid (CSF) studies demonstrate raised protein levels and cyto-albuminological dissociation.
- Decreased or absent myotatic reflexes
- Other causes of AFP are to be ruled out

Pathophysiology: GBS is considered to be an autoimmune disease. It is usually preceded by bacterial or viral infection. Commonly identifies organisms are *Campylobacter jejuni, Mycoplasma pneumoniae*, Epstein–Barr virus, etc., antibodies that are produced in response to these infection crossreact with neural antigens leading to demyelination and

inflammation. The area of nerve predominantly damaged determines to variant of GBS which will be manifested. If myelin is predominantly damaged it leads to acute inflammatory demyelinating polyneuropathy (AIDP), while nodes of Ranvier are involved in acute motor axonal neuropathy (AMAN). *GBS is classified into four subtypes*: (1) AIDP, (2) AMAN, (3) the Miller Fisher syndrome (MFS), and (4) acute motor and sensory axonal neuropathy (AMSAN).

Clinical features: Common clinical features of AIDP are weakness of limbs usually start in lower limbs and progress proximally. Limb weakness may be associated with tingling or pain. As the weakness progress it may involve respiratory muscles, as a result of which patients require mechanical ventilation. Involvement of respiratory muscles is common in patients with rapid progression of illness, involvement of upper limbs or bulbar paralysis. Other types of GBS involve facial, oculomotor, and pharyngeal muscles. Involvement of autonomic nervous system leads to fluctuations in blood pressure, cardiac arrhythmias, urinary retention, etc.

Investigations: Diagnosis of GBS is mainly dependent on clinical features. Investigations which may support the diagnosis are CSF studies which will reveal raised CSF protein level and cyto-albuminological dissociation. Investigations which will help to rule out other causes of paralysis are nerve conduction studies, electromyography (EMG), magnetic resonance imaging (MRI) brain, and spinal cord.

Treatment: The course of illness in GBS is unpredictable; hence, all patients with GBS must be admitted for observation. Involvement of respiratory of bulbar muscles can cause respiratory failure. Autonomic system involvement may cause life-threatening complications. Hence continuous hemodynamic monitoring is advised. Factors indicating need for mechanical ventilation are—inadequate cough, bulbar symptoms, vital capacity <15 mL/kg, neck muscle weakness, and declining single breath count. Definitive treatment are as follows:

- Plasma exchange aids in removal of immune complexes from circulation. It thus reduced the need or duration of mechanical ventilation, helps to reduce the severity of illness. For optimal response, plasma exchange must be initiated early in the course of illness.
- Intravenous immunoglobulin is considered in patients with rapidly progressive paralysis or respiratory muscle involvement. Recommended dose of immunoglobulin is 400 mg/kg/day for 5 days. It is less invasive than plasma exchange therapy.

Prognosis: Factors which may predict poor outcome are older age, need for mechanical ventilation, and rapid progress of symptoms. Mortality rate is approximately 3%. Approximately 20% of affected patients have persistent long-term neurological disability.

MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder mainly caused by antibodies to muscle acetylcholine receptors at the level of neuromuscular junctions, leads to muscle weakness and fatigue. In >85% of patients muscle weakness become generalized affecting the limb muscle with other features such as diplopia and ptosis. Laboratory diagnosis is supported by antiacetylcholine receptor (anti-AChR) radioimmunoassay (definite diagnosis if positive >90% +ve in generalized MG and in 50% cases of ocular MG), single fiber EMG (confirmatory test), edrophonium chloride test, and repetitive nerve stimulation test.

- *Disorder associated with MG:* Thymoma hyperplasia, thymic abnormalities, and other autoimmune diseases such as thyroiditis, Graves' disease, and rheumatoid arthritis.
- *Disorders that aggravates MG:* Hyperthyroidism, hypothyroidism, and occult infections.
- *Disorders that may interfere with MG therapy*: Tuberculosis, diabetes mellitus, renal disease, hypertension, asthma, and osteoporosis.
- *Treatment modalities for M*G: There are four options for MG treatment:
  i. *Symptomatic treatment (acetylcholine inhibition)*: Amount of acetylcholine available at neuromuscular junction is increased.
  ii. *Chronic immunosuppressive therapy*: Glucocorticoid and nonglucocorticoid therapies.
  iii. *Rapid and short acting immunomodulating therapy*: Plasma exchange and intravenous immunoglobulin.
  iv. *Surgical treatment* (thymectomy).

TRANSVERSE MYELITIS

It is a neurological disorder caused by inflammation of spinal cord. It can occur at any age, but the peak of incidence is seen in age groups of 1–19 years and 30–39 years.

Etiology

- Idiopathic
- *Infections*: Syphilis, tuberculosis, Lyme disease, Epstein–Barr virus, and cytomegalovirus infection.
- *Immune system disorders*: Multiple sclerosis, postvaccine or infection.
- *Inflammatory disorders*: Sarcoidosis, scleroderma, and systemic lupus erythematosus (SLE).

Clinical Features

Pain: Symptoms usually start with pain, which may be lower backache or pain radiating from back to limbs.

Limb weakness: Weakness might start as paraparesis which later progresses to paraplegia. If the lower levels of spinal cord are involved the limb weakness occurs in lower limbs, if thoracic region is affected then both upper and lower limbs are affected. Lesions involving high cervical region result in tetraplegia and involve the phrenic nerve (C3–C5). These patients need invasive mechanical ventilation.

Sensory symptoms: Transverse myelitis can lead to paresthesia or loss of sensations.

Bowel and bladder dysfunction: Common symptoms are bowel or bladder incontinence, increased frequency, and constipation.

Investigations

Magnetic resonance imaging of spine: Lesions of transverse myelitis are seen as high signal intensity on T2–weighted images. It more commonly involves central region of spinal cord. MRI also helps to rule out other causes of paralysis. Other investigations include blood tests for infections, tests for autoimmune diseases such as Sjögren's syndrome A (SS-) antibody, Sjögren's disease, antidouble stranded deoxyribonucleic acid (anti-dsDNA) antibody, etc.

Cerebrospinal fluid analysis: Oligoclonal band is seen in multiple sclerosis associated with transverse myelitis.

Diagnostic Criteria for Acute Idiopathic Transverse Myelitis

Inclusion Criteria

- Dysfunction of sensory, motor, and autonomic nervous system due to spinal cord lesion.
- Signs and symptoms seen bilaterally.
- Clearly defined sensory level.
- Signs of inflammation seen either on CSF studies or on MRI.
- Peak of the disease seen between 4 hours and 21 days after the onset of symptoms.

Exclusion Criteria

- CSF or MRI studies suggestive of multiple sclerosis.
- History of irradiation to spine in last 10 years.
- Evidence of spinal artery thrombosis or arteriovenous malformation.
- Laboratory findings suggestive of infections such as human immunodeficiency virus (HIV), herpes simplex virus, cytomegalovirus, etc.
- Laboratory findings suggestive of systemic connective tissue diseases such as SLE, sarcoidosis, Sjögren's disease, etc.
- Neuroimaging suggestive of extra-axial compression.
- History or diagnostic studies suggest neuromyelitis optica.

Treatment

The treatment for transverse myelitis has to be individualized.

Steroids: Up to 1g of methylprednisolone for 3–5 days. Further decision to continue steroids or add a new treatment modality is decided on the initial response to steroids.

Plasma exchange: Patients who fail to respond to initial steroids or who have severe form of transverse myelitis can be offered plasma exchange.

Immunomodulators: Use of B-cell modulators or intravenous immunoglobulin is not recommended.

Analgesia: Transverse myelitis can be severely painful. Apart from analgesics such as acetaminophen and naproxen other medications which can be used are muscle relaxants (baclofen), anticonvulsants (like pregabalin or gabapentin), and antidepressants.

Rehabilitation: Patients may suffer from long-term neurological disabilities. Such patients need consultation with rehabilitation specialist such as physiotherapy, vocational therapy, occupational therapy, etc.

Prognosis: Most patients have partial recovery. Patients who fail to show any signs of improvement in initial 3–6 months usually do not have complete recovery later. Rapid worsening of symptoms usually is associated with poor outcome. Relapsing transverse myelitis symptoms are seen in patients with multiple sclerosis and neuromyelitis optica.

BOTULISM

Botulism is derived from Latin word Botulism-Sausage. In southern Germany about 1,700 people died because of eating tainted sausage. Botulism is a paralytic disease starts with the cranial nerve involvement and progress to extremities. Botulism is considered in an afebrile mentally intact patient with symmetric descending paralysis without sensory findings. Botulism may be confused with *MG* (rule out with EMG and antibodies studies), *GBS* (ascending paralysis, sensory abnormalities, and increase protein in CSF), and *Fisher variant of GBS* (descending paralysis difficult to differentiate from botulism). Demonstration of organism/toxins in vomitus or gastric fluid suggestive of diagnosis. Management includes hospitalization with close monitoring by spirometry, pulse oximetry, arterial blood gases, and intubation mechanical ventilations if respiratory failure. Use of antibiotics has no proven value.

INFLAMMATORY MYOPATHY

The inflammatory myopathies are a group of diseases, with unknown etiology, clinically presents as chronic muscle inflammation and muscle weakness. Polymyositis, dermatomyositis, and inclusion body myositis (IBM) are the three main types of chronic, or persistent, inflammatory myopathies in **Table 2**. Clinical features of inflammatory myositis other than muscle weakness are fever malaise, weight loss, arthralgia, joint contracture dysphagia, and other gastrointestinal (GI) symptoms. Cardiac manifestations are atrioventricular (AV) conduction defect, tachyarrhythmia, dilated cardiomyopathy, low-ejection fraction, congestive heart failure, and myocarditis. Pulmonary manifestations may present as thoracic muscle weakness and drug induced pneumonia. Subcutaneous calcifications shin ulceration and infections may also present. Treatment modalities for inflammatory myopathies are:

- *Glucocorticoids:* Initial treatment of choice is oral prednisolone 1 mg/kg/day, after 3–4 weeks start tapering the dose over a period of 10 weeks to 1 mg/kg alternate day. If no serious side-effects and on the basis of efficacy maintain lowest possible dose with control of disease.
- *Immunosuppressive drugs:* Generally, initiated when a patient fails to responds to glucocorticoid after 3 months of trials. Azathioprine up to 3 mg/kg/day and methotrexate (faster onset of action) 7.5 mg weekly for first 3 weeks with gradual dose escalation by 2.5 mg/week.

SYSTEMIC OR METABOLIC DISORDERS CAUSING ACUTE FLACCID PARALYSIS

While evaluating the AFP metabolic causes are also considered in differential. Rare cause of AFP is acute hypokalemic

TABLE 2: Characteristic features of various inflammatory myopathies.

Characteristics	*Polymyositis*	*Dermatomyositis*	*Inclusion body myositis*
Onset	>18 years	Adult and childhood	>50 years
Familial association	No	No	In some cases
Associated conditions	SLE RA SS MCTD	SS MCTD	In 20% cases
Malignancy	No	Yes 15% cases	No
Viruses	With HIV	Unproven	Unproven
Drugs	Yes	Yes	No
Muscles	Myopathic muscle weakness (affecting proximal > distal)	Myopathic muscle weakness (affecting proximal > distal)	Myopathic muscle weakness and early involvement of distal muscle
Muscle enzyme	Raised up to 50-folds	Raised up to 50-folds/N	Raised up to 50-folds/N
Muscle biopsy	Diagnostic	Diagnostic	Diagnostic

(MCTD: mixed connective tissue disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: systemic sclerosis)

periodic paralysis. Hypokalemic familial periodic paralysis, a disease of autosomal-dominant inheritance. Familial periodic paralyses is divided into three main forms according to precipitating factors and the patient's potassium level at the time of an attack: (1) Hypokalemic familial periodic paralysis is usually precipitated by a meal rich in carbohydrates, and it has the tendency to manifest in the morning hours after rest. (2) Potassium-sensitive familial periodic paralysis usually has age of onset <10 years of age; considered as less severe than hypokalemic form and tend to occur during the daytime. (3) In familial adynamia episodica hereditaria, glucose prevents potassium-induced attacks of AFP. Diagnosis of familial periodic paralysis, is established by the demonstration of changes in serum potassium levels during the attack, the presence of electromyographic and electrocardiographic abnormalities, and the use of muscle biopsy, and potassium-, glucose-, or insulin-loading tests.

Thyrotoxic periodic paralysis is a syndrome manifests as clinical, electromyographic, biochemical, and microscopic features. Acute-onset progressive symmetrical weakness of the extremities and other muscle groups is the prominent clinical manifestations which is induced by excess levels of exogenous or endogenous thyroid hormones after high carbohydrate ingestion or heavy exertion.

Acute intermittent porphyria may also manifests as rapidly progressing peripheral neuropathy with motor and sensory clinical presentation and followed by AFP. Acute intermittent porphyria may have other clinical features also such as abdominal pain and psychological and neurologic signs (disturbances of consciousness and mentation, convulsions), but not all attacks progress to the neurologic stage. The initial episode often occurs in early adolescence. The classic ruby-red coloration or measurement of porphyrins (porphobilinogen and 8-aminolevulinic acid) in the urine helps to confirm the diagnosis.

WEAKNESS ASSOCIATED WITH CRITICAL ILLNESS

Acute weakness syndromes in critically ill patients can be classified into three major groups with different etiologies: (1) Critical illness polyneuropathy; (2) Neuromuscular junction abnormalities, subdivided into myasthenia-like syndromes and prolonged neuromuscular blockade; and (3) Myopathy, including acute disuse (cachectic), necrotizing, and thick filament (myosin) loss myopathy. In critically ill patients nondepolarizing neuromuscular blocking agents, is frequently used and associated with prolonged muscle weakness.

In intensive care unit status asthmaticus patients are treated with bronchodilators, antibiotics, and high-dose corticosteroids and paralyzed with vecuronium to facilitate mechanical ventilation may develop flaccid quadriplegia with areflexia. Prolonged neuromuscular blockade usually causes brief period weakness (recovers in hours to days), while more prolonged weakness (several weeks to months) is due to myopathy. Clinically, patient of AFP is differentiated by presence of intact sensation and cognition. Typical presentation of critical illness polyneuropathy is inability to wean from ventilatory support despite full cardiopulmonary recovery and flaccid quadriplegia.

Electrophysiologic studies are performed to demonstrate the presence of axonal polyneuropathies, abnormalities of neuromuscular transmission, or acute myopathies. Recovery in muscle strength usually occurs over a period of weeks to months. Variants of critical illness polyneuropathy may affect end stage renal or diabetic patients developing axonal, and predominantly motor polyneuropathy.

TRAUMA INDUCED ACUTE FLACCID PARALYSIS

Acute traumatic sciatic neuritis is associated with intramuscular gluteal injection, the potential risk of direct trauma or postinjection neuritis. A history of recent injections for febrile illness in paralyzed limbs provide important clue for diagnosing traumatic neuritis. Postoperative spinal cord damage due to ischemia (high aortic clamping and hypotension) may occur because of the interruption of critical radicular arteries at the lower thoracic or high lumbar vertebral levels, and may result in total paraplegia or paraparesis. The clinical examination in such cases reveals AFP, areflexia, sensory loss, patulous sphincter, and reflex neurogenic bladder.

EVALUATION OF ACUTE FLACCID PARALYSIS

Approach to patient with acute flaccid paralysis: History, physical examination, and investigations are important in distinguishing causes of acute flaccid paralysis (**Table 3**). Assess airway and breathing—bulbar involvement or involvement of respiratory muscles predisposes the patient to respiratory failure or aspiration pneumonia. Assess circulation—infection and autonomic involvement may lead to hypotension or hypertension, and arrhythmias. Detailed history regarding symptom must be obtained. It will help in identifying the etiology, thus helping to initiate treatment. Onset of symptoms and pattern of progression of symptoms/fluctuation in weakness.

Fatigability: Usually seen in neuromuscular junction disorders. Autonomic involvement, sensory involvement, and history of systemic symptoms such as fever, joint pain, rash, recent immunization, history of dog bite, and exposure to drugs or toxins (e.g., lead).

Physical examination: Assessment of airway, breathing, and circulation. Involvement of bulbar muscles or muscles of respiration predisposes the patient to aspiration pneumonia and respiratory failure. If the autonomic system is involved it may cause hypertension, postural hypotension, tachycardia, arrhythmia, etc. single breath count and examination of limb weakness. Evaluation of other sites for weakness—extraocular muscles, bulbar weakness, and facial muscles.

Reflexes: Reflexes may be absent in neuropathies, anterior horn cell disorders, and polyradiculopathies.

Assess for sensory impairment: Evaluate if the pathology appears to be upper motor nerve lesion or lower motor nerve lesion. Signs of upper motor nerve lesion such as brisk reflexes, definite sensory level, bladder or bowel involvement, and extensor plantar reflex.

Investigations: Arterial blood gas analysis—to evaluate for respiratory failure, complete blood count, serum electrolytes, thyroid function test, liver function tests, blood culture if suspicion of infection, and chest X-ray, Consider: MRI spine, nerve conduction studies, lumbar puncture, and CSF analysis. Summary for evaluation of AFP is given in **Flowchart 1**.

LATHYRISM

It is important to discuss lathyrism in Indian context as lathyrism has old history (since 1844 epidemic reported by Sleeman) which can develop in otherwise healthy person who consumed lathyrus sativus (grass peas) for 3–4 months. Patient can develop *severe spastic paraparesis due to* presence of potent neurotoxin 3-N-oxalyl-L-2,3-diaminopropanoic acid (β-ODAP) in the seed is the main causative factor to develop lathyrism. The first detailed description of the epidemic of lathyrism was written by General Sleeman in 1844 (Sleeman, 1844), who presented the detailed situation of lathyrism occurred in one of the Indian States, i.e., Madhya Pradesh in 1831 following prolonged consumption of lathyrus sativus as the exclusive diet.

The crop has tolerance to moisture stress, salinity, and required minimum management, thus widely grown in the States of Madhya Pradesh, West Bengal, Maharashtra, Karnataka, Telangana, and parts of eastern Uttar Pradesh. Main clinical features are pain in calf muscles especially during night, painful muscle spasm in calf (both legs) weakness and heaviness in legs, painful restriction of knee and ankle joints. Stiffness of muscles (spasticity) and atrophy of thigh and leg muscles. A detail dietary history should be taken, and differentiate from other conditions. There are no specific investigations/biomarkers for lathyrism. Lathyrism is irreversible neurotoxic damage condition and no known cure. Symptomatic treatment is the mainstay of management and prevention is preferred.

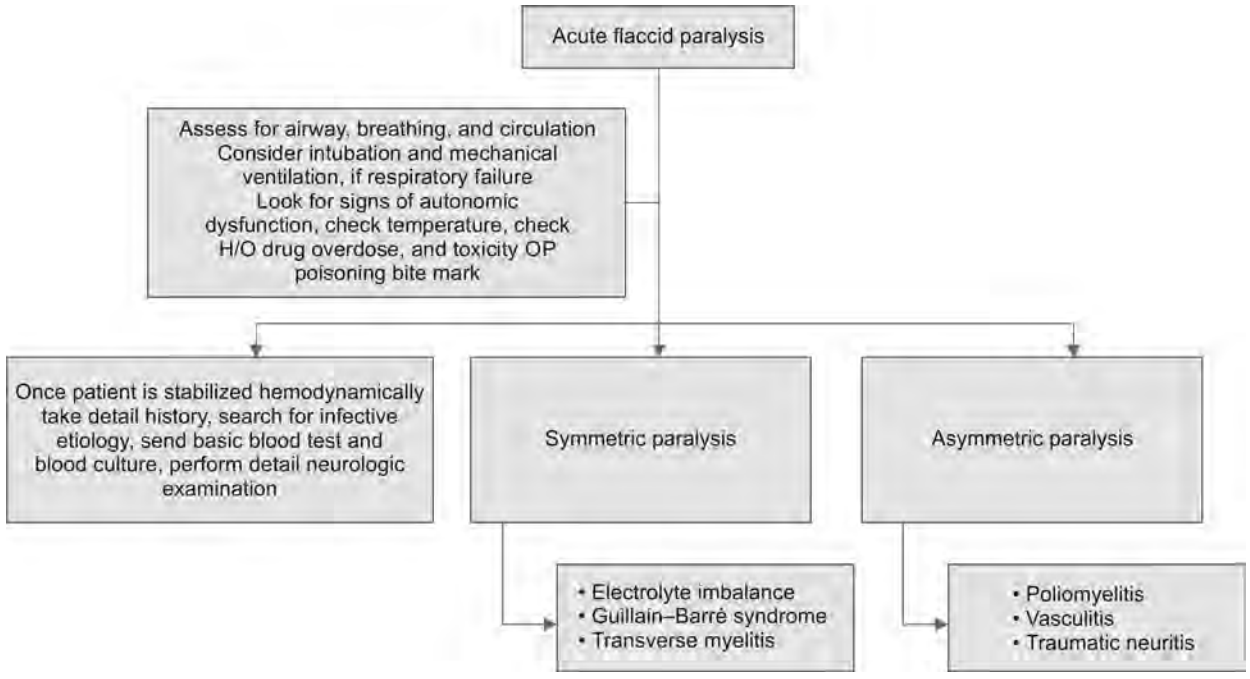
SUMMARY

Acute flaccid paralysis is a complex clinical syndrome of varied etiology characterized by rapid onset of weakness of limbs, which may include muscles of respiration and swallowing, rapidly progressing to maximum severity within few days. Early diagnosis in emergency department significantly improves the outcome of the patient. AFP can occur in any age group and need urgent evaluation, prompt, and appropriate therapeutic intervention.

TABLE 3: Distinguishing features of acute flaccid paralysis.

Causes	*Distinguishing features*	*Investigations*
Myasthenia gravis crisis	History of myasthenia gravis, descending limb weakness with ocular and bulbar involvement, sensory system spared, fatigable, and normal CSF studies	Anti-MuSK titers, anti-Ach IgM
Botulism	Weakness associated with gastrointestinal symptoms such as nausea, vomiting; dysarthria, ophthalmoplegia, and CSF studies-normal	Stool culture and culture of gastric secretions if possible
Poliomyelitis	Seen commonly in endemic areas and acute flaccid paralysis is accompanied with fasciculation and myalgia, fever, and CSF–pleocytosis	Stool sample for isolation of virus
Spinal cord diseases	Extensor plantar response and hyperreflexia	MRI spine
Vasculitis	Polyneuropathy and systemic symptoms such as rash, fever, painful, and multiorgan involvement	ESR, CRP, and specific antibodies like ANA

(ANA: antinuclear antibodies; Anti-Ach: anti-acetylcholine; Anti-MuSK: anti-muscle-specific tyrosine kinase; CRP: C-reactive protein; CSF: cerebrospinal fluid; ESR: erythrocyte sedimentation rate; IgM: immunoglobulin M; MRI: magnetic resonance imaging)


Acute flaccid paralysis
Assess for airway, breathing, and circulation
Consider intubation and mechanical ventilation, if respiratory failure
Look for signs of autonomic dysfunction, check temperature, check H/O drug overdose, and toxicity OP poisoning bite mark
Once patient is stabilized hemodynamically take detail history, search for infective etiology, send basic blood test and blood culture, perform detail neurologic examination
Symmetric paralysis
Asymmetric paralysis
• Electrolyte imbalance
• Guillain–Barré syndrome
• Transverse myelitis
• Poliomyelitis
• Vasculitis
• Traumatic neuritis

(OP: organophosphorus pesticide)

FLOWCHART 1: Approach to acute flaccid paralysis.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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123 CHAPTER

Meningitis Encephalitis and Brain Abscess

Atul Tungikar, Priyanka G Mahale, Devendra Richhariya

INTRODUCTION

"Meningitis is a clinical syndrome characterized by inflammation of membranes of the brain or spinal cord." It is associated with high morbidity and mortality. Timely recognition of clinical features and prompt initiation of empirical antimicrobial treatment substantially improves the prognosis of the patient. Initial evaluation and treatment of patients with suspected meningitis occurs in emergency department. It is crucial for emergency physician to treat promptly patients with suspected meningitis to achieve optimal outcome.

Risk factors and etiology: Common pathogens for community acquired disease are *Streptococcus pneumonia*, *Haemophilus (H) influenzae* meningitis, and *Neisseria meningitidis*. However, *H. influenza* meningitis is seen less in vaccinated child.

- Age—elderly and younger child
  - *Neonates (<1 week)*: *Escherichia (E) coli*, *Listeria (L) monocytogens*, Group B *Streptococcus*
  - *Neonates (>1 week)*: *L. monocytogens*
  - *Infants and children*: *N. meningitidis* and *S. pneumoniae*
  - *Young adults*: Meningitides and *S. pneumoniae*
  - *Elderly*: *N. Meningitidis, S. pneumoniae*, and *L. monocytogens*
- Malnutrition, overcrowding and low social economic status, and exposure to epidemic.
- Head and neck infections—otitis media and mastoiditis
- Major medical illness—liver disease, renal disease, and diabetes mellitus (DM)
- Immunocompromised—patients on steroids, chemotherapy, cancer patients, complement deficiency, and splenectomy patients.
  - *S. pneumoniae*, *H. influenzae*, and *Listeria monocytogenes*.
- *Patients with cochlear implant or basilar skull fracture:*
  - *S. pneumoniae*, *H. influenzae*, and Group A beta-hemolytic streptococci
- *Patient with neurosurgery or basilar skull fracture:*
  - *Staphylococcus aureus*, coagulase negative staphylococci, and pseudomonas
- *Viral causes:*
  - Common viruses which can cause meningitis are arboviruses, herpes simplex viruses (HSV), coxsackieviruses, echoviruses, human enteroviruses, human immunodeficiency virus (HIV), varicella zoster, and Epstein–Barr (EB) virus.
- *Subacute causes of meningitis*: Tuberculosis, fungal, autoimmune disorders such as systemic lupus erythematosus (SLE), malignancy, and drugs are uncommon.

EVALUATION OF MENINGITIS

Clinical Presentation

Clinical features may vary depending on duration and severity of illness, causative organism, and host characteristics. Initial symptoms may be nonspecific and comprise a prodrome such as fever, malaise, and headache. Hence, emergency physician must have low threshold to suspect meningitis. Patients lying in extremes of age group, immunocompromised patient, and partially treated may not have classical symptoms. Presentation of subacute meningitis such as fungal and tuberculous meningitis is also obscure. The classic triad of fever, altered mental status, and neck stiffness is seen in <50% of patients with meningitis. At least 2 of 4 symptoms of fever, altered mental status, neck stiffness, and headache will be present in 95% of patients. Associated symptoms—genitourinary complaints, rash, and cough.

Enquire about: Comorbidities, immunization history, and history of tuberculosis.

Travel history: For example, Japanese B infection is common in south-east Asia

Social history: For example, residence in closed dormitories is risk factor for meningococcal meningitis.

Physical Examination

Kernig's signs—with the patient lying supine and hip flexed to right angle, attempt to straighten the leg to full extension inability to do so is a positive Kernig's sign.

Brudzinski's signs—with the patient in supine position attempt to passively flex the neck causes flexion at hip joint.

Head jolt test: The patient is asked to move their head back and forth in the horizontal plane at a rate of 2–3 turns/second. If the patient's headache worsens, it is considered positive.

Signs of brain parenchymal irritation: Altered mental status, seizures, personality changes, and focal neurological deficit. In advanced stages of meningitis cerebral edema develops which causes symptoms such as vomiting, headache, and cranial nerve abnormalities.

Investigations

Complete blood count: Total leukocyte count may be increased in bacterial meningitis. However, a normal total leukocyte count does not rule out meningitis. Measure blood sugar levels frequently. Coagulation profile will be required before performing lumbar puncture.

Chest X-ray: 50% of patients with pneumococcal meningitis have evidence of chests infection in initial X-ray. Blood cultures are to be collected as soon as possible in a patient suspected with meningitis. Blood cultures are positive in 50–80% cases of bacterial meningitis.

Other ancillary tests: Liver function tests and renal function test. Blood biomarkers of inflammation such as procalcitonin and C-reactive protein (CRP) can be used to guide treatment.

Neuroimaging: It is not mandatory to perform neuroimaging before initiating treatment in clinically suspected meningitis. Urgent computed tomography (CT) brain should be performed in patients with signs of increased intracranial tension before performing lumbar puncture.

Indications of Performing Computed Tomography before Lumbar Puncture

New onset seizure and signs of raised intracranial tension such as papilledema, bradycardia, focal neurological deficit, and Glasgow coma scale (GCS) < 14, immunosuppression, and history of central nervous system (CNS) disease such as stroke, neoplasm, etc. CT may demonstrate hypodense lesion on temporal lobe in cases of HSV encephalitis, though magnetic resonance imaging (MRI) demonstrates this much earlier in course of illness.

Cerebrospinal Fluid Analysis

At least 3 sterile tubes containing 1–1.5 mL of cerebrospinal fluid (CSF) each should be collected. Parameters to be assed in CSF—opening pressure, turbidity, xanthochromia, glucose, protein, CSF lactate, CSF to serum glucose ratio, cell counts, gram staining, acid fast staining, and CSF culture. CSF finding in different types of meningitis is summarized in **Table 1**.

Polymerase chain reaction (PCR) for viral nucleic acid: Commonly used test for specific diagnosis of HSV, cytomegalovirus (CMV), EBV, varicella zoster virus (VZV), enteroviral viruses, and more sensitive than viral culture. PCR is helpful for identification of CNS infection caused by *mycoplasma pneumonia.*

Serologic studies: For diagnosis of acute viral infection serology studies are commonly used. Detection of virus specific immunoglobulin M (IgM) and IgG with related to clinical presentation is helpful for diagnosis of acute viral meningitis.

MANAGEMENT OF MENINGITIS

Priority of treatment is prompt administration of antibiotics (**Flowchart 1**).

Bacterial meningitis: After stabilization of airway, breathing, and circulation appropriate empirical antibiotics must be administered. If the clinical suspicion is high, empirical antibiotics should be started before performing lumbar puncture. Choice of empirical antibiotics will depend on the infection suspected based on patient's age and premorbid condition (**Table 2**). Dexamethasone may attenuate the inflammatory response and its consequences such as vasculitis, cerebral edema, etc. and shown to reduce overall mortality and neurological sequelae. First dose of dexamethasone should be administered at least 10–20 minutes before administration of antibiotics. Dose is 0.15 mg/kg. It is continued every 6 hours for next 4 days. Other corticosteroids have poor CNS penetrations, hence not to be used. All patients with meningitis have to be hospitalized and started on intravenous antibiotic therapy.

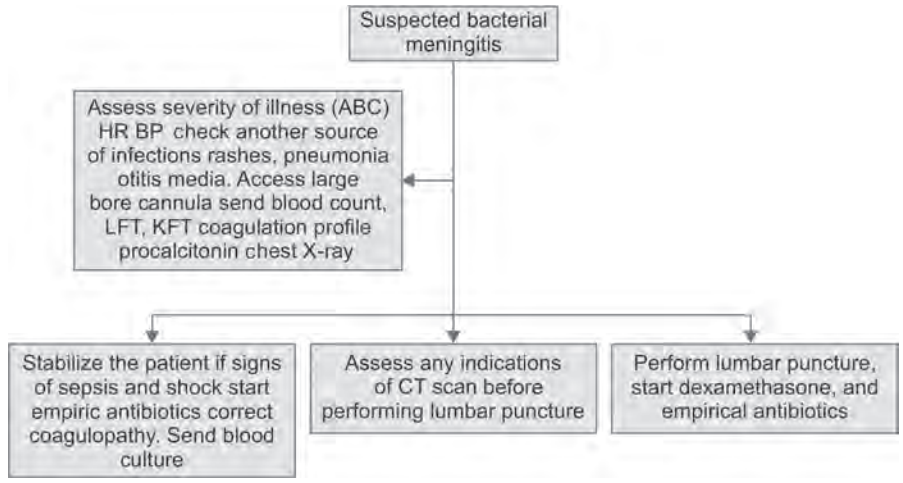
Viral meningitis: There is no specific treatment for viral meningitis and the treatment is largely supportive. Acyclovir 10 mg/kg 8 hourly can be given in HSV meningitis/encephalitis. Other aspects which may need emergent management in meningitis are septic shock, metabolic complications such as hypoglycemia, acidosis, hypokalemia, raised intracranial tension, seizure, and coagulopathy.

Complications: Risk of development of complications is higher with *N. meningitidis* and *S. pneumoniae*. Early complications include cerebral edema and hydrocephalus. Extracranial

TABLE 1: CSF findings in different types of meningitis.

	Normal	***Bacterial***	***Viral***	***Fungal***	***Tubercular***
Opening pressure (cm CSF)	<170 mm	>300	200	300	Raised
Appearance	Clear	Turbid/purulent	Clear	Clear	Clear
CSF WBC (cells/μL)	<5	1,000–5,000	5–1,000	5–100	5–100
Predominant cells	None	Neutrophil	Lymphocytes	Lymphocytes	Lymphocytes
CSF protein	28–32 mg/dL	Raised	Normal-mildly raised	Markedly raised	Raised
CSF glucose (mg/dL)	45	Very low	Normal/slightly low	Very low	Low
CSF plasma glucose ratio	0.66	Very low	Normal/slightly low	Very low	Low
CSF lactates	Normal	>35 mg/dL	Normal	>25 mg/dL	
% of PMNs	0	>80%	1–50%	1–50%	<30%

(CSF: cerebrospinal fluid; PMNs: polymorphonuclears; WBC: white blood cell)


Suspected bacterial meningitis
Assess severity of illness (ABC) HR BP check another source of infections rashes, pneumonia otitis media. Access large bore cannula send blood count, LFT, KFT coagulation profile procalcitonin chest X-ray
Stabilize the patient if signs of sepsis and shock start empiric antibiotics correct coagulopathy. Send blood culture
Assess any indications of CT scan before performing lumbar puncture
Perform lumbar puncture, start dexamethasone, and empirical antibiotics

(BP: blood pressure; CT: computed tomography; HR: heart rate; KFT: kidney function test; LFT: liver function tests)

FLOWCHART 1: Algorithm for managing bacterial meningitis.

TABLE 2: Empirical antibiotic therapy for meningitis.

Age group	*Empirical antibiotic therapy*
Neonates	Ampicillin (150 mg/kg/day) +3rd generation cephalosporin, e.g., Cefotaxime (100–150 mg/kg/day)
Infant and children	Cefotaxime or ceftriaxone (80–100 mg/kg/day) + vancomycin (60 mg/kg/day)
Adults	Ceftriaxone (80–100 mg/kg/day) + vancomycin (30–60 mg/kg/day)
Immunocompromised patient	Cefotaxime (8–12 g/day) or ceftriaxone (4 g/day) + ampicillin (12 g/day) + vancomycin (30–60 mg/kg/day)
Suspected nosocomial infection	Vancomycin (30–60 mg/kg/day) + ceftazidime (6 g/day) or cefepime (6 g/day) or meropenem (6 g/day)

complications—sepsis, multiple organ dysfunction syndrome (MODS), arthritis, and syndrome of inappropriate antidiuretic hormone (SIADH). Long-term sequelae—cognitive impairment and sensorineural hearing loss

Differential diagnosis: Meningitis should be differentiated from encephalitis, subdural hematoma subarachnoid hemorrhage, brain abscess, and brain tumor.

ENCEPHALITIS

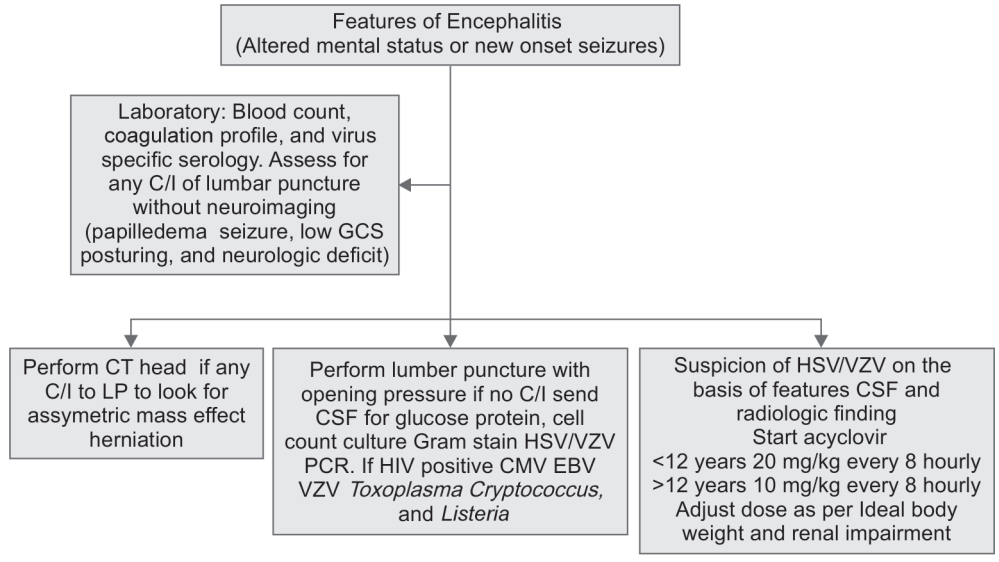
Encephalitis is the pathologic diagnosis but clinically it signifies inflammation of the brain parenchyma. Encephalitis is associated with broad differential diagnosis and possible causes are categorized into infectious (viral, bacterial, or parasitic), postinfectious, and noninfectious (metabolic, toxic, autoimmune, and paraneoplastic). Viral encephalitis may be due to either direct infection of the brain parenchyma (e.g., West Nile virus) or viral reactivation in neuronal tissue (e.g., HSV and VZV). The later (viral reactivation) is a postinfectious encephalomyelitis (also known as acute disseminated encephalomyelitis), an autoimmune phenomenon mostly seen in children and young adults after a disseminated viral illness or vaccination. Direct viral infection is responsible for majority of the acute encephalitis. Incidence of encephalitis due to all causes in adult ranges from 1 to 10/100,000 and 10 to 15/100,000 in children. Due to limited diagnostic availability and emerging pathogens most of the causative agents of encephalitis remain unidentified. Most common cause of sporadic viral encephalitis in industrialized nations is HSV encephalitis (HSV-1) followed by VZV. In immunocompromised individuals, VZV actually more common than HSV accounting for 20–30% of encephalitis.

Clinical presentation: If CNS infection is suspected in any patient, first step is to determine if bacterial meningitis is present, emergent empiric antibiotic therapy should be started. Consider encephalitis if evidence of brain parenchymal involvement and neurological findings or seizures are present. Brain parenchymal involvement (functions of involved part of brain) and clinical presentation correlates well (**Table 3**). HSV encephalitis is typically involving the temporal lobes. Personality changes, psychosis, and olfactory or gustatory hallucinations are the clinical features which may be mistaken as psychiatric disorder initially. Upper-quadrant visual field defect and inability to recall new information are the features if there is inferior frontal and temporal lobe involvement. When the dominant hemisphere is involved hemiparesis with greater involvement of the face and arm, or aphasia is presenting features. Tremors or other movement disorders also presentation of West Nile virus and eastern equine encephalitis virus (basal ganglia and thalamus involvement). Brainstem encephalitis clinically presents as autonomic dysfunction, lower cranial nerve involvement, and respiratory drive disturbance, e.g., enterovirus-71, flaviviruses (e.g., West Nile virus and Japanese encephalitis virus), and alphaviruses (e.g., eastern equine encephalitis virus). One thing need to know that no individual signs and symptoms or CSF finding alone or in combinations with other clinical features can distinguish one cause of encephalitis from another.

Approach to diagnosis: The initial approach to diagnosis of encephalitis is almost similar to meningitis (**Flowchart 2**). Evaluate the patient for any contraindications of lumbar puncture and need for CT head before lumbar puncture procedure. All patients should have lumbar puncture done unless contraindicated (a coagulation abnormality,

TABLE 3: Clinical presentation and treatment of selected causes of viral encephalitis.				
Pathogen	***Other neurologic symptoms (fever, headache altered mental status are common in all)***	***Nonneurologic features***	***Diagnostic test***	***Treatment***
HSV (Usually young and elderly; no seasonal predilection)	Seizures, olfactory/gustatory hallucinations, aphasia, personality changes, hemiparesis (face/arm > leg), and upper visual field defect	Rash	HSV-1, HSV-2 PCR (CSF)	Acyclovir 10 mg/kg every 8 h (adjust for renal function)
VZV (Most common in immuno-compromised)	Cranial nerve palsies and cerebellitis	Shingles	VZV PCR (CSF)	Acyclovir 10 mg/kg every 8 h (adjust for renal function)
CMV (Immuno-compromised)	Behavior changes and coma	Pneumonitis, retinitis, and myelitis	CMV PCR (CSF)	Ganciclovir 5 mg/kg every 12 h
Enterovirus (Usually young)	Rhombencephalitis (myoclonus, tremors, ataxia, cranial nerve palsies), polio such as acute flaccid paralysis and neurogenic shock	Hand-foot-mouth disease, rash, myocarditis, pericarditis, conjunctivitis, and pulmonary edema	Enterovirus PCR (CSF)	Supportive care

(HSV: herpes simplex virus; VZV: varicella zoster virus; CMV: cytomegalovirus; PCR:polymerase chain reaction)


Features of Encephalitis
(Altered mental status or new onset seizures)
Laboratory: Blood count, coagulation profile, and virus specific serology. Assess for any C/I of lumbar puncture without neuroimaging (papilledema seizure, low GCS posturing, and neurologic deficit)
Perform CT head if any C/I to LP to look for assymetric mass effect herniation
Perform lumber puncture with opening pressure if no C/I send CSF for glucose protein, cell count culture Gram stain HSV/VZV PCR. If HIV positive CMV EBV VZV Toxoplasma Cryptococcus, and Listeria
Suspicion of HSV/VZV on the basis of features CSF and radiologic finding
Start acyclovir
<12 years 20 mg/kg every 8 hourly
>12 years 10 mg/kg every 8 hourly
Adjust dose as per Ideal body weight and renal impairment

(HSV: herpes simplex virus; VZV: varicella zoster virus; CMV: cytomegalovirus; PCR: polymerase chain reaction; EBV: Epstein Barr virus; CSF: cerebrospinal fluid; CT: computed tomography; HIV: human immunodeficiency virus; GCS: Glasgow coma scale)

FLOWCHART 2: Approach to encephalitis.

local infection at the lumbar puncture site, or evidence of significant mass effect on imaging studies). Indications of performing CT head before lumbar puncture are: moderate-to-severe impairment of consciousness, focal neurologic deficit, posturing, papilledema, seizures, relative bradycardia with hypertension, or immunocompromise. All patients with suspected encephalitis should be tested for HIV infection in addition to a standard laboratory evaluation, because subsequent diagnostic testing and empiric treatment will be changed.

In HSV encephalitis, CSF findings are variable (normal/lymphocytic pleocytosis/hemorrhagic). No CSF findings can reliably distinguish HSV from other causes of viral encephalitis. Thus, molecular (e.g., PCR) and serologic testing are important for establishing a specific diagnosis. Other point to note that initial diagnostic tests may be negative during early infection, normal CSF profile, and a negative HSV PCR. Repeat lumbar puncture at 24–48 hours if diagnosis is strongly suspected.

From the emergency medicine perspective, antibiotic therapy should be initiated rapidly in a patient with suspected CNS infection, the most frequent question to ask when you suspect encephalitis is whether a patient requires antiviral coverage in addition to standard antibiotics. Treatable causes of viral encephalitis are HSV and VZV, and immediate care in emergency department is not influenced by sending a battery of expensive diagnostic molecular test. However, CSF specimen can be preserved so that other clinicians (neurologist) can expand the initial diagnostic workup as needed without repeating the lumbar puncture.

Magnetic resonance imaging is more sensitive than CT in detecting the early changes of viral encephalitis, and with the most characteristic findings there are edematous changes in the orbital surfaces of the frontal lobes and medial temporal lobe. MRI also able to identify alternative causes of encephalitis, with suspected encephalitis in whom the diagnosis remains uncertain. An electroencephalogram (EEG) is not indicated

routinely for encephalitis but useful adjunct in patients who are comatose or poorly responsive, EEG may reveal nonconvulsive status epilepticus requiring antiepileptic management.

Treatment: In any patient suspected to have viral encephalitis, empiric treatment with intravenous acyclovir is indicated until a definitive diagnosis can be achieved. Antiviral treatment should be started as early as possible, ideally within 6 hours of presentation.

Acyclovir dose is calculated according to weight and age. The ideal body weight (IBW) should be calculated for the acyclovir dose [Males: IBW (kg) = 50 kg + 2.3 kg for each inch over 5 feet; females: IBW (kg) = 45.5 kg + 2.3 kg for each inch over 5 feet].

The dose should be reduced in patients with pre-existing renal impairment because acyclovir is renally excreted. Patients should be well hydrated to maintain adequate urine output in order to prevent acyclovir-induced crystalluria and nephrotoxicity. Concurrent administration of nephrotoxic drugs should be minimized.

BRAIN ABSCESS

Brain abscess is collection of infective and purulent materials within CNS. It may be located in subdural, epidural or intracranial location. It also may be found in intramedullary or epidural spinal locations. Cerebral abscess is representative of localized infection of brain parenchyma characterized by pus collection within a well vascularized capsule. They begin as a localized area of cerebritis and develop into an encapsulated collection of pustular materials presenting as a mass-like lesion, similar to the abscess in other sites. Incidence is more among male as compared to female. Pulmonary infections and endocarditis are one of the common causes of hematogenous spread. Contiguous spread from dental infections, mastoiditis, etc. Other causes are neurosurgical intervention and penetrating head injury cryptogenic.

Microbiology: varies as per the etiology of abscess.

Clinical features: Most patients will have nonspecific symptoms; hence, high degree of clinical suspicion is needed for clinical diagnosis. Classical triad of fever, headache, and focal neurological deficit is seen only in minority of patients. Brain abscess should be suspected in patients with progressive headache, gradual onset of neurological deficit, and signs of increased intracranial tension.

Investigations: Laboratory investigations are not very helpful for diagnosis. Leukocytosis and elevated erythrocyte sedimentation rate may be found. CSF may be normal or have low glucose and elevated proteins. Neuroimaging is one the most important tools for definitive diagnosis. MRI has better specificity and sensitivity than CT scan to diagnose pyogenic infections. Diffusion weighted MRI may help to differentiate from neoplastic lesion.

Treatment: Treatment of brain abscess may require both medical and surgical intervention. Prompt administration of empirical antibiotics should be ensured. Antibiotic coverage should extend to gram-positive, gram-negative, and anaerobic organisms. The choice of antibiotics is based on patient factors such as age, prior comorbidities, immunity status, and local microbiological profile of causative organisms. Intravenous cefotaxime and metronidazole are preferred as empirical therapy. In patient with immune-compromised condition empirically sulfadiazine and pyrimethamine is considered. Corticosteroids are not routinely considered, and should be used only in patients with evidence of significant perilesional edema causing mass effect or raised intracranial tension. Surgical therapy is required in most cases. Patients who are to be managed only medically should be carefully selected. Patients with intact mental status and without signs of increased intracranial pressure in whom there is little doubt of diagnosis. All patients have to be admitted and they require prolong duration of intravenous antibiotic administration.

Prognosis: Prognosis has improved in recent times due to better suspicion, availability of neuroimaging, and effective antibiotics. Severity of neurological deficit at the time of initial presentation is a strong predictor for outcome. Patients with rapid progression of disease have relatively poorer outcome.

Common residual effects of brain abscess are epilepsy and focal neurological deficit like hemiparesis.

MULTIPLE CHOICE QUESTIONS

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124 CHAPTER

Coma: Evaluation and Management

Noel Fernando

INTRODUCTION

Consciousness has spectrum of clinical presentation. Coma lies at the extreme end of the spectrum. Coma is one of the most common presentations to emergency department. It is a life-threatening emergency and needs urgent attention. As an emergency physician, we should develop the skill of quick examination, appropriate investigation, and management.

PATHOPHYSIOLOGY

Consciousness refers to one's self-awareness to environment which includes arousal and awareness. The cerebral cortex is responsible for maintaining a person's consciousness.

The arousal is initiated by subcortical structures, most importantly by ascending reticular activating system (ARAS). The ARAS neurons are located in the pons and midbrain. It receives all sensory inputs (such as visual, auditory, olfactory, and gustatory…) and relays them to thalamus and cerebral cortex. Any damage to these cortical, subcortical structures or axonal projections may lead to depressed consciousness or coma.

DIFFERENTIAL DIAGNOSIS

As an emergency physician, we should keep broad differential diagnosis in an undifferentiated coma patient which could avoid a diagnostic error. A quick focused history and physical examination helps to narrow down the differentials. Also, this kind of vigilant approach helps us to initiate an urgent treatment for the patients.

Even though the differential diagnosis of coma is broad, the basic pathology is the brain dysfunction involving any area from cortex to brainstem. It can be a massive neuronal dysfunction to small injury to the critical areas of brain. This can be due to structural brain disease or nonstructural causes such as electrolyte imbalance, drug induced, and infections.

Special consideration should be given to geriatric population and immunocompromised patients. The older population are prone for frequent infections, accidental drug overdose, and drug interactions. Immunocompromised patients like cancer patients undergoing chemotherapy are prone for infections which have a higher possibility for altered conscious levels. There are also few coma mimics which should also be considered during the diagnosis.

The differentials are broad, we can grossly divide into structural, nonstructural causes, and coma mimics (**Table 1**).

CLINICAL FINDING

It will be a challenge for us to get history from a patient with depressed consciousness. We should focus on the information from the prehospital team, which could guide you through the management. It is also very essential to focus on collateral history from any family, friends, next of kin, and police officers at scene. The time and pattern of onset of depressed consciousness is very important. This information will help us immensely in diagnostic evaluation. An abrupt onset of coma suggests a stroke, cardiac event or any acute poisoning, whereas a gradual onset suggests more of infectious or metabolic cause.

Any information on the prodromal symptoms is also very essential in the evaluation.

A preceding headache suggests—intracerebral hemorrhage, cervical artery dissection, and cerebral venous sinus thrombosis.

A preceding fever suggests—meningitis or encephalitis.

The patient's medication history should be reviewed carefully, as any change in the medication doses or new medications to the list may also be a probable cause. Nowadays most of the patient carry a medical file or medical alert bracelet. Therefore, it is important to get essential information from history which is very useful in diagnosis.

CLINICAL EXAMINATION

Once the patient is received in the emergency department, the initial observations such as heart rate, blood pressure, respiratory rate, oxygen saturations, blood glucose, and the level of consciousness should be recorded.

Immediate ABCDE assessment and stabilization should be done. Following which a complete head to toe examination is required. If head injury is suspected, look for any external injuries such as scalp lacerations, hematoma, periorbital ecchymosis (raccoon eyes), retroauricular ecchymosis (battle sign), hemotympanum, cerebrospinal fluid (CSF) otorrhea

TABLE 1: Causes of coma: Differential diagnosis.

	Nonstructural causes		
Structural CNS diseases	***Metabolic***	***Toxic***	***Coma mimics***
• Intracranial hemorrhage • Cerebellar infarct • Cortical infarct • Hydrocephalus • Neoplasia • Metastatic lesions	• Electrolyte imbalance (Hypo- and hyperglycemia, hyponatremia, and hypercalcemia) • Endocrine (Adrenal crisis, pituitary apoplexy, thyrotoxic crisis, and myxedema coma) • Hepatic encephalopathy • High altitude cerebral edema	• Hypoglycemic agents • Opioids • Carbon monoxide • Methemoglobinemia • Sedatives • Toxic alcohols • Anticonvulsants • Anticholinergics • Psychiatric medications • Beta-blockers • Salicylates • Neuroleptic malignant syndrome • Serotonin syndrome	• Locked in syndrome • Neuromuscular paralysis • Psychogenic unresponsiveness

(CNS: central nervous system)

or rhinorrhea. Any tongue laceration suggests a possible seizure. Always it's better to immobilize the C-spine unless any C-spine injuries are rule out. The presence of meningismus suggests meningitis, subarachnoid hemorrhage or any space occupying lesions. Look for stridor which indicates large airway obstruction possibly caused by infection, anaphylaxis, trauma or foreign body. Most of the patients with altered mental status due to myxedema coma or thyroid storm will be having a goiter.

A quick examination of chest should be done, looking for any tracheal deviation, external injuries, dilated veins, any rashes, and chest movements. More focused examination of heart rate, rhythm, murmurs, and abnormal lung sounds is essential. A 12 lead electrocardiogram (ECG) is mandatory to rule out any arrhythmias or any acute cardiac event.

Abdominal examinations should focus on the abdominal distension, any dilated veins, hepatosplenomegaly, and pulsatile abdominal mass. A quick focused assessment with sonography for trauma (FAST) and extended (E)-FAST scan may provide more information essential for diagnosis. Bladder scan helps to rule out any urinary retention. A rectal examination should be done to look for gastrointestinal bleeding and foreign bodies.

The patient should be undressed fully to start the evaluation of skin. A dry skin with loss skin turgor suggests dehydration. Look for rashes, patches, signs of infection or trauma. Also look for signs of liver cell failure such as jaundice, palmar erythema, spider angiomata, and caput medusae. Petechiae or purpura could suggest meningitis, vasculitis or disseminated intravascular coagulation (DIC). Unusual odors also provide additional diagnostic clues.

Neurologic examination should include evaluation of patients level of consciousness, cranial nerves, brainstem reflexes, and motor responses. In an emergent situation alert, verbal, pain, unresponsive (AVPU) scale can be used to assess the level of consciousness. The two most widely used scales are the Glasgow coma scale (GCS) and full outline of unresponsiveness score (FOUR). While comparing both the scores, the FOUR score has higher reliability than GCS scale as it incorporates more detailed assessment of brainstem reflexes and has greater predictive value in intubated patients.

The cranial nerves should be assessed for all comatose patients, in particular for eyes. The pupillary size, symmetry, and reactivity provides important diagnostic clues. *Pinpoint pupils* pontine hemorrhage/infarction, drugs opioids, clonidine, and organophosphates dilated *pupils* oculomotor nerve injury/brain injury, and brain herniation

Eye position and movements should be noted, as it gives us a lot of important information.

- *Horizontal conjugate eye gaze*: Brain injury (ipsilateral) or pontine injury (contralateral), and seizures.
- *Horizontal disconjugate eye gaze*: Sedation, intoxication, and metabolic disorders.
- *Vertical disconjugate gaze*: Cerebellum or brainstem lesion.
- *Roving eyes*: Bihemispheric dysfunction.
- *Nystagmus*: Brainstem dysfunction, overdose (anticonvulsants, lithium, ketamine, and ethanol)

Fundoscopic Examination

It is a valuable examination tool to identify the raised intracranial pressure (ICP) quickly. The presence of papilledema, and retinal hemorrhages suggest raised ICP, which could be confirmed by optic nerve sheath measurement with ultrasound.

We can evaluate the brainstem function by various brainstem reflexes such as oculocephalic reflex, oculovestibular reflex, corneal reflex, and gag reflex. Always make sure that there is no suspicion for C-spine injury. Motor function should be assessed by spontaneous movements or reflexive response to noxious stimuli. Reflexive responses such as decorticate rigidity, and decerebrate rigidity is usually seen in focal brain lesions. But this is not very conclusive, as it is also seen in toxic and metabolic disorders. Muscle tone is assessed by passive movement of extremities. Muscle rigidity occurs most commonly with upper motor neuron (UMN) brain lesions, malignant hyperthermia, and neuroleptic malignant syndromes and in certain intoxications. Myoclonus is very

poor prognostic marker which is usually seen in brain injuries, nonconvulsive status epilepticus, and hypercarbic respiratory failure.

GRADING OF COMA

Two major grading systems are used to assess the depths of coma (**Table 2**). Grading systems allow emergency physician to quickly convey a general sense of the patient's condition. This grading is helpful during emergency medical service communications when one provider conveys the grading to emergency department physician/nurses over telephonic discussion who cannot examine the patient. The GCS, first described in 1974, GCS is a 15-point composite score of eye, motor, and verbal responses developed to assess patients with head trauma. The FOUR score, first described in 2005, is a 16-point scale that assesses eye, motor, brainstem reflexes, and respirations. Both gradings rely on clinical findings and can be performed quickly. The FOUR score has a benefit over GCS in that one of three of the GCS criteria is unreliable in intubated patients. The FOUR score is also a better predictor of mortality in critically ill patients.

TABLE 2: Grading of coma.

Glasgow coma scale (GCS)	***Full outline of unresponsiveness score (FOUR)***
Eye opening response: • Spontaneously, 4 • To speech, 3 • To pain, 1	*Eye response:* • Open and tracking or blinking to command, 4 and open but not tracking, 3 • Closed but open to loud voice, 2 • Closed but open to pain, 1 • Closed with pain, 0
Best verbal response: • Oriented, 5 • Disoriented, 4 • Inappropriate words, 3 • Incomprehensible sounds, 2 • No response, 1	*Motor response:* • Thumbs up, fist or peace sign, 4 • Localizes pain, 3 • Flexion response to pain, 2 • Extension response to pain, 1 • No response to pain or myoclonic status, 0
Best motor response: • Obeys commands, 6 • Localizes pain, 5 • Withdrawal from pain, 4 • Decorticate flexion, 3 • Decerebrate extension, 2 • No movement, 1	*Brainstem reflexes:* • Pupil and corneal reflexes present, 4 • One pupil wide and fixed, 3 • Pupil or corneal reflexes absent, 2 • Pupil and corneal reflexes absent, 1 • Absent pupil, corneal, and cough reflex, 0
	Respiration: • Not intubated, regular pattern, 4 • Not intubated, Cheyne–Stokes pattern, 3 • Not intubated, irregular breathing, 2 • Breathes above ventilator rate, 1 • Breathes at ventilator rate or apnea, 0

INVESTIGATIONS

General Management

The most important bedside investigation for patients with reduced consciousness is blood glucose levels to rule out hypoglycemia. The routine blood investigations such as full blood count, urea, electrolytes, coagulation profile, renal function, ammonia, and liver function test should be done. This helps us to rule out infections, anemia, thrombocytopenia, and electrolyte imbalance, renal and hepatic dysfunction. Blood gas gives plenty of information about the patient's clinical status. It helps us to assess the oxygen and carbon dioxide levels. In a patient with metabolic acidosis, widened metabolic acidosis suggests ketosis, lactic acidosis, uremia, or intoxications. An elevated prothrombin and activated partial thromboplastin time (aPTT) is usually seen in liver disease, blood dyscrasias, and anticoagulant use. Urinary catheterization must be done in comatose patients to monitor the fluid status. Urinalysis helps to rule out dehydration (high specific gravity), infections (positive leukocytes and nitrates), and ethylene glycol ingestion (presence of calcium oxalate crystals).

Toxicologic screen including paracetamol and salicylate levels should be done as they are prone to cause unexplained acidosis. Serum alcohol levels could also be included. In carbon monoxide/methemoglobinemia poisoning co-oximetry is very useful. Blood and urine cultures should be sent to rule out infections.

Electrocardiogram is very useful to look for arrhythmias, electrolyte abnormalities, hypothermia, and structural brain lesions.

Chest X-ray helps to look for pneumonia, pneumothorax, foreign body, cardiomegaly, and aortic dissection.

Noncontrast computed tomography (CT) scan of brain is the most commonly used modality of imaging in comatose patients. This helps to identify any ischemic stroke, subarachnoid hemorrhage, intracranial hemorrhage, cerebral edema, hydrocephalus, and mass lesions. CT angiography is useful in identifying intracranial aneurysm, cerebral venous thrombosis, basilar, and vertebral artery stenosis. Magnetic resonance imaging (MRI) helps us to identify posterior circulation lesions and brainstem lesions. Even though it is much superior than noncontrast CT brain in identifying the brain lesions, it is not used much in emergency department due to its restricted availability during out of hours.

Electroencephalogram (EEG) is not only used in nonconvulsive status epilepticus, but also used in patients with refractory seizures.

It is better to have quick algorithm guide to run through during the management of the comatose patients in emergency department.

TREATMENT

Treatment of coma is based on the three basic causes such as structural, metabolic, or toxins (**Table 3**).

First: Coma from structural cause can be treated surgically targeted medication or mechanical ventilation. Neurosurgeon is involved for early intervention for intracranial hemorrhage and hydrocephalus.

Second: Coma due to metabolic induced neuronal dysfunction, conditions such as hypoglycemia and hyponatremia should be corrected.

TABLE 3: Coma: Causes, clinical findings, and treatment.

Diagnosis	*Causes*	*Examination findings*	*Treatment*	*Comments*
Structural	*Intracranial hemorrhage*	Headache—sudden onset, blurred vision, and raised ICP signs	• CT brain • Reversal of anticoagulation —if drug induced	Early neurosurgical team involvement
	Cerebral infarct	Sudden drop in GCS and focal neurological deficit	• CT brain • Stroke team review • Thrombolysis	If patient is in the window period—thrombolysis is indicated
	Cerebellar infarct	Headache, nausea, vomiting, vertigo unsteady gait, and cerebellar signs-nystagmus dysarthria, in coordination	• MRI—gold standard investigation • Stroke team review • Thrombolysis	Early stroke team and neurosurgical team involvement
Metabolic derangement	*Hypoglycemia*	Tachycardia, diaphoresis, drowsy, seizures, and coma	• Oral carbohydrate • Oral glucogel • IV dextrose • IV/IM glucagon • IV octreotide	Check BM for all patients with reduced consciousness. Do not give glucagon in liver failure and alcohol dependent patients due to low stores of glucose
	Hyperglycemia	Nausea, vomiting, tachypnea, abdominal pain, and signs of dehydration	• IV fluid (normal saline) • IV insulin	Identify the severity of ketoacidosis and start insulin infusion early
	Hyponatremia	Headache, nausea, vomiting, confusion, anorexia, and seizures	• Hypertonic saline—in emergency situations • Water restriction	Rapid administration of hypertonic saline—pontine myelinolysis
	Hypercalcemia	Lethargy, polyuria, dehydration, and constipation	• IV fluids • Diuretics • IV bisphosphonates • Prednisolone	Suspect malignancy
Endocrinal disorders	*Adrenal crisis*	Weight loss, weakness, hypotension, and hyperpigmentation	• IV fluids • IV hydrocortisone • IV glucose • Antibiotics—for infections	• Biochemical abnormalities • Metabolic acidosis • Hyperkalemia • Hyponatremia, low urea, and hypoglycemia
	Pituitary apoplexy	Headache-acute onset, nausea, vomiting, visual impairment, and hormonal imbalance	• IV fluids • Correct electrolyte abnormalities • IV hydrocortisone	Common in postoperative period, during pregnancy
	Thyrotoxic crisis	Tachycardia, fever, sweating, vomiting, and diarrhea	• IV fluids • Beta-blockers • Propylthiouracil	Give antibiotics if infection suspected
	Myxedema coma	Bradycardia, weight gain, tired, lethargy, edema, depression, hair loss, and constipation	• IV fluids • Thyroxine • IV hydrocortisone	
Hepatic disorders	*Hepatic encephalopathy*	Jaundice, lethargy, fetor hepaticus, asterixis, ascites, and dilated veins	• Lactulose • Ascitic drainage	Anticipate SBP, sepsis, and GI hemorrhage
Altitude illness	*High altitude cerebral edema (HACE)*	Headache, rapid ascent, vomiting, confusion, and irritability	• Hyperbaric oxygen • Rapid descent • IV dexamethasone	More common in Amateur Trekkers
Toxic-drug induced	*Opioids*	Drowsy, bradypnea, confusion, irritability, seizure, and respiratory arrest	• Oxygen • Naloxone • Intubation if retaining CO_2	Early ITU involvement required

Continued

Continued

Diagnosis	Causes	Examination findings	Treatment	Comments
	Hypoglycemia agents	Drowsy, confusion, seizures, and suicidal symptoms	• IV glucose • IV octreotide-refractory hypoglycemia	Look for acidosis especially I metformin overdose
	Sedatives	Drowsy, bradypnea, respiratory arrest, confusion, and seizures	• Identify the sedative • Supportive	Most common—benzodiazepines do not use flumazenil in mixed overdose and long term benzodiazepines dependent patients
	Alcohols	Nausea, vomiting, drowsy, vision loss, confusion, seizures, reduced urine output, and renal failure	• IV fluids • Fomepizole • Folic acid	• Increased osmolar gap • Early dialysis required
	Carbon monoxide	Headache, nausea, vomiting, drowsiness, confusion, and seizures	Hyperbaric oxygen	More common due to fuel combustion
	Methemoglobinemia	Headache, cyanosis, lethargy, malaise, and seizures	• 100% oxygen • Methylene blue	Always do ABG to rule out hypoxia in these patients
	Anticonvulsants	Drowsiness, confusion, and slurred speech	Supportive	
	Anticholinergics	Tachycardia, hyperpyrexia, sweating, pupillary dilatation, and urinary retention	• Pyridostigmine • Benzodiazepines • IV fluids	
	Psychiatric medications	Tachycardia, sweating, drowsiness, hypotension, wide QRS, and metabolic acidosis	• IV fluids • Sodium bicarbonate	Most common is tricyclic antidepressants
	Beta-blockers	Bradycardia, hypotension, hypoglycemia, and seizures	• Atropine • Glucagon • Epinephrine • Transcutaneous pacing	Lipid emulsion will be necessary if initial measures fail
	Salicylates	Nausea, vomiting, delirium, drowsiness, tinnitus, and mixed acid base disorders	• IV fluids • Sodium bicarbonate • Hemodialysis	
	Neuroleptic malignant syndrome	Hyperpyrexia, drowsiness, delirium, autonomic instability, and raised creatine kinase	• IV fluids • Cooling methods • Benzodiazepines • Dantrolene sodium	• More common with depolarizing muscle relaxants • Prone for rhabdomyolysis and renal failure
	Serotonin syndrome	Tachycardia, hyperpyrexia, hypertension, muscle rigidity, autonomic instability, and raised creatine kinase	• IV fluids • Cyproheptadine • Benzodiazepines	• More common with depolarizing muscle relaxants • Prone for rhabdomyolysis and renal failure

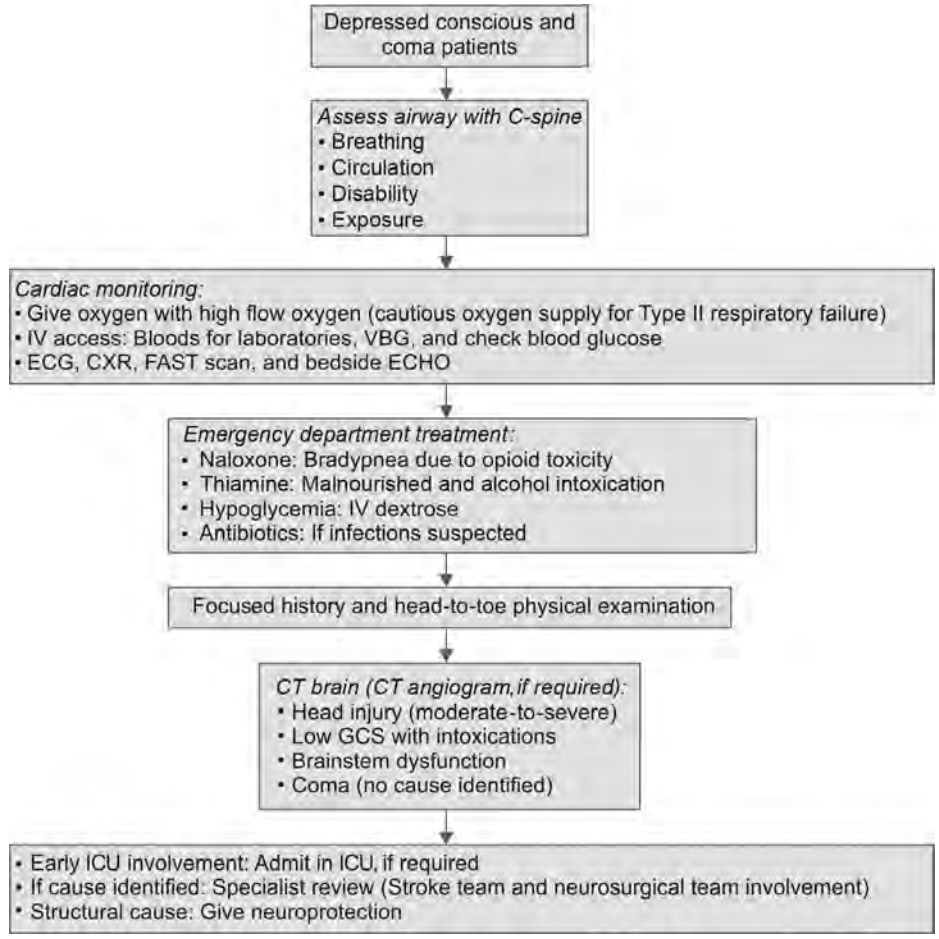
(ABG: arterial blood gas; CT: computed tomography: GCS: Glasgow coma scale; GI: gastrointestinal; ICP: intracranial pressure; IV/IM: intravenous/intramuscular; MRI: magnetic resonance imaging; SBP: spontaneous bacterial peritonitis; ITU: intensive treatment unit)

Third: Toxin induced neuronal dysfunction is managed by initiating the supportive care securing airway, adequate oxygenation, and ventilation, intravenous fluid, inotropes, and vasopressors if required and specific antidote if toxin is identified.

SUMMARY

Coma requires immediate stabilization and a structured approach to diagnosis and management because coma is a life-threatening process. The differential diagnosis for

coma is descriptive, and can be divided into structural and diffuse neuronal dysfunction either due to toxic or metabolic imbalance. History from reliable sources to determine the etiology of coma; focused physical examination can be helpful to narrow down diagnosis. The definitive management of coma is disease-specific and toxin induced coma is treated with conservative management and specific antidote. Approach to patient with coma is summarized in **Flowchart 1**.


Depressed conscious and coma patients
Assess airway with C-spine
• Breathing
• Circulation
• Disability
• Exposure
Cardiac monitoring:
• Give oxygen with high flow oxygen (cautious oxygen supply for Type II respiratory failure)
• IV access: Bloods for laboratories, VBG, and check blood glucose
• ECG, CXR, FAST scan, and bedside ECHO
Emergency department treatment:
• Naloxone: Bradypnea due to opioid toxicity
• Thiamine: Malnourished and alcohol intoxication
• Hypoglycemia: IV dextrose
• Antibiotics: If infections suspected
Focused history and head-to-toe physical examination
CT brain (CT angiogram, if required):
• Head injury (moderate-to-severe)
• Low GCS with intoxications
• Brainstem dysfunction
• Coma (no cause identified)
• Early ICU involvement: Admit in ICU, if required
• If cause identified: Specialist review (Stroke team and neurosurgical team involvement)
• Structural cause: Give neuroprotection

(CT: computed tomography; CXR: chest X-ray; ECG: electrocardiogram; ECHO: echocardiogram; FAST: focused assessment with sonography for trauma; GCS: Glasgow coma scale; ICU: intensive care unit; IV: intravenous; VBG: venous blood gas)

FLOWCHART 1: Approach to patient of depressed conscious and coma.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Type 1 Diabetes Mellitus and Insulins

Amit Gupta, Vinod Kumar

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease presenting with increased blood glucose levels (hyperglycemia), primarily because of the insulin deficiency that occurs as the consequence of the loss of the pancreatic islet β-cells. In majority of patients (70–90%), the loss of β-cells is the main cause of T1DM (formation of T1DM-associated autoantibodies); in a smaller group of patients, no autoantibodies are detected, and the cause of β-cell destruction remains unknown (idiopathic T1DM or type 1b diabetes mellitus); unless otherwise specified, the term T1DM refers to autoimmune T1DM. The diagnosis of T1DM in the absence of ketoacidosis and symptoms will be key to a better prognosis, particularly in the very young. Nowadays novel insulin analogs, pumps, pens, continuous glucose monitoring devices, in combination with better psychosocial support are available and all are important ways to improve the quality of life, of those already affected by T1DM.

TYPE 1 DIABETES MELLITUS

Diabetes mellitus is classified on the basis of etiology into T1DM, type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (**Table 1**). Type 1 diabetes mellitus is one of the most common chronic childhood disorders characterized by immune-mediated destruction of beta cells of the islet of Langerhans in pancreas leading to absolute deficiency of insulin. The child may present with classical signs of hyperglycemia such as increased thirst (polydipsia), increased urination (polyuria), and weight loss while diabetic ketoacidosis (DKA) remains the second most common presentation of T1DM. Most of the patients with T1DM have circulating antibodies against glutamic acid decarboxylase 65 (GAD65), zinc transporter 8 (ZnT8), and islet cell autoantibodies (IA2). The management of T1DM requires setting realistic goals balancing glycemic control and avoiding severe hypoglycemia, educating the patient and the family, and at the same time ensuring normal growth and development. The insulin therapy assumes the central role in management of hyperglycemia in patients with T1DM.

DIAGNOSIS

Diagnosis of diabetes can be done by any one of the criteria set by American Diabetic Association (**Box 1**). The criteria for prediabetic are fasting plasma glucose 100–125 mg/dL, glycated hemoglobin (HbA1c) 5.7–6.4%, 2-hour plasma glucose, and oral glucose tolerance test 140–199 mg/dL. Glycated HbA1c represents the average blood glucose level over the 2–3-month period. In emergency department, patient may present with higher level of blood sugar and features of hyperglycemia polydipsia and polyurea) or if they are in hyperglycemic crisis, should be considered as diabetic.

TABLE 1: Etiological classification of diabetes mellitus.

Type 1 diabetes mellitus (Destruction of β cell—absolute insulin deficiency)	• Idiopathic • Immune mediated
Type 2 diabetes mellitus (Relative insulin deficiency and insulin resistance secretory defect)	• Genetic defect of β-cell function • Genetic defects of insulin action • Exocrine pancreas disease (pancreatitis, trauma, and cystic fibrosis) • Endocrinopathies (Cushing's disease, pheochromocytoma, and hyperthyroidism) • Drug induced-steroids, thiazides, and thyroid hormone • Infections—congenital rubella and cytomegalovirus) • Immune-mediated diabetes (rare)—lupus • Diabetes associated with congenital syndrome—Down's, Klinefelter's, and Turner's syndrome)
Gestational diabetes mellitus	

BOX 1: Criteria for diagnosing the diabetes—American Diabetic Association.

- Glycated hemoglobin A1c (HbA1C) ≥6.5%
- Fasting blood glucose ≥126 mg/dL (fasting–no calorie intake for at least 8 h)
- Random blood sugars ≥200 mg/dL with symptoms of hyperglycemia or hyperglycemic crisis
- Oral glucose tolerance test (OGTT) 2-h plasma glucose ≥200 mg/dL

Hundred Years of Insulin Therapy (1921–2020)

It has been a hundred years since the discovery of insulin in 1921. Fred Banting and Charles H Best began their research in May 1921 with John R Macleod as formal supervisor. In August of 1921, Banting and Best after several failures, prepared an extract from the atrophied pancreas of a dog and conducted their famous experiment on the Marjorie (The Dog). The discovery of insulin in 1921 was a milestone in the world of medicine because before that everyone with T1DM was destined to die within weeks to year of the diagnosis. The Leonard Thompson, 14-year-old boy was the first human who received insulin prepared by Banting and Best on January 11, 1922. However the first test failed and could not bring down the sugar levels. JB Collip prepared a series of purified insulin preparations (bovine) and it was able to bring down the blood sugar levels of Leonard and he started to gain weight and after that everything is a history now. Over the last hundred years the landscape of insulin therapy has undergone dramatic changes. The first bottle of insulin contained U-10 insulin and 3–5 mL of it was injected at one time.

Protamine and protamine zinc insulin were developed in 1936, while neutral protamine Hagedorn (NPH) came into existence in 1946. In the year 1952 lente zinc insulin was developed, while the first human synthetic insulin was developed in 1965. In the late 70s, first recombinant human insulin was developed. It was also the time when lots of researchers were working on improving the delivery of insulin through insulin pumps. Insulin pen devices came into existence in 1981. The first human analog insulin lispro was approved for use in the USA in 1996. Insulin glargine and insulin detemir were approved in 2000 by the United States Food and Drug Administration (USFDA). Inhaled insulin was developed in the year 2006. In the last one decade with the launch of new preparations such as insulin degludec, glargine U300, Fiasp (fast-acting insulin aspart), and U-500 insulin, a wide range of insulins are available for use. The year 2020 has generated new hope with the talks of smart insulin and weekly insulin therapy. Advances in insulin therapy coupled with technology have led to availability of a variety of glucose sensors and insulin pumps. Do It Yourself (DIY) movement initiated by many patients and their parents with T1DM all across the world has accelerated the development and incorporation of newer technologies.

INSULIN

Insulin therapy is the principal treatment of patients with T1DM with a goal of replacing the deficient hormone and achieving good glycemic control. Endogenously insulin is secreted in the portal vein and there are minute-to-minute physiological variations in insulin secretion. It is extremely difficult to match the physiological insulin secretion and hence the idea of a near physiological replacement of insulin in T1DM remains elusive; however, with the development of newer insulins and sensor augmented closed loop insulin pumps the future is promising. The side effects of insulins are rare and hypersensitivity is uncommon. Hypoglycemia, weight gain, and lipohypertrophy are the other adverse effects of insulin therapy.

Insulin Preparations/Types of Insulin (Duration of Action)

- *Ultra-rapid-acting insulin*: Fiasp enters the bloodstream within 2–3 minutes of subcutaneous administration with onset of action in 10–15 minutes, peak in 1–3 hours and total duration of action 3–5 hours or even shorter. Till the time of writing this article, Fiasp is not approved for use in the pediatrics population.
- *Rapid-acting insulin analogs*: Insulin aspart (Novorapid), lispro (Humalog), and glulisine (Apidra) are rapid-acting insulins with onset of action within 15–30 minutes and peak in 1–3 hours with total duration of action 3–5 hours. Rapid-acting insulins are usually given 5–15 minutes before a meal. In younger children where meal intake is unpredictable, it can also be administered after the meal.
- *Short-acting insulin*: These insulin analogs have onset of action in 30 minutes to 1 hour with a peak effect in 2–4 hours, and with a duration of action 5–8 hours (e.g., Actrapid, Humulin, and regular human insulin). Short-acting insulin is given 20–30 minutes before the meals.
- *Intermediate-acting insulin*: NPH and lente insulin are intermediate acting as the onset of action is within 1–2 hours, with peak activity in 6–10 hours and duration of action varying from 10 to 16 hours.
- *Long/ultra-long-acting insulin*: Insulin glargine, biosimilar insulin glargine, and detemir are long acting while degludec and glargine-U300 are ultra-long-acting insulins. Insulin glargine, biosimilar insulin glargine, and detemir have duration of action up to 24 hours. Glargine-U300 has duration of action up to 36 hours while effective duration of action of insulin degludec is up to 42 hours. These insulins are usually given once or twice a day.

Insulin Delivery Devices

- *Syringe and needle*: Insulin syringes have been long in use. One advantage is that it is possible to mix two different types of compatible insulins in a syringe while key limitations are risk of incorrect dosing, difficulty in carrying along, and psychological impact.
- *Insulin pens*: A variety of insulin pens are available. Compared with syringes, pens are more convenient and flexible to use with greater accuracy, patients have greater acceptability for pens. They are also cost effective and easy to carry. The smallest needle is 31 gauge in size, and available in 4 mm and 6 mm length.
- *Insulin pumps*: Insulin pump is an electronic device which can automatically deliver insulin to the patient. Insulin pump represents an advancement in diabetes technology

and in a suitable patient it can help in improving glycemic control and minimize the risk of hypoglycemia.
- *Inhaled insulin*: A rapid-acting insulin (Technosphere approved by USFDA, Afrezza) is also available in the form of inhaler. The inhaled insulin is having many challenges such as inconsistent dose delivery, requires more training, and there are concerns regarding adverse effects on pulmonary functions.

Insulin Regimens

Insulin therapy regimens are of two types; conventional and intensive.

A conventional regime is simpler and requires administration of a short-acting insulin (e.g., NPH) with a rapid-acting insulin (e.g., regular insulin). Two insulins can be mixed in a syringe or a premixed insulin formulation can also be used. Two-thirds of the insulin dose is given in the morning before breakfast and one-third of the total insulin dose is given at the time of the dinner. The usual ratio in which short-acting and rapid-acting insulin are mixed is two-thirds short acting and one-third rapid acting. Some of the premixed insulin formulations are also available as 50:50 insulins. One of the major drawbacks of this regimen is that dose of the insulin is relatively fixed; allowing less flexibility in titration and at the same time it requires more lifestyle adjustment from the patient as well. However, there are various other regimens which use a variety of insulin preparations tailored according to the need of the patient.

An intensive insulin therapy regimen aims at achieving a stricter glycemic control with an intent to match the physiological insulin release as much as possible. It involves administration of a basal insulin to provide for basal insulin levels and use of rapid- and short-acting insulins before meals to cover the postprandial glucose excursions. The dose of prandial insulin is calculated by carbohydrate counting and the present blood glucose of the patient. This type of regimen requires proper education of the patient regarding carbohydrate counting and hypoglycemia. Since the dose of prandial insulin varies as per the carbohydrate intake, this allows greater meal flexibility. Use of insulin pump is also an intensive regimen. In the Diabetes Control and Complications Trial (DCCT), intensive glycemic control with intensive regimen was found to reduce the overall glycemic control and long-term risk of microvascular complications.

Multiple Daily Injections

Multiple daily injection (MDI) regimen combines a basal insulin at bedtime or in morning with multiple doses of prandial insulin given as pre meal bolus. The approach has shown better glycemic control and lesser incidences of hypoglycemia. The dose of prandial insulin is decided by blood glucose levels before meals, amount of carbohydrate in the meal, and expected level of activity or exercise before and after meals. Insulin glargine is one of the most common basal insulin used in children and is approved by the USFDA for use in children above 6 years of age however the benefit has also been seen in younger children. The use of insulin glargine and lispro has shown lesser incidences of nocturnal hypoglycemia when compared to NPH insulin in adolescents and young children.

Insulin Pump

Continuous subcutaneous insulin infusion (CSII) by insulin pumps is now widely used worldwide for pediatrics T1DM population. Use of insulin pumps is recommended in T1DM patients with recurrent severe hyperglycemia and large variations in blood glucose levels. Patients whose diabetes is suboptimally controlled, those who have microvascular complications, and those patients who have risk factors for macrovascular complications may also benefit from CSII. Some patients may choose CSII over conventional insulin therapy for the sake of greater flexibility. Insulin pumps may also be of value in infants, young children, and adolescents, during pregnancy and in T1DM patients involved in competitive sports. Rapid- or short-acting insulins are used in insulin pumps. When an insulin pump is combined with a continuous glucose monitoring sensor, it is called sensor augmented insulin pump therapy. A closed loop system is one which is fully automated, meaning the pump can reprogram itself based on automatically detected glucose values. Studies have shown that pump therapy may only be slightly better than MDI when it comes to glycemic control and frequency of hypoglycemia in adults. However, in the pediatric population, a meta-analysis on insulin pump therapy has shown to reduce the requirement of daily insulin with less frequent hypoglycemic episodes, better glycemic control, and lesser incidences of ketoacidosis. However, there are studies which have shown that it may not be possible to achieve similar results in newly diagnosed patients.

Insulin Dose

A child with newly diagnosed diabetes usually requires a dose of 0.5–1.0 unit of insulin per kg. The dose of insulin in children may also depend upon the age and pubertal stage of the child. Prepubertal children may require 0.25 units/kg of insulin while insulin requirement may increase during puberty. Basal insulin requirements are usually 40–50% of the total daily insulin dose. It is important to know about the insulin correction factor which is estimated as the amount of blood glucose reduced by injecting one unit of rapid-acting insulin. It is calculated by dividing 1,500 by total daily insulin dose. It is equally helpful to know insulin to carbohydrate ratio and is defined as the number of grams of carbohydrate which will be covered by 1 unit of insulin. It is usually calculated by dividing 500 with total daily insulin dose.

Honeymoon Phase and Type 1 Diabetes Mellitus

In patients with newly diagnosed T1DM, following initiation of insulin therapy there is a period in which insulin requirement may decrease as some of the beta cells may still be functioning. One should be judicious and frequently monitor blood glucose levels as likelihood of hypoglycemia is increased with insulin therapy. The phase may last from weeks to several years.

Diabetic Ketoacidosis and Insulin

The International Society for Pediatric and Adolescent Diabetes (ISPAD) defines DKA as blood glucose >200 mg/dL with metabolic acidosis (pH <7.3), and bicarbonate <15 mEq/L with presence of ketones in the blood and the urine. Though it is

beyond the scope of this chapter to discuss in detail regarding DKA, it is important to highlight some key points of insulin therapy in the management of DKA. An initial bolus dose of insulin is not necessary. The insulin is started as intravenous infusion and this rapidly archives the steady state levels in the serum. The rate of insulin infusion is usually 0.1 unit/kg/h; however, no difference in rate of fall of blood glucose is seen in some studies with lower doses of 0.05 units/kg/h.

SUMMARY

Insulin therapy is the cornerstone of T1DM management. The journey of insulin from discovery to completion of 100 years in 2021 is fascinating and an entire book can be written on insulin itself. We have tried to highlight the key points relevant to insulin therapy in management of type of diabetes.

MULTIPLE CHOICE QUESTIONS

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126 CHAPTER

Type 2 Diabetes Mellitus: Management

Ashok K Taneja

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global noncommunicable lifestyle disease (NCD) prevalent all over the world. The unfortunate part of this disease is its ever-increasing incidence in all socioeconomic groups of population. As per estimate of the World Health Organization (WHO) incidence of non-insulin-dependent diabetes mellitus (NIDDM) is 10% of world population. Whereas in India, the incidence is 11–14%. It is manifested by a chronic hyperglycemic state in conjunction with other metabolic derangements. If left untreated or treated poorly, it leads to complications such as end-stage renal failure, heart failure, coronary artery disease CAD, peripheral artery disease (PAD), strokes, retinopathy, erectile dysfunction, and many others. This leads to increased morbidity and mortality in general population.

Type 2 diabetes mellitus is primarily due to either insulin deficiency or insulin resistance or both. Both the states result in increased hepatic glucose output, reduced utilization of glucose by various organs, increased renal reabsorption of glucose, reduced incretin hormones, and increased production of glucagon among others.

Currently there is no known cure for the disease but can be controlled enabling the individual to have an improved quality of life. The main aim of management is directed at reducing acute and chronic complications, i.e., microvascular and macrovascular.

EPIDEMIOLOGY: PREVALENCE IN WORLD AND INDIA

There are estimated 72.96 million cases of diabetes in adult population of India. The prevalence in urban areas ranges between 10.9% and 14.2% and prevalence in rural India was 3.0–7.8% among population aged 20 years and above with a much higher prevalence among individuals aged over 50 years (INDIAB Study). Kerala has the largest number of diabetes patients followed by Tamil Nadu and Punjab.

World: It is estimated that 415 million people are living with diabetes in the world, which is estimated to be 1 in 11 of the world's adult population (9.9%). 46% of people with diabetes remain undiagnosed till complications ensue. The figure is expected to rise to 20% worldwide by 2040. China, followed by India has the highest incidence of T2DM. Lithuania, Sweden, Estonia, Ireland, and 35 more nations has the lowest incidence. Though, there is no sex preponderance in incidence of diabetes mellitus (DM) in males or females. Both are equally affected. Genetic effects, epigenetic mechanisms, nutritional factors, pregnancy, and sedentary lifestyle affect the risk and complications differently in both sexes. However, obesity, psychological stress, and higher incidence of myocardial infarctions are more prevalent in females.

The population above 18 years of age are most concerned group who are unaware of their diabetic status (52% of diabetes). The percentage of undiagnosed diabetes is highest among the Malays (53%) followed by the Chinese (49%) and the Indians (42%). In terms of diabetes control, only 23.8% of patients in primary care and 12.7% in tertiary institutions were able to achieve their specified glycemic targets.

RISK FACTORS

- *Biological risk factors*: Body mass index (BMI), body fat distribution, brown adipose tissue, metabolic syndrome, adipokines, imbalance of sex hormones, gestational diabetes mellitus (GDM), and insulin resistance (metabolic syndrome).
- *Health related*: Smoking, alcoholism, and lifestyle disorders including sedentary life. Excessive intake sugar sweetened beverages.
- *Psychological*: Stress, economic status, sleep deprivation, and drugs abuse.
- Pharmacological drug induced like steroids, etc.
- Genetics

ETIOLOGY AND PATHOGENESIS

Blood glucose levels are dependent on carbohydrate intake, hepatic glucose production, peripheral uptake, secretion, and action of insulin and glucagon. The basic pathophysiology of T2DM includes defect in insulin secretion or action or both at pancreatic or peripheral receptors level. The resistance to insulin action at muscles or adipose tissues level increase

insulin hypersecretion which ultimately leads to beta cell fatigue and dysfunction (cause of metabolic syndrome, i.e., insulin resistance, dyslipidemia, and hyperglycemia). There is fine balance between regeneration and apoptosis of islet cells. In beta cell fatigue or failure this balance is altered leading to T2DM. Multiple factors affect this balance. Factors contributing to beta-cell dysfunction are age, genetics, insulin resistance, incretin failure, lipotoxic glucotoxicity, amylin, and others including hexosamines.

Insulin resistance is an altered physiological phenomenon due to impaired response of insulin on glucose, lipids, and protein metabolism. The insulin resistance is mediated at liver, muscles, and adipose tissue levels and it leads to endothelial dysfunction affecting micro- and microvasculature.

Combination of insulin resistance and beta-cell dysfunction is termed as "the triumvirate".

Obesity also plays a very important role in insulin resistance, dyslipidemia, and hyperglycemia. Adiposity leads to increased levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 and 8.

Genetic predisposition also plays a role in development of T2DM. Presence of single nucleotide polymorphisms (SNPs) is associated with higher incidence of beta-cell dysfunction.

Dopamine and vitamin D also play very important role on glucose homeostasis.

DIAGNOSIS AND SCREENING

Blood glucose levels either in fasting state or postprandial, oral glucose tolerance test (OGTT) with 75 g glucose and lately glycated hemoglobin (HbA1c) are the mainstay of diagnosis and screening tools [American Diabetes Association (ADA) 2009 and International Diabetes Federation 2009 and Research Society for the Study of Diabetes in India (RSSDI) 2010]. Diagnostic criteria for diagnosis of diabetes are presented in **Box 1**. *In the presence of classical signs and symptoms*: Random blood sugar >200 mg%. *In the absence of classical symptoms*: OGTT with 75 g glucose (five readings to be taken every ½ hour): If two readings >200 status: Diabetes; if one reading 200 but 2 hours reading returning close to fasting (90–110) status: Impaired glucose tolerance (IGT), if all readings <200 and fasting (80–100)—post 2 hours (120–140) status: Normal but to be monitored periodically. Mass screening should be done in the society for asymptomatic individuals to detect undiagnosed cases. Criteria for screening in asymptomatic individuals are presented in **Box 2**.

BOX 1: Criteria for diagnosis of diabetes (DCCT and WHO protocol).

HbA1c > 6.5%. The test should be performed using NGSP certified and DCCT assay standardized.

OR fasting plasma glucose (FPG): 126 mg%. No calorie intake for 8 hours.

OR 2 hours plasma glucose (PP): >200 mg on OGTT with classical symptoms.

OR 2 hours post full meal plasma glucose: >160 mg%. If 140–160 mg% IGT, repeat periodically.

(DCCT: Diabetes Control and Complications Trial; HbA1c: glycated hemoglobin; IGT: impaired glucose tolerance; NGSP: National Glycohemoglobin Standardization Program; OGTT: oral glucose tolerance test; PP: postprandial; WHO: World Health Organization)

BOX 2: Criteria for screening in asymptomatic individuals.

1. **Individuals who are overweight (BMI >25 kg/m^2) with additional risk factors of:**
   - Physical inactivity
   - First-degree relative of diabetics
   - Women who delivered a baby weighing >4 kg or diagnosed with GDM
   - HDL cholesterol, 35 mg% or triglycerides >350 mg% on 12 h fasting
   - Glycated hemoglobin (HbA1c) >5.7%, IGT on previous testing
   - Insulin resistance syndrome, e.g., acanthosis nigricans
   - Nonhealing ulcer but no classical symptoms
   - Women with polycystic ovarian disorder
   - If lifestyle changes not working
   - NASH and NAFLD (nonalcoholic fibrotic liver disease)
   - Frequent burnout syndrome
2. **In the absence of above criteria, routine testing for all >45 years of age.**
3. **Prediabetes status—periodic testing.**

(BMI: body mass index; GDM: gestational diabetes mellitus; HDL: high-density lipoprotein; IGT: impaired glucose tolerance; NASH: nonalcoholic steatohepatitis)

MANAGEMENT

Type 2 diabetes mellitus is basically a combination of lifestyle disorder with genetic predisposition superimposed by pollution and other environmental factors. Obesity or metabolic syndrome further compounds the problem. Nonpharmacological measures are the most important faculties in managing diabetes. Next step is to add oral hypoglycemic agents (OHAs)-insulins. Surgery, especially in diabesity or stem cell, and pancreatic transplantation are the other options, but reserved for highly morbid conditions. *Author postulate 10 commandants for the management of T2DM: (1) nutrition therapy, (2) micronutrient therapy, (3) exercise, (4) sweeteners, (5) tobacco, (6) alcohol, (7) sex, (8) stress management, (9) environmental pollution, and (10) pharmacotherapy.*

Nonpharmacological Therapy

Nutrition (Diet) Therapy

Medical nutrition therapy (MNT) has a great role in preventing or delaying the onset of T2DM specifically with obesity (**Table 1**). The basic idea is to control the calories intake as appropriate for the body weight of the individual. Calorie intake depend on work style, BMI, place of work, gender, and ethnicity (decides muscle mass of the body). However, the calorie composition should be: Carbohydrates: Normal = 60% (diabesity = 40–50%); Proteins: Normal = 25–30% (diabesity = 30%, not to exceed 1 g/kg body weight); Fats:

TABLE 1: Recommended dietary composition for diabesity.	
Component	Energy intake (%)
Carbohydrates (sucrose should be <10%)	40–50%
Proteins	20–30% (not to exceed 1 g/kg body weight)
Fats	20–30%
n-6 PUFA	<10%
n-3 PUFA	<2%) oily fish is the main source. Once a week
MUFA	10–20%
Saturated	7–10%

- *Reduce saturated fat by 10% of total intake*
- *Increase MUFA by 40% of balance fat intake*
- *Increase PUFA by 40% of balance fat intake*
- *Eliminate transfats totally*
- *Increased vegetables to six servings/day*
- *Reduce refined carbohydrates. Use complex carbohydrate*
- *Consume high-quality protein*
- *Exercise 60 minutes daily including aerobics and resistance training*
- *Achieve ideal body weight, BMI, waist circumference, and body fat composition*

(BMI: body mass index; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid)

normal = 25–30% [diabesity = <30%, of which monounsaturated fatty acid (MUFA) = 10–20%, polyunsaturated fatty acid (PUFA) = 7–10%, and saturated = 7–10%). In weight reducing diets, a calorie reduction of 500–1,000 calories are planned with simultaneous increase in expenditure of 500–1,000 calories in the form of exercise. ADA, Diabetes Control and Complications Trial (DCCT), RSSDI, and Diabetes India recommend the healthy choice of foods and good physical activity to decrease the risk of diabetes and prevention of cardiovascular (CV) morbidity and mortality. Dietary Approaches to Stop Hypertension (DASH), Mediterranean, and ketogenic diets are other concepts for control of diabesity.

Micronutrient Therapy

Although use of micronutrients as nutrition therapy is a cornerstone of the management of diabetes, but uncertainty prevails in its guidelines. Zinc, chromium, iron, vitamin D, alpha-lipoic acid, carotenoids, vitamins E and C, selenium, and some of the B vitamins, notably folate, pyridoxine, and cyanocobalamin play an important role in managing diabetes. Best source of micronutrients are fruits, nuts, fresh vegetables, sprouts, seeds, sun-shine, fatty fish, egg, and supplements. Cooking oils, flours, rice, cereals, and juices are now being available in the market with fortified vitamin A, D, calcium, etc.

Exercise

Regular moderate exercise not only utilizes blood sugar but improves blood circulation removing oxidants from the body. It further, reduces the development and progression of atherosclerosis, hence reduction in cardiovascular disease (CVD)-related mortality. Exercise induces longevity by 1.1/2 years in moderate and 3.1/2 years in vigorous exercise individuals. The beneficial effects include reduction in HbA1c, blood sugar levels, triglycerides (TGs) (9.5%), low-density lipoprotein (LDL) (13.7%), and increase high-density lipoprotein (HDL) (9.6%). American College of Sports Medicine and American Heart Association (AHA) current recommendation for exercise is:

- 30 minutes of moderate exercise, i.e., mild increase in heart rate (HR) and breathing—5 days a week.
- 20 minutes of vigorous exercise, i.e., noticeable change in HR and breathing—5 days a week.

In addition, resistance training (weight training × 10 min) daily is recommended. All major muscle groups should be involved using 8–10 repetitions.

The WHO recommends 10,000 steps per day for a healthy living. Those who cannot walk should do sitting exercise, exercise on bicycle ergometer, swimming, pushups, weight training, and upper/lower body exercises depending on the deformity. Aerobic exercise, especially jogging/cycling/swimming are considered the best.

Sweeteners

Sweeteners are the ingredients that are added to food to bring sweetness, which can be sugar (nutritive) or sugar (non-nutritive) substitutes. Nutritive sweeteners are those sugars which contain carbohydrates and provide calories. Whereas, non-nutritive sugars provide only sweetness for taste and no calories. These are:

- Monosaccharides—sugar, jaggery, khand, etc.
- Disaccharides—fruit sugars
- Polysaccharides—honey and polyols
- Non-nutritive sugars: Artificial sweeteners—aspartame, sorbitol, stevia, tagatose, sucralose, etc.

Which sugars to be used in diabetes?

- *Naturals*: Polyols or polysaccharides-disaccharides with low glycemic index
- *Artificial*: Plant product-stevia or sucralose (minimum side effects)

Fresh or dried fruits can be used as adjuvants without much rise in blood sugar levels. Additional benefit is that these fruits add vitamins, minerals, and antioxidants to diet. One type (color) of fruit must be taken at least once a day. Fruits with moderate or high glycemic index should be taken before meals as it does not increase the blood sugar levels much.

Tobacco

Tobacco smoking and chewing are the leading causes of preventive mortality. The acute effects of tobacco smoking are sharp rise in blood pressure (BP) acutely and enhanced risk of renovascular, malignant, and masked hypertension. The effect is due to stimulation of sympathetic nervous system. Whereas chronic use promotes atherosclerosis with fall in HDL, rise in LDL cholesterol (LDL-C), rise in perfluorinated fatty acids (PFFAs) levels, thickening of arterial walls, especially the peripheral arteries, increased levels of carboxyhemoglobin with resultant coronary insufficiency, high platelets adhesiveness, high plasma fibrinogen levels, and increased risk of subarachnoid hemorrhages. A study from Canada indicated that women who smoke are more at

risk of preeclampsia and eclampsia. Smoking in diabetes increases the risk of CV mortality and peripheral neuropathy.

Alcohol

Alcohol use has been a very debatable issue for a very long time. Safe limit, however, is no alcohol.

Mild level of alcohol intake lowers the risk of thrombosis due to decreased inflammation markers and increased HDL levels. Moderate to heavy drinking impairs insulin release and hyperglycemia with increase in CVD-related mortality and liver failure and pancreatitis. Chronic and more than permissible alcohol intake is associated with increased LDL, TGs, increased inflammatory markers, insulin resistance, increased incidence of cardiomyopathy, vent, arrhythmias, and endothelial dysfunction.

One standard drink is 10 g of pure ethyl alcohol. This amounts to 375 mL of beer (5% alcohol); 150 mL of wine (12% alcohol), and 45 mL of whiskey (40% alcohol). This is considered safe limit in a day for men. For women it is 75% of above values. Red wine offers better protection due to presence of plant sterol-resveratrol. But wines and beers contain high levels of carbohydrates; hence, calorie count is must while taking alcohol. No alcohol is the best option.

Sex

Studies show that men with diabetes often have reduced testosterone levels, which can affect their sex drive. Moreover, diabetes damages the blood vessels, which affect blood flow to the penis leading to erectile dysfunction. Intimacy is ageless. It makes you young, energetic, and you live longer with good quality life.

Psychological Stress

Stress result in imbalance of hormones and catecholamines which has deleterious effects on blood sugar levels and BP. Stress act primarily on hypothalamus pituitary axis to produce more steroidal hormones, decrease insulin sensitivity and alter calcium-vitamin D metabolism, increased sympathetic stimulation, and decreased parasympathetic system. A variety of measures have been suggested to overcome stress and improve lifestyle. Yoga, meditation, music therapy, dancing, and laughter therapy are very helpful in alleviating stress. Professional counselors also play a very important role in managing stress. Enjoying holidays, family vacations, going to movies or theatres, doing arts, paintings, etc., also help in stress management. The United Kingdom Prospective Diabetes Study (UKPDS) over 12 years, observed the beneficial effects of stress management.

Lifestyle Heart Trial: Pranayama, surya namaskar, meditation, group support sessions, and music therapy all lead to correction of glycosylated HbA1c levels, dyslipidemias with reversal of atherosclerotic plaques.

Meditation, sound sleep for 6–7 hours, listening to music, and dancing all lead to reduction of stress hormones, relaxation of mind and body. This results in improving good quality of life.

Environmental Pollution

Air pollution: Particulate matter (PM) 2.5—SO_2 and CO_2 are the main culprits from vehicles, thermal plants, and increased construction activity. *Water pollution*: Contamination of underground water table with heavy metals such as arsenic and mercury. *Earth pollution*: Overuse of pesticides, chemical fertilizers, etc. *Noise pollution*: Affects catecholamine secretion and stress hormones such as corticosteroids and dopamine.

Pollutions affect the general health leading to anemia, hypocalcemia, vitamin D deficiency, and other micronutrients deficiency which alters sympathetic-parasympathetic axis dysfunction and hence, poor control of T2DM. The pollutants increase stress levels also, especially noise pollution. This leads to poor insulin secretion and efficacy.

Pharmacologic Therapy

Pharmacologic therapy (**Box 3**) includes oral hypoglycemia drugs, incretins, insulins, surgery like bariatric surgery, duodenal mucosal resurfacing (DMR), islet cells and pancreatic transplants, and genetic engineering to alter genes.

Oral Hypoglycemic Agents

Oral hypoglycemic drugs remain the mainstay of T2DM management after lifestyle modification (LSM) does not yield desired results. Different drugs with multiple, different pathophysiologic functions have been developed. Many new molecules have been developed. Different class of OHAs are available for clinician to manage T2DM. However, clinician has to decide himself the choice of drug to be used either singly or in combination.

Biguanides (Metformin)

Metformin lowers blood glucose, especially fasting blood glucose by decreasing hepatic glucose production and increasing the sensitivity of peripheral receptors to insulin. Metformin reduces A1c by about 1.5%. Usage in combination with other oral antidiabetic (OAD) agents has synergistic effect for further reduction in blood glucose levels and insulin requirements. It has beneficial effects on lipids also by reducing LDL and very low-density lipoprotein (VLDL). Metformin use shows improvement in diastolic dysfunction,

BOX 3: Pharmacologic therapy.

1. Biguanides
2. Sulfonylureas
3. Thiazolidines
4. Meglitinides
5. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors
6. Drugs working on gut peptides:
   - Dipeptidyl peptidase-4 (DPP-4) inhibitors
   - Incretins
7. Alpha glucosidase inhibitors
8. Dopamine receptor agonist
9. Others:
   - Hydroxychloroquine
   - Amylin agonist: Pramlintide
   - Probiotics
10. Insulins

reduction in plasminogen activator inhibitor, C-reactive protein (CRP), and platelets aggregation. It is useful for weight reduction also. Most common adverse effects are nausea, anorexia, and diarrhea. These are minimized if metformin is taken together with/or after meals. Or taking extended release (ER) formulation.

Sulfonylureas (Glibenclamide, Gliclazide, Glipizide, and Glimepiride)

Sulfonylureas (SU) reduces plasma glucose by increasing insulin secretion from pancreatic beta cells. In this era we use second-generation SUs, examples given above. They are available as normal preparations or ER.

Mechanism of action of SUs is that it binds to receptors on beta cell surface via kir6.2 channels to open calcium channels, which, in turn release insulin. When used as monotherapy it reduces an average A1c by 0.4–1.6%. Various SUs available have almost similar efficacy and UKPDS has demonstrated significant reduction of microvascular and macrovascular complications with all second-generation SUs. The major adverse effect is hypoglycemia. The risk is higher in renal impairment, liver cirrhosis, and the elderly. Glibenclamide is more intense to cause hypoglycemia, hence used very uncommonly these days. Whereas, gliclazide and glimepiride cause less incidence of hypoglycemia. Another unwanted side effect is the weight gain; in the range of 1.5–2.5 kg. Gliclazide versus glimepiride versus glipizide: Gliclazide has proved to have an edge: CV safety-better control. SUs can be prescribed as monotherapy or in combination. Works better in combination with other OHAs.

Thiazolidines (Glitazones): Pioglitazone

Thiazolidines (TZDs) modulates peroxisome proliferator-activated receptors (PPAR). TZDs are insulin sensitizers and increase insulin sensitivity in muscle, adipose tissue, and liver. Troglitazone and rosiglitazone are not used now, only pioglitazones being used. Glitazones are the most debated OHAs. Recently, few studies on pioglitazones showed increased incidence of bladder cancer. However, there is a sufficient data to suggest otherwise and has shown beneficial evidence of beta-cell rejuvenation, hepatic fat deposits, and CV risk reduction. Because of its effects on PPAR-alpha and gamma, TZDs play a very important role in glucose, fatty acids, and cholesterol metabolism. Hence, the effects include increasing insulin sensitivity, enhanced lipolysis, reduced levels of cytokines such as TNF-α, serum leptin levels, plasminogen activator infibitoe-1, endothelial dysfunction, vascular reactivity, albumin urea, and increased adiponectin and HDL levels. TZDs reduce A1c by 0.5–1.4%. It has rapid action but improvement in glycemic control may only be seen after 6 weeks with maximum effect at 6 months. They can be used as monotherapy or combined with other OAD(s).

Side effects include weight gain (due to redistribution of body fat), fluid retention, anemia, heart failure, macular edema, and osteoporosis. The majority of fractures associated with TZD use were in the distal upper or lower limb, as opposed to the classic sites of osteoporotic fractures.

Caution

TZDs are contraindicated in patients with congestive cardiac failure (CCF) and liver failure.

Meglitinides: Repaglinide

These are short-acting insulin secretagogues that bind to SU receptors but at different sites. Action is similar to SUs but insulin release is dependent on glucose levels. Hence risk of hypoglycemia is less. They stimulate first phase insulin release, hence very rapid acting. It has a shorter half-life and is rapidly absorbed from the gastrointestinal tract (GIT) with peak levels 1–2-hour postmeal intake. It reduces A1c by 1.0–1.2%. It is very good drug for postprandial hyperglycemia. So should be used with major meals and in patients who need flexible meal timings or Hindu people, who keep 8–12 hours fasts.

Sodium-glucose Transport Protein 2 Inhibitors

Gliflozins (canagliflozin, dapagliflozin, empagliflozin, and remogliflozin) are the newer class of drugs acting on proximal renal tubules. This class of drugs selectively inhibits SGLT-2, a transporter in the proximal tubule, thus reducing glucose reabsorption leading to an increase in urinary glucose excretion. It reduces A1c by 0.2–0.8%. Weight loss (2.5–3.0 kg) and modest BP reduction is the hallmark of this class of drugs. Has good CV safety with risk reduction in CV events. It is estimated that by blocking this transporter release up to 119 g of blood glucose per day, which corresponding to 476 kcal. Additional water is eliminated by osmotic diuresis, resulting in a lowering of BP.

Dapagliflozin is the most widely studied molecule. It has a profile of once daily dose drug with good oral bioavailability. Peak plasma concentration is reached in 2 hours with half-life of 11–17 hours. Canagliflozin and empagliflozin are now also being used extensively showing good CV risk reduction. However, it is not recommended for those on concomitant treatment with loop diuretic. Efficacy of SGLT-2-i is dependent on renal function and it is not recommended in patients with moderate-to-severe renal impairment [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2]. It also increases glucagon level and hence, using it with dipeptidyl peptidase-4 (DPP-4) inhibitor gives symbiotic results.

Side effects include significant increased genitalia and urinary tract infection. The United States Food and Drug Administration (USFDA) has issued a warning for canagliflozin related to reduced bone mineral density and increased risk of bone fracture.

A few cases of euglycemic diabetic ketoacidosis (DKA) also had been reported and caution should be exercised when prescribing these agents in those with severe beta-cell insufficiency, latent autoimmune diabetes, and in postsurgical patients.

The EMPA-REG clinical trial conducted in patients with T2DM at high risk for CV events showed a lower rate of cardiovascular events and all-cause mortality.

Drugs Working on Gut Peptides (Incretin-based Drugs)

There are two major glucose-dependent incretin hormones—insulinotropic polypeptide [gastric inhibitory polypeptide (GIP)] and glucagon-like peptide-1 (GLP-1). Both are gut based peptides and promote beta cell growth DPP-4 is an enzyme which degrades GIP (active 1–42 and inactive 3–42), secreted from K cells of duodenum. Whereas GLP-1 is the product of glucagon gene, being processed in L cells of ileum and colon.

Individuals with normal glucose metabolism, postprandial glucose levels stimulate the release of GLP-1 and GIP from the gut. These peptides regulate the release of insulin and glucagon from the pancreas and this process is termed as the incretin effect. In patients with T2DM, postprandial GLP-1 secretion is modestly impaired; while, GIP secretion is normal in T2DM patients. In this category, we have two classes of drugs, i.e., DPP-4 inhibitors and GLP-1 analogs.

Dipeptidyl Peptidase-4 Inhibitors (Gliptins) (Sitagliptin, Saxagliptin, Vildagliptin, and Teneligliptin)

Dipeptidyl peptidase-4 inhibitors (DPP-4Is) are the class of drugs which enhances the activity of hormone GLP-1, GIP, gastrin-releasing peptide and thus stimulate the release of insulin and inhibits the release of glucagon. After the meal GLP-1 levels increase three- to fourfold and DPP-4 inhibits the action of GLP-1. DPP-4Is drugs inhibit DPP-4 enzyme and increase the availability and half-life of GLP-1, which in turn stimulates the release of insulin. It lowers A1c by 0.5–0.8% as monotherapy and can be combined with other OHAs with synergistic effect. Good combinations are metformin and pioglitazones. DPP-4Is are weight neutral and has minimal risk of hypoglycemia. Its efficacy is not influenced by the duration of T2DM. Sitagliptin and vildagliptin are the most studied and used molecule. Recent introduction is the teneligliptin because of cost and OD dose. The common side effects are gastritis, upper respiratory infections, and diarrhea. Caution is reduction of dosage in chronic kidney disease (CKD) where GFR is <50 (half dosage) and <30 mL/min (one-fourth dosage). Hence, renal functions need to be assessed before starting DPP-4Is.

The SAVOR-TIMI 53 clinical trial has shown that saxagliptin use is associated with increased risk of heart failure. But the more recent TECOS study did not show any increased risk. In general, the use of DPP-4Is is not associated with any adverse cardiovascular outcomes.

Glucagon-like Peptide-I Analogs (Incretins) (Exenatide and Liraglutide)

Glucagon-like peptide-I is an incretin mimetic, stimulates insulin secretion and suppress glucagon secretion. GLP-1 levels are markedly reduced in T2DM. GLP-1 analogs are recombinant receptor agonists and are to be given by injectable form only since it is a peptide. They are of two types: (1) Human GLP-1 based; and (2) Exendin based.

Caution: GLP-1 analogs are not substitute for insulin. GLP-1 analog should not be used in patients with a history of pancreatitis. Exenatide should not be used if eGFR <30 mL/min and liraglutide if eGFR <60 mL/min.

Liraglutide

It is used as monotherapy with a once daily dose of 1.2 and 1.8 mg subcutaneous (S/C). It produces mean reduction of HbA1c by 1–1.5%. Welcome effects include weight reduction (2–4 kg); improvement in systolic BP and beta-cell functions. Risk of hypoglycemia is quite less, but increases if used in combination with SUs. It can be used as a part of combination therapy also. There are no major adverse effects except nausea, but may be associated with medullary thyroid carcinoma.

Exenatide

Immediate release (IR) and ER. This is a synthetic exendin-based GLP-1 analog peptide. It enhances the glucose dependent insulin secretion, suppresses elevated levels of glucagon and slows the gastric emptying. When used as monotherapy it reduces HbA1c by 0.5–1%. Exenatide (IR) is administered S/C twice a day with a dose of 5–10 μg, 60 minutes before meals. Can be used in combination therapy with metformin, pioglitazones, or SUs with good synergistic effect (HbA1c reduction 1.5–1.8%). 4–6 kg weight reduction is reported. ER formulation of exenatide is also available and used as 2 mg S/C once a week with or without meals. Side effects include nausea and vomiting and sometimes pancreatitis.

Alpha Glucosides Inhibitors (Acarbose and Voglibose)

Alpha glucosides inhibitors (AGIs) act on the proximal part of small intestine to reduce or delay the absorption of polysaccharides. AGIs work on intestinal brush borders to inhibit enzymes responsible for breaking oligosaccharide and disaccharides into monosaccharides. Thus, it reduces the sudden surge of plasma glucose levels. Hence has potential use in lowering postprandial glucose without causing hypoglycemia. It reduces HbA1c by 0.5–0.8%, but is less effective than SUs or metformin as a monotherapy. But, when used in combination, produce remarkable effects in lowering plasma glucose levels. AGIs also reduce serum TGs levels. The most common side effects are bloating, abdominal discomfort, diarrhea, and flatulence. Voglibose is used more often than acarbose because it inhibits all pancreatic enzymes.

Dopamine Receptor Agonist: Bromocriptine

This is an ergoline derivative, dopamine receptor agonist, mainly used in treatment of pituitary tumors, Parkinsonism, neuroleptic syndrome, acromegaly, hyperprolactinemia, and recently as antidiabetic.

It acts by reducing hyperglycemia by decreasing prolactin. This drug is mainly used in combination therapy with other OHAs, where hyperglycemia is not controlled. Major side effects include nausea, orthostatic hypotension, headaches, angina, Raynaud's phenomenon, panic attacks, and withdrawal symptoms.

Others

Hydroxychloroquine

Recently added to the armamentarium for the treatment of T2DM as anti-inflammatory drug with the belief that it may reduce degradation of insulin and increase its efficacy in tissues. It is not used as monotherapy but in a combination therapy along with SUs, metformin, DPP-4I, or SGLT-2-i. It can be used in combination with insulins also as it has synergistic effect on insulin. Dose: 200–400 mg/day. Hydroxychloroquine (HCQS) can be used in prediabetics and IGTs for prevention or retardation of progression of DM. It exhibits HbA1c reduction by 0.6–0.8% (>24 weeks). It has beneficial effect on lipid metabolism by reducing LDL.

Amylin Agonist: Pramlintide

Amylin is a hormone jointly secreted with insulin, hence, is deficient or inappropriate in DM. This hormone inhibits

glucagon, delays gastric emptying, and produces satiety. Pramlintide is a synthetic analog, available as S/C injection. Several large phase III clinical trials have shown its efficacy in lowering HbA1c both in T1DM and T2DM. This is used as premeal injection for postprandial hyperglycemia. It has low incidence of side effects and weight gain (unlike insulin).

Probiotics

Researchers have shown that T2DM and obesity are characterized by altered gut microbiota, inflammation, and gut barrier disruption, but the exact mechanism responsible for this is still not clear. Using probiotics, especially *Akkermansia* (common bacteria of gut flora) has shown tremendous potential in treating diabesity.

Insulin

Insulin is synthesized by beta cells situated in islet cells of the pancreas. Apart from beta cells secreting insulin, there are alpha cells secreting glucagon, pancreatic polypeptide (PP) cells and gamma cells secreting somatostatin. Glucagon stimulates secretion of insulin, whereas insulin inhibits secretion of glucagon, whereas, somatostatin inhibits both glucagon and insulin. Primary structure of insulin has two polypeptide chains linked with disulfide bridge. Pancreas forms proinsulin which is converted to single amino acid chain insulin and connecting peptide (C-peptide). All the insulin molecules are manufactured on this principle. Different types of commercial insulins are produced by recombinant deoxyribonucleic acid (rDNA) technology with the main differences in onset of action, duration of action, and rate of absorption. Different types of insulins available are given in **Table 2**.

Surgery—Bariatric and Duodenal Mucosal Resurfacing

Surgery is very effective in morbid diabesity and complicated diabetes with life-threatening comorbidities. Previously surgeons have been focusing on obesity with BMI >36 and now BMI of >32 is being included for criteria of bariatric surgery. Since Indian population have waistline obesity and hypertriglyceridemia, poor lifestyle, and as more population is inching towards diabetic status, many people are opting for bariatric surgery. In bariatric surgery, a part of stomach is ligated or cut to reduce the amount of ingested food and retard the absorption by creating malabsorption like condition. This helps in reducing weight, blood sugar, and lipid levels in the body. Types of bariatric surgeries are gastric bypass, sleeve gastrectomy, gastric band or balloon, and biliopancreatic diversion with duodenal switch. In DMR, duodenal mucosa is subjected to hypodermal circumferential ablation. This results in altered duodenal mucosal exposure to nutrients, hence reduction in blood sugar and lipid levels.

TABLE 2: Insulins.

Prandial insulin	• Short acting: Regular (onset: 30–60 min; peak: 2–4 h; duration: 6–10 h) • Analogs: Aspartate and lispro (onset: 0–20 min; peak: 1–3 h; duration: 3–5 h)
Basal insulin	• Intermediate acting: NPH (onset: 1–2 h; peak: 4–8 h; duration: 8–12 h) • Long-acting analogs: Glargine and detemir (onset: 30–60 min; duration: 16–24 h)
Premixed	• Mix 30:70 (regular + basal) (onset: 30–60 min; Peak duration: 16–24 h) • Mix 25:75 (regular + basal) (onset: 10–20 min; peak: 1–4 h; duration: 16–20 h) • Mix 50:50 (regular + basal) (onset: 10–20 min; peak: 0.5–2.5 h; duration: 16–18 h)
Inhalational	• Ultrafast acting: Afrezza

(NPH: Neutral Protamine Hagedorn)

Stem/Progenitor Cells Transplant

Researchers implanted insulin-producing cells into a fatty membrane in the stomach cavity. The resultant progress in controlling blood glucose and HbA1c levels is paving the way towards more people receiving artificial pancreases.

Pancreas Transplantation

It is usually done along with either liver or kidney transplants as a part of treating high comorbid complications of diabetes with CKD or liver failure.

STEPWISE APPROACH OF MANAGING TYPE 2 DIABETES MELLITUS

Stepwise approach is beneficial in managing the T2DM (**Box 4**):

- After LSM initiation if hyperglycemia not controlled then start OHAs.

BOX 4: Stepwise approach of type 2 diabetes mellitus management.

Plan A

Calculate body mass index, check HbA1c, and check presence of comorbidity

HbA1c <9.0:

1. Begin therapy with metformin. Except: Lean body weight/peptic ulcer/gastritis
2. Sulfonylureas: Gliclazide/glimepiride
3. DPP-4 inhibitors: Sitagliptin/Saxagliptin/Vildagliptin. *Teneligliptin (OD dose)

HbA1C >9.0:

1. Combination of sulfonylurea and metformin or DPP-4 inhibitor (Tenegliptin/Vildagliptin) and metformin

Postprandial hyperglycemia:

1. Combination of sulfonylurea + metformin + voglibose/acarbose/repaglinide

Severe comorbidity:

Add insulin

Continued

Continued

Plan B

If the first-line therapy fails or does not yield desired result:

1. Add SGLT-2-i—four drug combination or three drugs: Metformin + DPP-inhibitor + SGLT-2-i
2. Add insulin: Premix insulin (30:70) or Humalog (25:75) twice a day or basal at bed time
3. Alpha glycoside inhibitors are attractive options in Indian diabetics because of high carbs meals
4. Thiazolidinediones are also good option
   Author's experience of DPP-4 inhibitor + metformin + pioglitazone, especially in obese with fatty liver is encouraging
5. If infections or surgery or pregnancy: Insulin

Plan C

In case of failure of second line:

- Use of 4-OHA plus insulin (premix) twice a day
- Use of 4-OHAs plus basal insulin at bed time
- OR three to four drugs with multiple timing regular insulin
- One can use newer insulin such as ultra-long-acting insulin detemir (Levemir) and insulin degludec
- One can opt for GLP-1 analogs like insulin liraglutide (Victoza) or insulin exenatide (Byetta). Additional benefit is weight reduction
- In all these insulins cost is the major issue
- Surgery like bariatric or DMR for morbid obesity
- Pancreatic transplant/stem cell/islet cells transplant, etc.

(DMR: duodenal mucosal resurfacing; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin; SGLT-2-i: sodium-glucose cotransporter-2 inhibitor; OHA: oral hypoglycemic agent)

- Choice of medication should be based on individual needs, cost-benefit ratio, economic conditions, drug interactions, and presence of other comorbidities.
- Each initiation or dose increment should be monitored for response in 8–10 weeks.
- Patients compliance with the dosage schedule is must and check every time he/she visits you.
- Side effects and inadequacy of effect warrants immediate withdrawal.
- Talk to the patient particularly about hypoglycemia or weight gain/loss.

SUMMARY

Goals of therapy for T2DM patients include evaluation of diabetic status, BMI, work style (i.e., sedentary or hard worker), socioeconomic status, presence of comorbidities, and patient's willingness or compliance with the drugs management. Always start with LSM followed by oral drugs with or without insulin, depending on the patient's condition and parameters. Diet prescribed to the patient must confirm to his/her tastes, availability, and affordability. Diet should be a balanced diet, rich in proteins, must include seasonal fruits. Drugs used should also be easily available, affordable, and the regime should be tailor made to the patient. If socioeconomic status is not good, there is no fun of writing fancy, expensive medicines, which, patient will not take in long run. Patient counseling is must so that he/she understands the modality of treatment and the need of initiating insulin therapy or undergoing surgery. The ideal target of control of diabetes is HbA1c of 6.5–7.0% in Indian population. Though, it may be difficult to achieve in elderly, but tight control always give benefit in terms of reducing complications and hence, enhanced morbidity and mortality.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Hypoglycemia

Jugal Kishor Sharma, Dinesh Sharma

INTRODUCTION

As defined by American Diabetes Association (ADA) and European Medicines Agency, hypoglycemia is any abnormally low plasma glucose concentration that causes potential harm to a subject with plasma glucose value <70 mg/dL (<3.9 mmol/L). The problem of hypoglycemia was recognized since the use of insulin in 1922. In Diabetes Complications and Control Trial (DCCT), it was found that intensive glycemic control decreased the long-term complications of diabetes with increased frequency of hypoglycemia. The United Kingdom Prospective Diabetes Study (UKPDS) and recent population-based data showed that hypoglycemia continues to be a major problem in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Based on clinical manifestations, hypoglycemia can be classified into mild (blood sugar 60–70 mg/dL), moderate (blood sugar 50–60 mg/dL), severe (blood sugar <40 mg/dL). The blood glucose (BG) level that produces symptoms of hypoglycemia varies from person to person and in the same person under different circumstances. Hypoglycemia is a medical emergency; however, most individuals recover completely. Hypoglycemia, which is not reversed, can progress from lethargy to coma, and finally death. There are some cases of long-lasting severe hypoglycemia which can lead to transient and even permanent cerebral damage. Iatrogenic hypoglycemia associated with diabetes medications are the most common causes of hypoglycemia in patients with diabetes. It is common in insulin-treated diabetic patients, more common in T1DM and may occur in patients taking an insulin secretagogue. Hypoglycemia may also result from certain other conditions such as pancreatic or nonislet cell tumors, autoimmune conditions, endocrine diseases, dietary toxins, alcohol consumption, organ failure, inborn errors of metabolism, stress, starvation, severe excessive exercise, infections, and sepsis. Patient education, timely detection of hypoglycemic symptoms, and early treatment of hypoglycemia can prevent the serious complications and death of a patient.

ETIOLOGY

Several factors can cause hypoglycemic episodes in a person living with diabetes such as a mismatch in the timing, amount or type of insulin, and the food intake. Diabetic patients who are undergoing therapeutic intervention with meglitinides, sulfonylurea, or insulin, these drugs are the most common cause of hypoglycemia. Hypoglycemia is not seen in patients with diabetes who are treated with medical nutrition therapy, metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinediones, and it is rare in people taking alpha-glucosidase inhibitors. Other causes of hypoglycemia include pancreatic or nonislet cell tumors, organ failure, autoimmune conditions, inborn errors of metabolism, alcohol consumption, stress, starvation, severe excessive exercise, infection, and sepsis. Risk factors for hypoglycemia are summarized in **Table 1**.

TABLE 1: Rick factors for hypoglycemia.

Common risk factors	• Mismatch of insulin timing, amount, or type of carbohydrate intake • Oral secretagogues without appropriate carbohydrate intake • History of severe hypoglycemia • General anesthesia or sedation that places the patient in an altered consciousness • Reduction of oral intake • New nil per orally (NPO) status • Unexpected transport after injection of rapid- or fast-acting insulin • Critical illnesses (hepatic, cardiac, and renal failure; sepsis; and severe trauma)
Less common risk factors	• Endocrine deficiencies (cortisol, growth hormone, or both), non-β-cell tumors • Ingestion of large amounts of alcohol or salicylates • Sudden reduction of corticosteroid dose • Emesis • Reduction of rate of intravenous dextrose • Unexpected interruption of enteral feedings or parenteral nutrition • Drug dispensing error

PATHOPHYSIOLOGY

The counterregulatory mechanism of the body prevents the hypoglycemic episodes, which includes the interplay of hormones and neural signals to regulate the release of endogenous insulin, increase the hepatic glucose output, and alter peripheral glucose utilization. The regulation of insulin production plays a significant role in the counterregulatory mechanism. The decrease in insulin production is the first-line defense response to low BG in the body. Low insulin levels are necessary for the endogenous glucose production in the liver by glycogenolysis. Low insulin levels in response to decreased BG level leads to increased hepatic/renal gluconeogenesis and hepatic glycogenolysis. Glycogenolysis can maintain serum glucose levels up to 8–12 hours until the glycogen stores are depleted; in the meantime, hepatic gluconeogenesis also contributes to maintaining that euglycemic state of a person. Other counterregulatory measures occur once the serum glucose level falls beyond the physiological range. Secretion of glucagon from pancreatic alpha cells is the next defense against hypoglycemia followed by adrenomedullary epinephrine secretion as the next counterregulatory mechanism. All three counterregulatory mechanisms occur in the acute stage of hypoglycemia. After the failure of all the above counterregulatory mechanisms growth hormone and cortisol release is also seen in cases of prolonged hypoglycemic conditions

CLINICAL FEATURES

Clinical features of hypoglycemia can be classified as neuroglycopenic or neurogenic (**Table 2**). Neuroglycopenic signs and symptoms result from decreased BG supply to the central nervous system (CNS) as the brain has limited glycogen stores. This results in rapid CNS dysfunction. If warning signs are not taken care, the BG continues to fall leading to more severe hypoglycemia and alteration in the mental function which causes impairment of concentration, confusion, headache, disorientation, irritability, slurred speech, lethargy, malaise, irrational behavior, focal seizures, and hemiplegia. If BG continues to fall, then shallow breathing, bradycardia, hypertonicity, coma, and finally death. Neurogenic signs and symptoms can be adrenergic or cholinergic. These symptoms are anxiety, irritability, dizziness, diaphoresis, tachycardia, headache, pallor, shakiness, and hunger. These signs and symptoms may not be present when there are sympathetic dysfunctions such as in the case of diabetic autonomic neuropathy or when adrenergic blocker drugs are being used. The neurogenic and neuroglycopenic symptoms usually occur below the blood sugar level of 50–55 mg/dL, but this can vary from individual to individual. Diabetic patients may develop hypoglycemic symptoms at relatively higher BG levels because chronic hyperglycemia alters the set point where these symptoms become apparent. This phenomenon is referred to as "pseudohypoglycemia" because the serum glucose levels are within normal limits, but the patient is having the symptoms of hypoglycemia.

TABLE 2: Clinical features of hypoglycemia.

Early adrenergic symptoms	• Pallor • Diaphoresis • Tachycardia • Shakiness • Hunger • Anxiety • Irritability • Headache • Dizziness
Neuroglycopenic signs	• Confusion • Slurred speech • Irrational or uncontrolled behavior • Extreme fatigue • Disorientation • Loss of consciousness • Seizures • Pupillary sluggishness • Decreased response to noxious stimuli

DIAGNOSIS

Since 1938, Whipple's triad has been used to describe hypoglycemia, which includes recognition of symptoms of hypoglycemia, low blood sugar detection, and relief of symptoms by correction of the low blood sugar levels. Other tests such as insulin, proinsulin, and C-peptide levels are to be measured, if insulin levels are high in the presence of low C-peptide levels then it show that the patient has received the exogenous insulin. Elevated insulin levels with elevated C-peptide levels are seen with secretagogue agents such as sulfonylurea administration. Other routine investigations such as hemogram, liver function test (LFT), kidney function test (KFT), chest X-ray, ultrasonography, CT, and MRI abdomen/brain may be required to rule out other causes of hypoglycemia.

CLASSIFICATION OF HYPOGLYCEMIC EVENTS

The ADA workgroup on hypoglycemia in June 2004 classified hypoglycemic events as:

- Severe hypoglycemia which requires assistance from another person to administer carbohydrates, glucagon, or other resuscitative measures. These episodes are associated with neuroglycopenia to induce seizure and coma. Plasma glucose measurements may not be available, but neurological recovery to the restoration of a normal glucose is sufficient evidence to confirm hypoglycemic events.
- Symptomatic hypoglycemia which shows typical hypoglycemic symptoms and documented plasma glucose concentration is <70 mg/dL (3.9 mmol/L).
- Asymptomatic hypoglycemia—there are no typical symptoms of hypoglycemia, but blood sugar is <70 mg/dL (3.9 mmol/L) because the activation of glucagon and epinephrine secretion is normally at 65–70 mg/dL glucose concentration.
- Probable symptomatic hypoglycemia in which symptoms of hypoglycemia are not associated with plasma glucose determination, but probably caused by plasma glucose concentration <70 mg/dL. These people with diabetes treat

symptoms with oral carbohydrates without plasma glucose measurement.
- Relative hypoglycemia—in this diabetic patient reports the symptoms of hypoglycemia, but the measured plasma glucose is >70 mg/dL. This is experienced by patients with chronically poor glycemic control.

TREATMENT

In hypoglycemic episodes, assess the patient for level of consciousness, respiratory and circulatory status, blood sugar level, take the history about insulin dosage and antidiabetic medicines, food intake, and look for other causes of hypoglycemia such as renal, hepatic, and alcohol intake. If the patient is conscious, follow the rule of 15–15. Give 15 g of carbohydrate orally and check the blood sugar after 15 minutes if the blood sugar is still below 70 mg/dL then again give 15 g of carbohydrate and recheck. Repeat the step till the BG levels reach above 70 mg/dL. The readily available 15 g carbohydrate is present in 4 oz orange juice or apple juice, 4 oz regular sugar-sweetened cola, 6 oz sugar-sweetened ginger ale, 3 BD glucose tablets, and 4 Dextrose 4 glucose tablets. Once BG returns to normal, give a meal or snack to the patient so that the blood sugar does not fall again. If the patient is unresponsive to oral treatment or is on nil per orally (NPO), then intravenous (IV) administration of dextrose or intramuscular (IM) injection of glucagon is to be given—25 g (50 mL) 50% dextrose or glucagon 1 mg IM. Be careful not to overtreat hypoglycemia. Monitor blood sugar frequently until the glucose levels stabilize. After treatment of hypoglycemia, we should search for the cause and correct accordingly. Hospitalization is required of emergency room patient with hypoglycemia (BG <70 mg/dL). Treat according to severity, if there are risk factors. Evaluate for a cause in all patients and treat the cause.

Patient Able to Eat

Give 30 g (two tablespoons) of oral glucose or milk for patients on alpha-glucosidase inhibitors. Follow-up with some complex carbohydrates:
- One cup fruit juice
- One slice bread
- One cup milk
- Two to three biscuits

Patient not Able to Eat

Administer 20 mL of 50% dextrose IV bolus and then 5% and 10% dextrose fluids IV at 100 mL/h until stabilized. If available, injection glucagon 1 mg (1 mL) single dose can be administered instead of dextrose. Monitor BG every 30 minutes till >100 mg/dL. Once BG >100 mg/dL, evaluate for cause. Change in medication/diet/activity, infection, new medication, etc. Decide if further monitoring and observation required.

PREVENTION

In patients living with diabetes, controlling the hyperglycemia without causing hypoglycemia is the main aim of treatment.

Patient Education

Patients must understand and adhere to the treatment plans in terms of lifestyle modification, diet, and medications. Educate the patient and his family members about early identification of hypoglycemic symptoms, its causes, preventive measures, and the treatment options. Also educate about the importance of frequent self-monitoring of blood glucose (SMBG), regular follow-up with their doctor, and record-keeping preventing hypoglycemic episodes.

Blood Glucose Monitoring

Regular BG testing is the most effective way of identifying asymptomatic hypoglycemia. This is an effective component of self-management in people with diabetes with insulin treatment. Glucose monitoring can be done either by SMBG or by continuous glucose monitoring (CGM). SMBG can help and detect early hypoglycemia and will help the appropriate insulin dose adjustment. This is usually advised in T1DM and T2DM patients who are on insulin therapy. To detect hypoglycemia or a high-risk pattern, periodic 7-point profile testing should be performed. The recent ADA Standards of Care recommends SMBG testing at least six to eight times daily for patients using multiple daily insulin injections or continuous subcutaneous insulin infusion.

Use of Agents with a Low Hypoglycemic Incidence

Selection of appropriate regime with no hypoglycemic risk and good glycemic control prevent the risk of hypoglycemia. Low risk hypoglycemic agents are metformin, DPP-4 inhibitors, and GLP-1 receptors agonists. DPP-4 inhibitors inhibit the prolonged activity of endogenously released GLP-1 and gastric inhibitory polypeptide (GIP) by inhibiting the DPP-4 enzyme. They have extremely low hypoglycemic risk because of their glucose-dependent action. Alpha-glucosidase inhibitor and thiazolidinediones may be considered in place of high-risk category hypoglycemic agents such as insulin, sulfonylurea, and meglitinides.

Insulin Therapy

The standard insulin sliding scale should be avoided as it is ineffective, having a high risk of hyperglycemia and hypoglycemia. The basal and bolus insulins provide more physiological response to insulin treatment. Ideal insulin therapy should include the long-acting basal insulin, which mimics the 24 hours insulin secretion and bolus or short-acting insulin which mimics the normal physiological insulin response to the meal. The development of insulin analogs which are closer to endogenous insulin with better glycemic control reduces the risk of hypoglycemia as compared to traditional human insulin should be used. Newer insulin analog which mimics 24-hour endogenous insulin secretion are long-acting basal insulin such as detemir, glargine, short/rapid-acting insulin analogs such as aspart, glulisine and premixed insulin analogs such as biphasic insulin aspart and insulin lispro are to be preferred. Recognition of causative factors such as the timing of meals, oral hypoglycemic drugs, and insulin doses can avoid

hypoglycemia. Presence of other comorbid conditions such as adrenal, renal, and pituitary insufficiency which may lead to increased risk of hypoglycemia can be identified in time will prevent hypoglycemia.

SUMMARY

Hypoglycemia which is often neglected complication of diabetes therapy is one barrier to provide optimal glycemic control in diabetic patients. This has clinical, economic, and social impact in the management of diabetes, identifying the risk factors, avoiding traditional sliding scale of insulin regimes, implementation of protocols, effective patient education, use of newer antidiabetic medications with little or no risk of hypoglycemia, and use of newer insulins. Making aware of the risk of hypoglycemia, preventive strategies, and individualized treatment plan can decrease the frequency and severity of hypoglycemia.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Diabetic Ketoacidosis

Rajeev Chawla, Shalini Jaggi, Sidhant Trehan

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute, major, and life-threatening complication of diabetes caused by insulin deficiency. It is characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. It occurs in patients with type 1 diabetes mellitus (T1DM), but it is not uncommon in some patients with type 2 diabetes mellitus (T2DM). Although the incidence of this complication has been reducing due to increased awareness among patients and physicians, this tends to cause serious effects in patients, resulting in significant mortality and morbidity. A recurring and central theme in the management of diabetes and related complications is the need for implementing preventive strategies, which include routine monitoring and patient education.

EPIDEMIOLOGICAL ASPECT

Available data indicate the incidence of DKA at 1 per 2,000 patients. Results of the Rhode Island Hospital Study from Fishbein et al. showed an estimated DKA incidence of 4.6 per 1,000 diabetic patients per year with a greater incidence in younger age groups and women. DKA occurs mostly in patients with T1DM, but is not uncommon among patients with T2DM. The mortality rate is 5% in experienced centers.

PATHOGENESIS OF DIABETIC KETOACIDOSIS

Relative or absolute insulin deficiency in the presence of catabolic counter-regulatory hormones (glucagon, catecholamines, growth hormones, and cortisol) is the basic underlying mechanism (**Fig. 1**). This leads to hepatic overproduction of glucose, unrestrained hepatic fatty acid oxidation, and release of free fatty acids (FFAs) into the circulation from adipose tissue (lipolysis) and to production of ketone bodies [β-hydroxybutyrate (β-OHB) and acetoacetate], resulting in ketonemia and metabolic acidosis. Hyperglycemia results in osmotic diuresis leading to dehydration and loss of electrolytes. Sodium depletion is worsened as insulin deficiency further diminishes renal sodium reabsorption. Metabolic acidosis leads to loss of intracellular potassium in exchange for hydrogen ions, and insulin deficiency also causes potassium loss from cells. Thus, there is high circulating plasma potassium.

PRECIPITATING FACTORS FOR DIABETIC KETOACIDOSIS

The most common precipitating factor is intercurrent infection. The other common factors are listed in **Box 1**. The frequency of each factor varies according to the age and ethnicity. Many a times, no obvious cause could be determined. Recurrent DKA is particularly seen in young girls.

PRESENTING FEATURES FOR DIABETIC KETOACIDOSIS

The symptoms of DKA include increasing polyuria and thirst, weight loss, weakness, drowsiness, and eventually coma (in about 10% of cases) (**Box 2**).

On physical examination, there is dehydration, hypotension, tachycardia, and hypothermia. Acidosis stimulates the respiratory center resulting in deep and rapid (Kussmaul) respiration. In some patients, the smell of acetone may be obvious in patient's breath.

KETOSIS PRONE TYPE 2 DIABETES MELLITUS

Diabetic ketoacidosis commonly occurs in T1DM. However, it can also occur in African American and Hispanic population who subsequently can be treated without insulin and thus behave as T2DM patients. This phenomenon is termed as ketosis prone T2DM. Their clinical features are listed in **Box 3**.

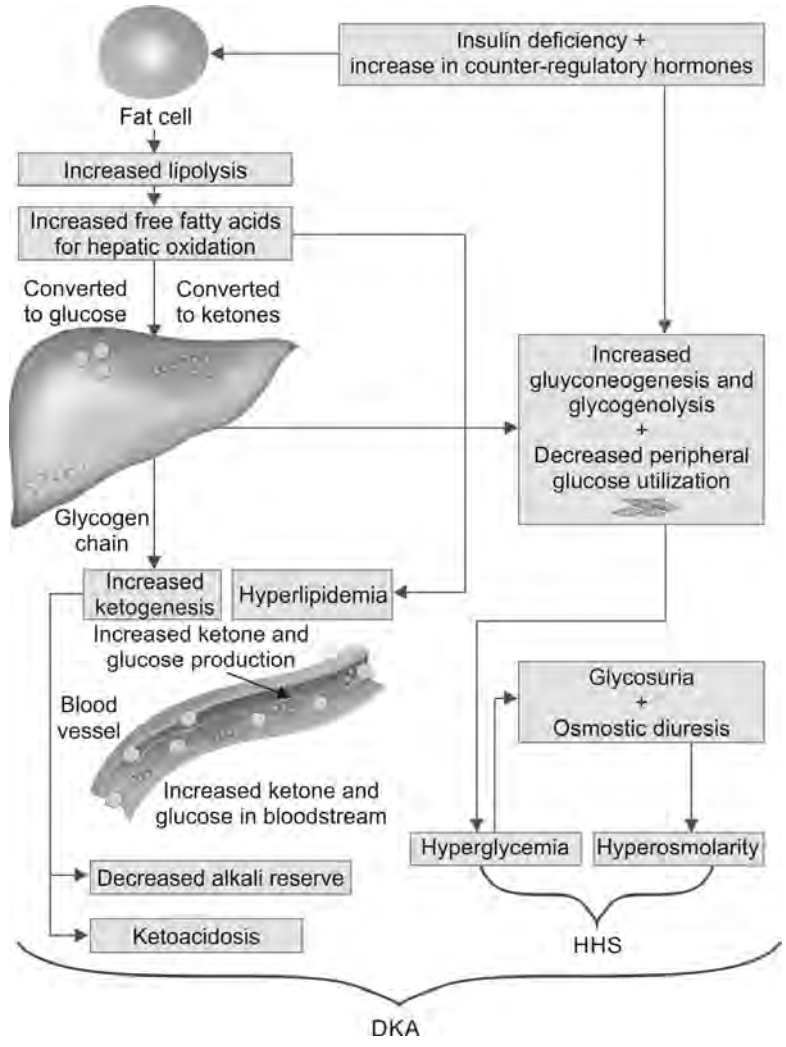


FIG. 1: Schematic representation of pathogenesis of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).

BOX 1: Precipitating factors for diabetic ketoacidosis.

- Infection
- Insulin error/omission
- Newly diagnosed cases
- Cardiovascular (myocardial infarction/stroke)
- Pancreatitis
- Pulmonary embolism
- Alcohol excess
- Steroid use

BOX 2: Clinical features of diabetic ketoacidosis.

- Polyuria and nocturia
- Thirst
- Weight loss
- Weakness
- Blurred vision
- Acidotic (Kussmaul) respiration
- Abdominal pain, especially in children
- Leg cramps
- Nausea and vomiting
- Confusion and drowsiness
- Coma

EVALUATION OF PATIENT FOR DIABETES KETOACIDOSIS

Diabetic ketoacidosis is a medical emergency. Therefore, a rapid history, physical examination, and bedside tests should allow a provisional diagnosis in the emergency department and avoid treatment delays (**Fig. 2**).

DIAGNOSTIC CRITERIA FOR DIABETIC KETOACIDOSIS

Based on the biochemical and clinical characteristics, DKA can be arbitrarily divided into mild, moderate, and severe (**Table 1**).

BOX 3: Features of ketosis prone type 2 diabetes mellitus (T2DM).

- Acute presentation
- Mean age > 40 years
- Male preponderance
- BMI ≥ 28 (for African American, less for Hispanic and Taiwanese)
- Newly diagnosed diabetes
- Strong family history of T2DM
- HbA1c > 12% at presentation
- Autoimmune markers of T1DM negative
- Fasting C-peptide detectable
- Most do not require long term insulin therapy

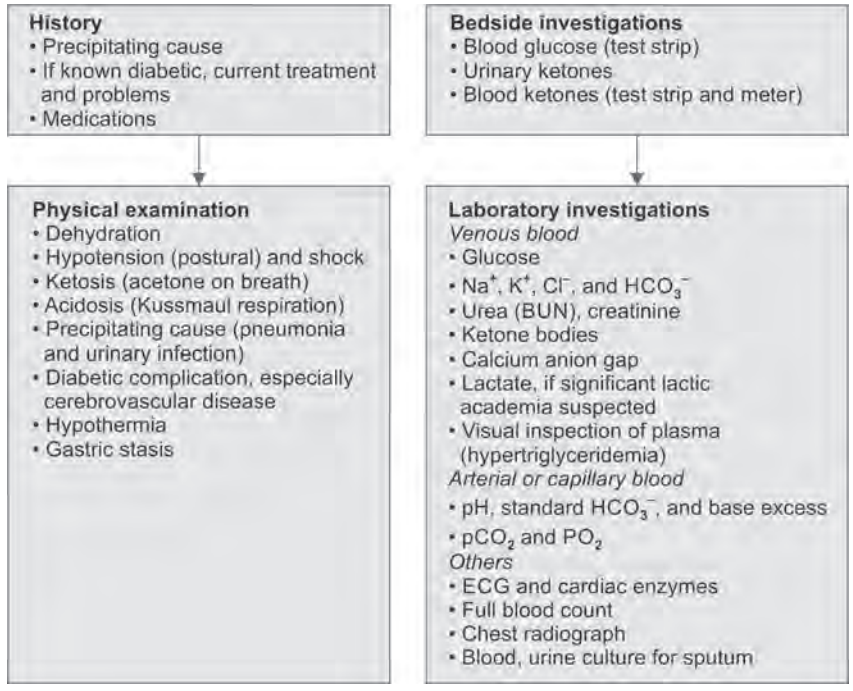
(BMI: body mass index; HbA1c: glycated hemoglobin)

TREATMENT GOALS FOR DIABETIC KETOACIDOSIS

Successful treatment of DKA aims for correction of dehydration, hyperglycemia, and electrolyte imbalances and identification of comorbid precipitating events; and above all, frequent patient monitoring (**Flowchart 1**).

Fluid Correction in the Management of Diabetic Ketoacidosis

The total body water and electrolyte deficit is shown in **Table 2**. Initial treatment involves rehydration, usually with isotonic saline (0.9% NaCl) at a rate of 15–20 mL/kg body weight/h or greater during the first hour (1–1.5 L in the average adult). Fluid therapy is directed toward expansion of the intravascular


History
• Precipitating cause
• If known diabetic, current treatment and problems
• Medications
Bedside investigations
• Blood glucose (test strip)
• Urinary ketones
• Blood ketones (test strip and meter)
Physical examination
• Dehydration
• Hypotension (postural) and shock
• Ketosis (acetone on breath)
• Acidosis (Kussmaul respiration)
• Precipitating cause (pneumonia and urinary infection)
• Diabetic complication, especially cerebrovascular disease
• Hypothermia
• Gastric stasis
Laboratory investigations
Venous blood
• Glucose
• Na+, K+, Cl−, and HCO3−
• Urea (BUN), creatinine
• Ketone bodies
• Calcium anion gap
• Lactate, if significant lactic academia suspected
• Visual inspection of plasma (hypertriglyceridemia)
Arterial or capillary blood
• pH, standard HCO3−, and base excess
• pCO2 and PO2
Others
• ECG and cardiac enzymes
• Full blood count
• Chest radiograph
• Blood, urine culture for sputum

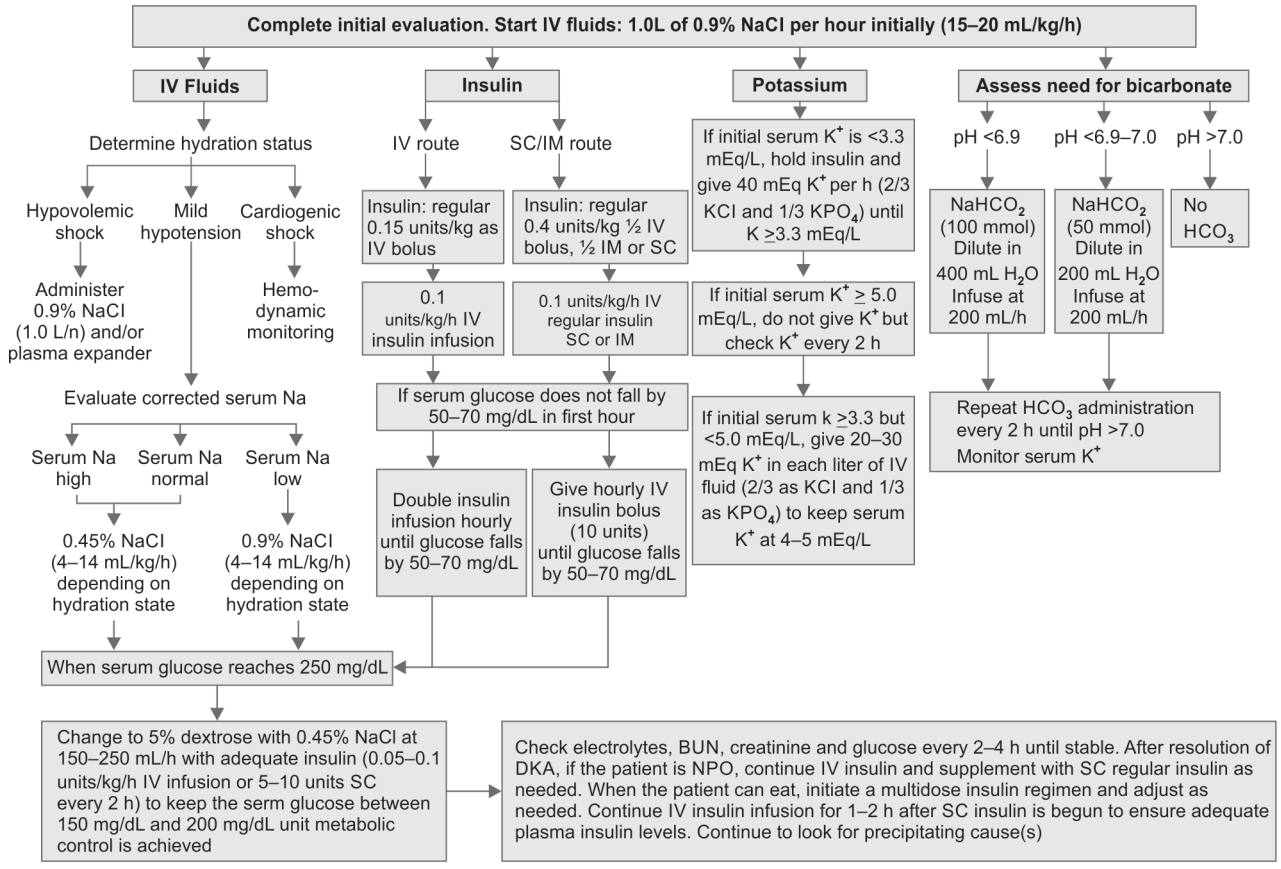
(BUN: blood urea nitrogen; ECG: electrocardiogram; pCO_2: partial pressure of carbon dioxide; PO_2: partial pressure of oxygen)

FIG. 2: Initial evaluation for diabetic ketoacidosis.

TABLE 1: Diagnostic criteria for diabetic ketoacidosis.

	Mild	*Moderate*	*Severe*
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25–7.30	7.00–7.24	<7.00
Serum bicarbonate (mEq/L)	15–18	10–15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)†	Variable	Variable	Variable
Anion gap‡	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

*Nitroprusside reaction method; †calculation: 2[measured Na (mEq/L)] + glucose (mg/dL)/18; ‡calculation: (Na^+) (Cl + HCO_3) (mEq/L)


Complete initial evaluation. Start IV fluids: 1.0L of 0.9% NaCl per hour initially (15–20 mL/kg/h)
IV Fluids
Insulin
Potassium
Assess need for bicarbonate
Determine hydration status
IV route
SC/IM route
If initial serum K+ is <3.3 mEq/L, hold insulin and give 40 mEq K+ per h (2/3 KCl and 1/3 KPO4) until K ≥3.3 mEq/L
pH <6.9
pH <6.9–7.0
pH >7.0
Hypovolemic shock
Mild hypotension
Cardiogenic shock
Insulin: regular 0.15 units/kg as IV bolus
Insulin: regular 0.4 units/kg ½ IV bolus, ½ IM or SC
NaHCO2 (100 mmol) Dilute in 400 mL H2O Infuse at 200 mL/h
NaHCO2 (50 mmol) Dilute in 200 mL H2O Infuse at 200 mL/h
No HCO3
Administer 0.9% NaCl (1.0 L/n) and/or plasma expander
Hemo-dynamic monitoring
0.1 units/kg/h IV insulin infusion
0.1 units/kg/h IV regular insulin SC or IM
If initial serum K+ ≥ 5.0 mEq/L, do not give K+ but check K+ every 2 h
Evaluate corrected serum Na
If serum glucose does not fall by 50–70 mg/dL in first hour
Repeat HCO3 administration every 2 h until pH >7.0
Monitor serum K+
Serum Na high
Serum Na normal
Serum Na low
Double insulin infusion hourly until glucose falls by 50–70 mg/dL
Give hourly IV insulin bolus (10 units) until glucose falls by 50–70 mg/dL
If initial serum k ≥3.3 but <5.0 mEq/L, give 20–30 mEq K+ in each liter of IV fluid (2/3 as KCl and 1/3 as KPO4) to keep serum K+ at 4–5 mEq/L
0.45% NaCl (4–14 mL/kg/h) depending on hydration state
0.9% NaCl (4–14 mL/kg/h) depending on hydration state
When serum glucose reaches 250 mg/dL
Change to 5% dextrose with 0.45% NaCl at 150–250 mL/h with adequate insulin (0.05–0.1 units/kg/h IV infusion or 5–10 units SC every 2 h) to keep the serm glucose between 150 mg/dL and 200 mg/dL unit metabolic control is achieved
Check electrolytes, BUN, creatinine and glucose every 2–4 h until stable. After resolution of DKA, if the patient is NPO, continue IV insulin and supplement with SC regular insulin as needed. When the patient can eat, initiate a multidose insulin regimen and adjust as needed. Continue IV insulin infusion for 1–2 h after SC insulin is begun to ensure adequate plasma insulin levels. Continue to look for precipitating cause(s)

(BUN: blood urea nitrogen; DKA: diabetic ketoacidosis; IM: intramuscular; IV: intravenous; NPO: nil per os; SC: subcutaneous)

FLOWCHART 1: The protocol for the management of adult patients with DKA.

TABLE 2: Typical total body deficits of water and electrolytes in diabetic ketoacidosis.

Total water (L)	6
Water (mL/kg)	100
Na^+ (mEq/kg)	7–10
Cl (mEq/kg)	3–5
K^+ (mEq/kg)	3–5
PO_4 (mmol/kg)	5–7
Mg^{++} (mEq/kg)	1–2
Ca^{++} (mEq/kg)	1–2

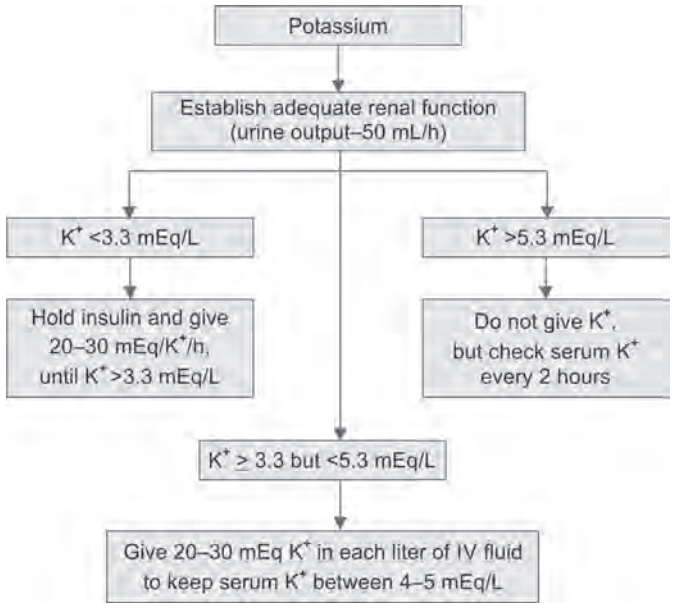
and extravascular volume and restoration of renal perfusion. Subsequent choice for fluid replacement depends on the state of hydration, serum electrolyte levels, and urinary output. In general, 0.45% NaCl infused at 4–14 mL/kg/h is appropriate if the corrected serum sodium is normal or elevated; 0.9% NaCl at a similar rate is appropriate if corrected serum sodium is low.

The success of fluid replacement is observed by hemodynamic monitoring (improvement in blood pressure), measurement of fluid input/output, and clinical examination. Fluid replacement should correct estimated deficits within the first 24 hours. The induced change in serum osmolality should not exceed 3 mOsm/kg H_2O/h. In patients with renal or cardiac compromise, monitoring of serum osmolality and frequent assessment of cardiac, renal, and mental status must be performed during fluid resuscitation to avoid iatrogenic fluid overload.

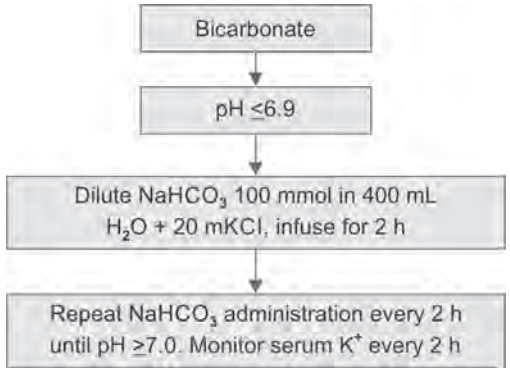
Correction of Electrolyte Imbalance and Acidosis

Sodium deficit is corrected by normal saline. Once renal function is assured, the infusion should include 20–30 mEq/L potassium (2/3 KCl and 1/3 KPO_4) until the patient is stable and can tolerate oral supplementation. Although phosphate and magnesium depletion are also present, there is no evidence that routine replacement is beneficial. However, serum phosphate levels < 0.35 mmol/L can cause muscle weakness and myocardial dysfunction and need correction. Similarly, serum magnesium levels <0.7 mmol/L should also be corrected (**Flowcharts 2** and **3**).

The role of intravenous (IV) bicarbonate is controversial. There is no proven benefit in patients with arterial pH ≥6.9. There are good theoretical reasons why IV bicarbonate should not be added and its use is associated with the development of cerebral edema. The American Diabetes Association (ADA) guidelines recommend 100 mmol diluted and given over 2 hours in patients with a pH <6.9 or in whom the acidosis is thought to be contributing to deteriorating clinical status.


Potassium
Establish adequate renal function (urine output–50 mL/h)
K+ <3.3 mEq/L
K+ >5.3 mEq/L
Hold insulin and give 20–30 mEq/K+/h, until K+ >3.3 mEq/L
Do not give K+, but check serum K+ every 2 hours
K+ ≥ 3.3 but <5.3 mEq/L
Give 20–30 mEq K+ in each liter of IV fluid to keep serum K+ between 4–5 mEq/L

FLOWCHART 2: Protocol for correcting electrolyte imbalance.


Bicarbonate
pH ≤6.9
Dilute NaHCO3 100 mmol in 400 mL H2O + 20 mKCl, infuse for 2 h
Repeal NaHCO3 administration every 2 h until pH ≥7.0. Monitor serum K+ every 2 h

FLOWCHART 3: Management of acidosis.

Management of Hyperglycemia in Diabetic Ketoacidosis

Unless the episode of DKA is mild, regular insulin by continuous IV infusion is the treatment of choice. In adult patients, once hypokalemia (K^+<3.3 mEq/L) is excluded, an IV bolus of regular insulin at 0.15 units/kg body weight, followed by a continuous infusion of regular insulin at a dose of 0.1 unit/kg/h (5–7 units/h in adults), should be administered.

When the plasma glucose reaches 250 mg/dL, it may be possible to decrease the insulin infusion rate to 0.05–0.1 unit/kg/h (3–6 units/h), and dextrose (5–10%) may be added to the IV fluids. Thereafter, the rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain the above glucose values until acidosis is resolved.

Patients with mild DKA should first receive a "priming" dose of regular insulin of 0.4–0.6 units/kg body weight, half as an IV bolus and half as a subcutaneous or intramuscular injection. Thereafter, 0.1 unit/kg/h of regular insulin should be given subcutaneously or intramuscularly.

Criteria for resolution of DKA include a glucose <200 mg/dL, serum bicarbonate ≥ 18 mEq/L, and a venous pH of > 7.3. Once DKA is resolved, if the patient is nil per os (NPO), continue IV insulin and fluid replacement and supplement with subcutaneous regular insulin as needed every 4 hours. In adult patients, this can be given in 5-unit increments for every 50 mg/dL increase in blood glucose above 150 mg/dL for up to 20 units for blood glucose of 300 mg/dL. In case the patient is able to eat, a multiple-dose schedule should be started that uses a combination of short- or rapid-acting and intermediate-or long-acting insulin as needed to control plasma glucose. Continue IV insulin infusion for 1–2 hours after the subcutaneous regimen is begun to ensure adequate plasma insulin levels on board. **Table 3** presents key features in management of DKA.

TABLE 3: Key features in management of DKA.

Insulin treatment	Immediate insulin therapy is extremely crucial for reversal of DKA and must be initiated at the earliest
Electrolyte imbalance	Potassium loss is lesser in DKA as compared to HHS; however, potassium replenishment is needed in patients with DKA

(DKA: diabetic ketoacidosis; HHS: hyperosmolar hyperglycemic state)

COMPLICATIONS OF DIABETIC KETOACIDOSIS

The most common complications of DKA include:

- Hypoglycemia due to overzealous treatment with insulin
- Hypokalemia due to insulin administration and treatment of acidosis with bicarbonate
- Hyperglycemia secondary to interruption/discontinuance of IV insulin therapy after recovery without subsequent coverage with subcutaneous insulin
- Hyperchloremia caused by the use of excessive saline for fluid and electrolyte replacement and transient nonanion gap metabolic acidosis as chloride from IV fluids replaces ketoanions lost as sodium and potassium salts during osmotic diuresis

Cerebral edema is a rare but frequently fatal complication of DKA, occurring in 0.7–1.0% of children with DKA. Hypoxemia and, rarely, noncardiogenic pulmonary edema may also complicate the treatment of DKA.

PREVENTIVE MEASURES FOR DIABETIC KETOACIDOSIS

Better access to medical care, proper education, and effective communication with a healthcare provider during an intercurrent illness may be helpful in preventing many cases of DKA. Cessation of insulin therapy for economic reason is disturbing and needs to be addressed.

Better education of care givers as well as patients regarding signs and symptoms of new-onset diabetes; conditions, procedures, and medications that worsen diabetes control; and the use of glucose monitoring could potentially decrease the incidence and severity of DKA.

SUMMARY

- Insulin deficiency with raised levels of counter regulatory hormones leads to DKA and hyperosmolar hyperglycemic state (HHS).
- DKA occurs mostly in T1DM, whereas HHS is more common in T2DM.
- Increased lipolysis and increased supply of FFA for hepatic fatty acid oxidation lead to ketoacidosis.
- The most common symptoms of DKA are polydipsia and polyuria. The most common symptom of HHS is altered sensorium.
- Metabolic acidosis in DKA needs to be corrected by IV bicarbonate infusion, only if pH ≤6.9.
- Glucose levels must be reduced with caution in children to avoid cerebral edema.

MULTIPLE CHOICE QUESTIONS

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129 CHAPTER

Hyperosmolar Hyperglycemic Syndrome

Dheeraj Kapoor

INTRODUCTION

Hyperosmolar hyperglycemic syndrome (HHS) is a metabolic derangement that arises from a complication of diabetes mellitus mostly associated with type 2 diabetes mellitus (T2DM). In 1880s, Won Frerichs and Dreschfeld described the first cases of HHS in patients with an "unusual diabetic coma" characterized by severe hyperglycemia and glycosuria, positive urine acetone test, and fruity smell in breath but absence of Kussmaul breathing. The nomenclature of clinical situation such as nonketotic hyperglycemic coma, hyperosmolar hyperglycemic nonketotic syndrome, and hyperosmolar nonketotic coma (HONK) are no longer used.

DIABETES OVERVIEW

Diabetes is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Insulin is an anabolic hormone produced by the beta cells in the islets of Langerhans in the pancreas in response to the physiological rise in blood glucose associated with a carbohydrate meal. The primary action of insulin is to maintain blood glucose levels between 3 and 8 mmol/L or 60–140 mg/dL and this is done through three actions of insulin:

1. Promoting uptake of glucose by the target cells and its subsequent breakdown into energy (glycolysis) or storage as glycogen (glycogenesis)
2. Inhibiting gluconeogenesis (formation of new glucose from noncarbohydrate source such as fats and protein) or production of glucose by the liver
3. Suppressing lipolysis (breakdown of fat)

Types of Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) results from the autoimmune destruction of pancreatic beta cells. The autoimmune component appears to be influenced by genetic predisposition, as it is strongly associated with the major histocompatibility complex human leukocyte antigen (HLA) class II region on chromosome 6p21. The attack on the beta cells appears to be triggered or modified by environmental or biologic events such as viral infections, early infant diet, and toxins. Approximately about 5–10% of all diabetes falls into this category and the most common complication is diabetic ketoacidosis (DKA).

Type 2 diabetes mellitus is a metabolic disorder with multiple causes, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism, accounts for about 90–95% of diabetes cases. It generally results from a combination of insulin resistance and loss of beta-cell function. Insulin resistance places an increased secretory demand upon the beta cell, leading to beta-cell dysfunction as the disease progresses. Type 2 diabetes mellitus affects a number of organs in the long-term and is associated with increased risk of macrovascular disease and also microvascular complications such as retinopathy, nephropathy, and neuropathy. Most of the time T2DM remains unnoticed for many years and studies suggest >50% of individuals have evidence of vascular disease at diagnosis.

Hyperosmolar hyperglycemic syndrome is a serious and potentially life-threatening complication of T2DM accounting for about 0.5% of primary diabetes hospital admissions. The mortality rate in HHS is 20% much higher than seen in DKA. Factors that determined clinical outcome and prognosis in HHS are age, the degree of dehydration, and the presence or lack of other comorbidities.

ETIOLOGY

History of T2DM is a main risk factor for HHS. But some time HHS may occur in those without a prior history of diabetes or with T1DM. Triggers include infections, stroke, trauma, certain medications, and heart attacks. Other risk factors include:

- Lack of sufficient insulin (but enough to prevent ketosis) or noncompliance with oral hypoglycemic or insulin therapy can result in HHS
- Poor kidney function
- Poor fluid intake (dehydration)
- Older age (50–70 years)
- Certain medical conditions [cerebral vascular injury, MI, sepsis, acromegaly, Cushing syndrome (e.g., endogenous, exogenous, and ectopic), and neuroleptic malignant syndrome)

- Certain medications (glucocorticoids, beta-blockers, thiazide diuretics, calcium channel blockers, and phenytoin)
- Patients on total parenteral nutrition (TPN) solutions and intravenous (IV) fluid that contain dextrose are also at risk for HHS.

PATHOPHYSIOLOGY

The syndrome is characterized by severe hyperglycemia, a marked increase in serum osmolality and clinical evidence of dehydration without the accumulation of β-hydroxybutyric or acetoacetic ketoacids which makes it different from DKA. Both conditions are due to deficiency of insulin. As a consequence of deficiency of this key hormone, there is decrease glucose utilization by the peripheral tissue causing hyperglycemia. The peripheral tissues enter a state of "starvation". The release of counterregulatory hormones glucagon, growth hormone, cortisol, and catecholamine stimulate gluconeogenesis and glycogenosis (**Table 1**). The main defect is that there is enough insulin to prevent lipolysis and ketogenesis but not enough to cause glucose utilization (as it takes 1/10 as much insulin to suppress lipolysis as it does to stimulate glucose utilization) possibly smaller incrase in counter regulatory hormones (**Flowchart 1**).

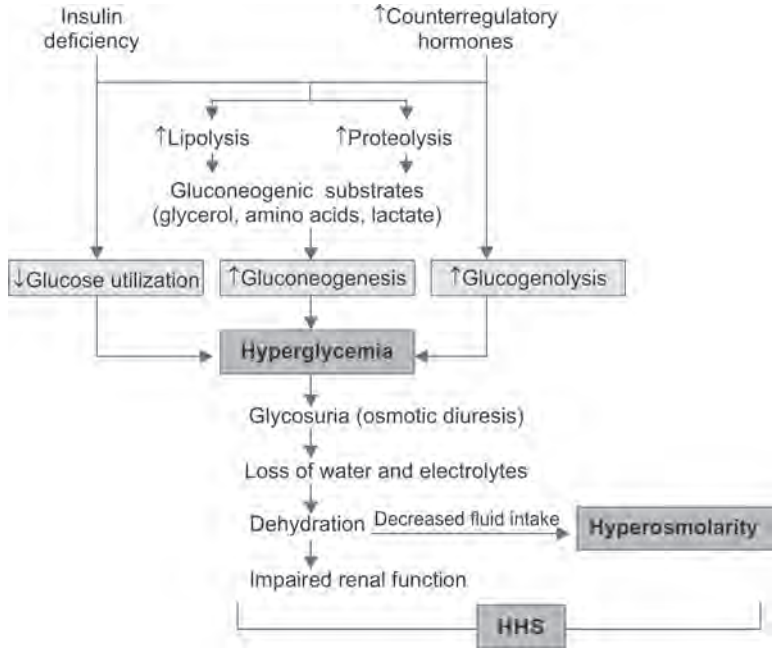
As there is rise in osmolality in the extracellular fluid it causes a shift of water from the intracellular to the extracellular space resulting in intracellular dehydration. Once the blood glucose exceeds the renal threshold (normal range 180–250 mg/dL) glycosuria and osmotic diuresis occurs. In the initial phase, glycosuria temporarily protects the patients from becoming the hyperglycemic. But persistent osmotic diuresis, significant depletion of intravascular volume, decreasing renal perfusion and the ability of the kidneys to excrete large quantities of glucose, profound hyperglycemia, and a further increase in plasma osmolality occur.

The stress of profound hyperglycemia and resultant hyperosmolarity and dehydration, as well as the precipitating illness, contributes to increased production of counter regulatory hormones which accentuates the degree of hyperglycemia. This creates a system of vicious cycle where there is increase level of glucose in the serum, but decreases uptake by the peripheral tissues for tissue metabolism.

In addition to glucose, electrolytes such as sodium, potassium, phosphate, and magnesium are also lost during the osmotic diuresis. Sodium depletion leads to further decrease in intravascular volume, but urinary losses of water always exceeds that of sodium leading to development of hypertonic dehydration.

TABLE 1: The effect of different hormones on glucose metabolism and regulation of ketogenesis.

	Ketogenesis	*Gluconeogenesis*	*Glycogenolysis*	*Glycolysis*	*Glycogen synthesis*
Insulin	Decreased	Decreased	Decreased	Increased	Increased
Glucagon	Increased	Increased	Increased	Decreased	Decreased
Cortisol	Increased	Increased	Increased	Decreased	Decreased
Growth hormone	Increased	Increased	Increased	Decreased	Decreased
Catecholamines	Increased	Increased	Increased	Decreased	Decreased



FLOWCHART 1: The diagrammatic representation of pathogenesis of hyperosmolar hyperglycemic syndrome (HHS).

The effect of hypertonic dehydration on the brain can be very profound. The brain produces idiogenic osmoles (osmotically active substance) to preserve the intracellular volume. The main functions of the idiogenic osmoles are to prevent movement of the fluid from the intracellular space into extracellular space and maintain a balanced equilibrium. The risk of developing cerebral edema is mostly related to how fast the serum osmolarity is decreasing. If the decline is too rapid, then the chances of fluid moving into the brain cell and causing swelling are higher. Hence, in the treatment of HHS, the goal of treatment is a slow correction of the hyperglycemia.

DIAGNOSIS

History and Physical Examination

The history and physical examination are very crucial in the diagnosis of HSS due to significant overlap in the signs and symptoms seen in HHS and DKA. The important points should be noted during the history taking and the initial assessment are insulin regimen, missed doses of the oral hypoglycemic agent, over consumption of carbohydrate-rich diet, and simultaneous use of medications that can trigger hyperglycemia or cause dehydration.

Clinical Features

The patient presents typically with increased urination (polyuria) and increase water intake (polydipsia) due to stimulation of the thirst centre in the brain from severe dehydration and increased serum osmolality (**Table 2**). Weakness, malaise, and lethargy can also be part of the complaint. The most important differentiating feature in HHS is the presence of neurological signs. Decreased cerebral blood flow from severe dehydration can cause focal neurological deficit, disturbance in visual acuity, delirium, and coma.

A system-based approach is necessary for the physical assessment. Patient with HSS are generally ill appearing with altered mental status. Cardiovascular features include tachycardia, orthostatic hypotension, weak and thready pulses, respiratory rate can be normal, tachypnea might be present if acidosis is profound, delayed capillary refill, poor skin turgor, and decreased urine output. Focal neurological deficit and lethargy with low Glasgow Coma Score are the prominent clinical features. In severe cases of HSS, patients might be comatose.

TABLE 2: Depicts sign and symptoms of the patients in the following conditions.

Precipitating factor	*Sign and symptoms*
An infectious process precedes hyperosmolar hyperglycemic syndrome	Fever, malaise, general weakness, tachypnea, and tachycardia
Cardiac or vascular conditions	Chest pain, chest tightness, headache, dizziness, and palpitation
Poor glycemic control	Acanthosis nigricans, oral thrush, vulvovaginitis, and multiple pustular skin lesion

Evaluation

Hyperosmolar hyperglycemic syndrome is a medical emergency that require urgent recognition and treatment. The initial approach to these patients should include a rapid but thorough history and physical examination with special focus on patency of airways, mental status, state of hydration, cardiovascular and renal integrity, and potential sources of infection. Initial laboratory evaluation for HHS is presented in **Table 3**.

Diagnostic features of HSS according to the American Diabetes Association (ADA) include:

- Plasma glucose level >30 mmol/L (>600 mg/dL)
- Serum osmolality >320 mOsm/kg
- Severe dehydration, average of 9 L fluid deficit, and thirst
- Serum pH > 7.30
- Bicarbonate > 15 mEq/L
- Small ketonuria (~+ on dipstick) and absent-to-low ketonemia (<3 mmol/L)
- Some alteration in consciousness
- Blood urea nitrogen (BUN) > 30 mg/dL (increased)
- Creatinine > 1.5 mg/dL (increase)

DIFFERENTIAL DIAGNOSIS

The following are some examples of condition that can cause an alteration in mental status:

- Hypoglycemia
- Hyponatremia
- Hypernatremia
- Hyperammonemia
- Severe intoxication with drugs or alcohol
- Uremic encephalopathy
- Diabetic ketoacidosis

TABLE 3: Initial laboratory evaluation for HHS.

Metabolic evaluation	• Glucose • Serum ketones • Electrolytes (Na, K, Cl, HCO_3, Ca, PO_4, and Mg) • Serum osmolality • BUN and creatinine • Arterial blood gases • Liver function test • Amylase Lipase • HbA1c • Urine analysis
Infectious disease evaluation	• CBC with differential • Urine culture • Blood culture • Viral nasal swab
Others	• ECG • Urine toxicology panel • Urine pregnancy test

(BUN: blood urea nitrogen; CBC: complete blood count; ECG: electrocardiogram; HbA1c: glycated hemoglobin; HSS: hyperosmolar hyperglycemic syndrome)

- Diabetic insipidus
- Central nervous system (CNS) infection
- Severe dehydration
- Myocardial infarction (MI)
- Pulmonary embolism
- Arrhythmia
- Hypotension
- Other causes of dehydration
- Acute blood loss (gastrointestinal or other)
- Excessive diuretic use

TREATMENT APPROACH

Hyperosmolar hyperglycemic syndrome treatment requires a multidisciplinary approach. It is recommended to consult an endocrinologist and intensive care specialist. The main goals in the treatment of HHS are as follows:

- To rehydrate the patient vigorously while maintaining electrolyte homeostasis
- Correction of hyperglycemia
- To treat underlying diseases
- To assist and monitor cardiovascular, renal, pulmonary, and CNS function

Airway Management

Patient of HHS presents with mental status changes, obtundation, or unconsciousness so maintenance of airway is mandatory and secure the airway if the Glasgow Coma Score is <8. Mechanical ventilation is necessary in patients with respiratory failure and circulatory collapse. If patients present with metabolic acidosis, hyperventilation is instituted as it generates respiratory alkalosis, which compensates for the metabolic acidosis and also decreases the risk of cerebral edema.

Intravenous Access

Intravenous access with large bore needle or central venous access is useful. Fluid deficit is large in HHS and in view of profound dehydration peripheral IV access is generally difficult so centrally placed catheter offers an opportunity for vigorous rehydration.

Fluid Resuscitation

To avoid cardiovascular collapse and to perfuse vital organs, aggressive fluid resuscitation is the key in the treatment of HHS. Fluid deficits in adults are large in HHS, being about 9 L on average. According to the ADA guidelines, to expand the extracellular volume fluid, resuscitation with 0.9% saline at the rate of 15–20 mL/kg/h or greater is indicated in the first hour. This amount to about 1–1.5 L in an average sized person. Slower rates are indicated in patients with cardiac or renal disease. Patients with HHS severe volume depletion state, a greater rate of fluid resuscitation is needed but should not exceed 50 mL/kg in the first 4 hours.

Patient's hydration status, serum electrolytes, and urinary output determine the choice of fluids after initial resuscitation. 0.45% normal saline may be used at a rate of 10 mL/kg/h if the patient's sodium level is normal or elevated. 0.9% normal saline may be used if the patient is hyponatremic. First half of the patient's fluid deficit should be corrected in the first 18–24 hours. The plasma osmolality should not change over 3 mmol/kg/h during fluid resuscitation. When the blood glucose concentration reaches 250 mg/dL, change the infusion to 5% dextrose in 0.45–0.7% normal saline. This is to prevent a quick fall in glucose, which may be associated with cerebral edema. In pediatric patients with suspected HHS, to reduce the risk of cerebral edema, correcting fluid deficits over a longer period (48 hours) may help. Potassium replacement initiated when the serum potassium is between 4 mmol/L and 4.5 mmol/L. 20–40 mEq/L of potassium chloride should also be included in the IV fluids to treat hypokalemia. Patients may require pressor support with persistent hypotension in the intensive care unit (ICU) while rehydration is being accomplished. An important endpoint of fluid therapy is to restore urinary output to 50 mL/h or more.

Insulin

Dose of insulin required to reduce the hyperglycemia may be less in HHS patients as compared to those with DKA. Correcting hypovolemia can reduce hyperglycemia considerably by fluid replacement alone, which then increases both glomerular filtration and renal excretion of glucose. Insulin treatment should therefore be delayed unless the patient has significant ketonemia (beta-hydroxybutyrate >1 mmol/L). Start the insulin infusion rate at 0.05 unit/kg/h (bolus is not needed) and titrate to lower blood glucose levels by 50–70 mg/dL/h (2.8–3.9 mmol/L/h). Once the patient has stabilized and the blood glucose falls to around 250 mg/dL (13.9 mmol/L), insulin can be given subcutaneously. A too-quick reduction in osmolality can lead to cerebral edema.

Phosphate

If severe hypophosphatemia [serum phosphate <1 mg/dL (0.32 mmol/L)] develops during insulin therapy, phosphate replacement can be given as described for ketoacidotic patients (at 3 mmol/h).

Monitoring during Treatment

Mortality associated with HHS remains high. Cardiorespiratory monitoring is warranted because of profound electrolyte and metabolic abnormalities present during treatment. Endotracheal intubation and mechanical ventilation are indicated when gas exchange has been compromised. Neurologic monitoring is indicated in all patients with HHS who present with altered mental status. Many neurologic syndromes may trigger by hyperosmolarity. If a patient has seizures, phenytoin is not used, because endogenous insulin secretion is inhibited and in general it is ineffective in persons with HHS. Appropriate decrease is osmolality and volume resuscitation and will decrease the chance of seizures. Patients with HHS may also require telemetry monitoring if cardiac workup suggests a cardiac etiology, such as MI, for HHS.

PROGNOSIS

Fluid replacement remains the primary approach to the prevention of complications. MI, stroke, pulmonary embolism, mesenteric vein thrombosis, and disseminated intravascular coagulation can develop as a result of severe dehydration and low output state. Prophylactic low-dose heparin can be added.

The overall mortality rate of HHS is more than ten times that of DKA, because of its higher incidence in older patients with multiple comorbid conditions and excessive dehydration. Older patient may have compromised cardiovascular systems also. Other contributory factors for poor prognosis are delay in recognition and treatment. The mortality rate can be reduced from nearly 50% to that related to the severity of coexistent disorders when prompt therapy is instituted. Insulin treatment should be continued for few weeks, but patients usually recover sufficient endogenous insulin secretion to make a trial of diet or diet plus oral agents worthwhile. Education of the diabetic patient and caregivers should be instituted.

SUMMARY

The HHS is the most serious acute hyperglycemic emergency in patients with T2DM. Current diagnostic HHS criteria include a plasma glucose level >600 mg/dL and increased effective plasma osmolality >320 mOsm/kg in the absence of ketoacidosis. The reported mortality is between 10 and 20%, which is about 10 times higher than the mortality rate in patients with DKA. Treatment of HHS is includes replacing volume deficit and correcting hyperosmolality, hyperglycemia, and electrolyte disturbances, as well as management of the underlying illness that precipitated the metabolic decompensation.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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130 CHAPTER

Hypothyroidism and Myxedema Coma

Ajay Agarwal, Danendra Sahu, Rupak Wadhwa

INTRODUCTION

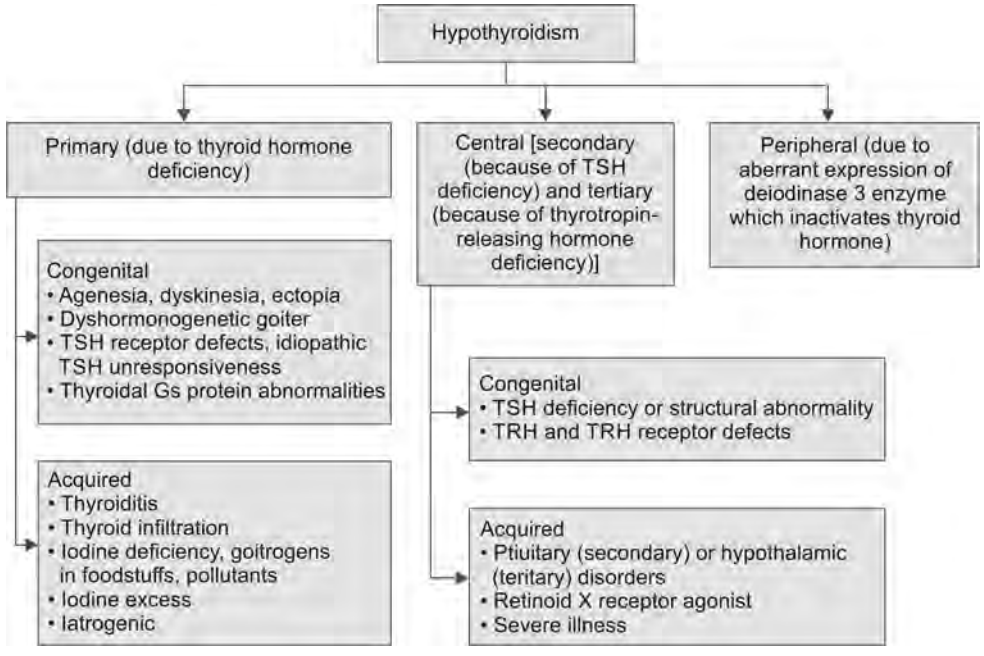
Hypothyroidism, a common metabolic disorder, occurs due to undersecretion of the thyroid hormones, thyroxine (T4), and triiodothyronine (T3). It leads to low serum T4 and T3 and high thyroid-stimulating hormone (TSH) due to compensatory rise. It occurs more commonly in females and elderly population.

CLASSIFICATION AND ETIOPATHOGENESIS

Hypothyroidism can be classified into primary, central, and peripheral types (**Flowchart 1**). Primary hypothyroidism is the most common type (~99%). Iodine deficiency is the most common cause of congenital and primary hypothyroidism globally, whereas chronic immune thyroiditis (Hashimoto's thyroiditis) is the most common cause of acquired hypothyroidism. Other causes include thyroidectomy (total or subtotal), radioactive iodine (RAI) therapy, radiotherapy to head and neck for cancer treatment, thyroid inflammatory diseases, pituitary or hypothalamic disorders, and several drugs (methimazole, propylthiouracil, amiodarone, lithium, and interferon-α) that affect the thyroid hormone availability. Under secretion of thyroid hormones (T4 and T3) from the thyroid gland is the most common cause of primary hypothyroidism whereas pituitary and hypothalamic causes may also affect thyroid gland functioning.

CLINICAL PRESENTATION

The clinical presentation of hypothyroidism includes a wide variety of symptoms, which may differ with age, gender, and disease duration. The most common symptoms are lethargy, hoarseness of voice, constipation, cold intolerance, dry skin, fatigue, menstrual disturbances, and weight gain (**Fig. 1**).


Hypothyroidism
Primary (due to thyroid hormone deficiency)
Central [secondary (because of TSH deficiency) and tertiary (because of thyrotropin-releasing hormone deficiency)]
Peripheral (due to aberrant expression of deiodinase 3 enzyme which inactivates thyroid hormone)
Congenital
• Agenesia, dyskinesia, ectopia
• Dyshormonogenetic goiter
• TSH receptor defects, idiopathic TSH unresponsiveness
• Thyroidal Gs protein abnormalities
Acquired
• Thyroiditis
• Thyroid infiltration
• Iodine deficiency, goitrogens in foodstuffs, pollutants
• Iodine excess
• Iatrogenic
Congenital
• TSH deficiency or structural abnormality
• TRH and TRH receptor defects
Acquired
• Ptiuitary (secondary) or hypothalamic (teritary) disorders
• Retinoid X receptor agonist
• Severe illness

(TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone)

FLOWCHART 1: Classification and etiopathogenesis of hypothyroidism.

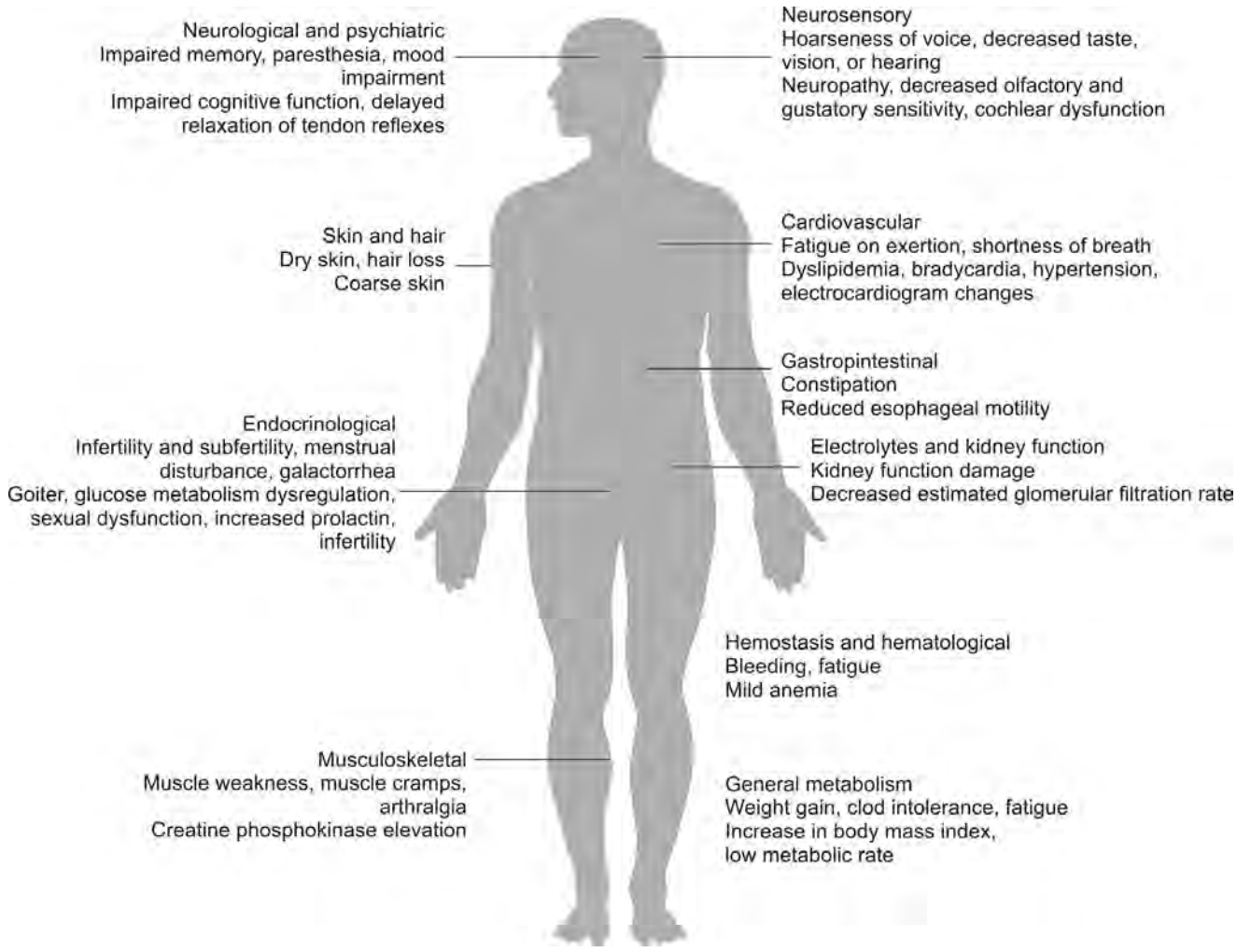


FIG. 1: Clinical manifestations of hypothyroidism.

DIAGNOSIS

The clinical signs and symptoms of hypothyroidism alone are not sufficient for the diagnosis as these are common and can be observed with other diseases or in the healthy state too. Measurement of serum T4 and TSH remains the only validated method for testing thyroid function. However, the standard reference ranges for these assays are still debated as these differ with age, gender, and race. These reference ranges do not consider the symptoms, risk of the disease, and adverse events. The algorithm for the diagnosis of suspected hypothyroidism is shown in **Flowchart 2**.

MYXEDEMA COMA

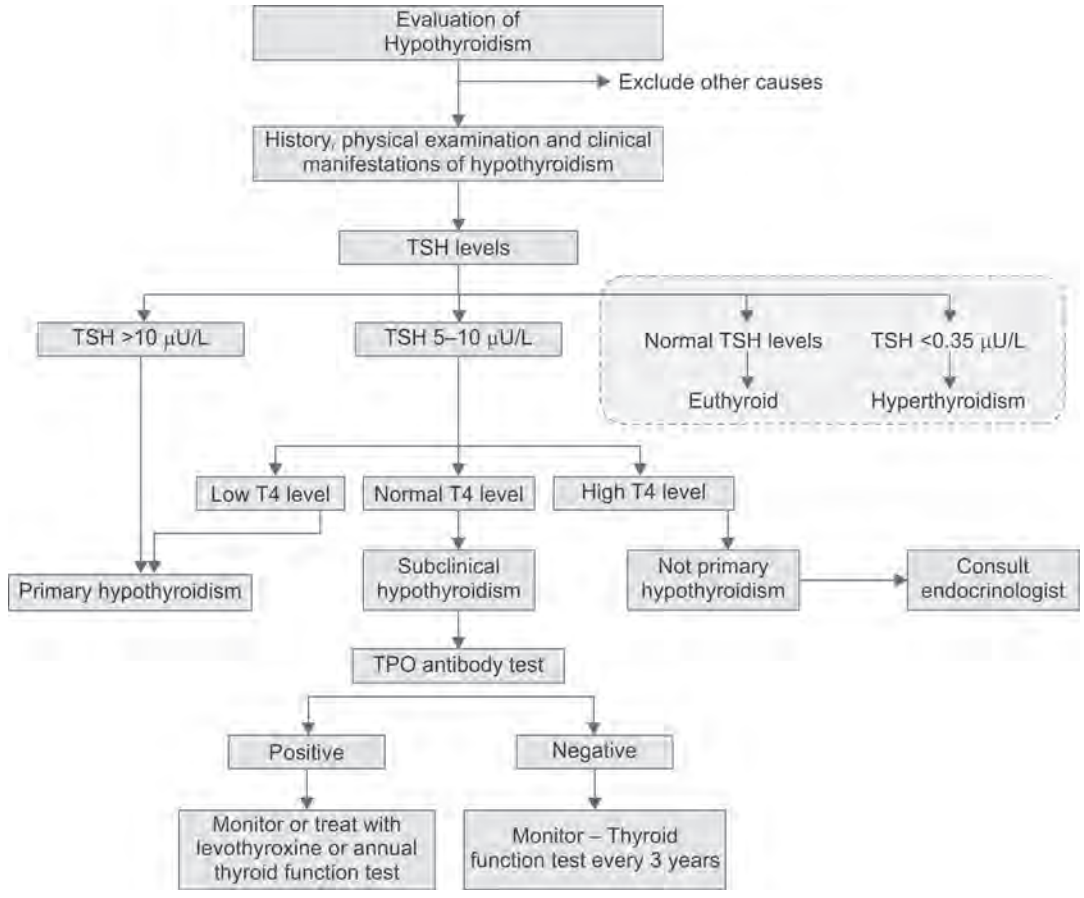
Severe hypothyroidism untreated for a prolonged duration may lead to a rare fatal disease, myxedema coma, in which the body's homeostasis goes haywire due to precipitating factors. These factors include infection, certain medications (amiodarone, anesthesia, barbiturates, β-blockers, diuretics, lithium, narcotics, phenothiazines, phenytoin, rifampin, and tranquilizers), and failure to reinstate thyroid replacement therapy during hospitalization, stroke, surgery, burns, hypoglycemia, hypothermia, gastrointestinal hemorrhage, or trauma among others. Most (95%) of the myxedema coma cases occur due to primary hypothyroidism while hypothalamic or pituitary causes account for the remaining (5%) cases.

Clinical Presentation and Pathogenesis of Myxedema Coma

Patients with myxedema coma generally present with altered sensorium, lethargy, confusion, and possibly obtundation rather than coma. Other characteristics include hypoglycemia, bradycardia, hypoventilation, hypotension, hypothermia, (usually <95.9°F), hyponatremia, increased levels of serum creatinine, and creatinine kinase. The clinical presentation of myxedema coma is shown in **Table 1**. **Flowchart 3** outlines the pathogenesis of the myxedema coma.

Diagnosis

The suspected diagnosis of myxedema coma includes clinical presentation of any patient with coma or compromised mental status with hypercapnia, hypothermia, and/or hyponatremia, and with decreased T3 and T4 concentrations. Measurement of serum cortisol is required to rule out coexisting adrenal insufficiency. However, there is a nonspecific presentation of clinical features in several instances such as altered mental status without coma, which makes it difficult to diagnose



(TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone)

FLOWCHART 2: Diagnosis of suspected hypothyroidism.

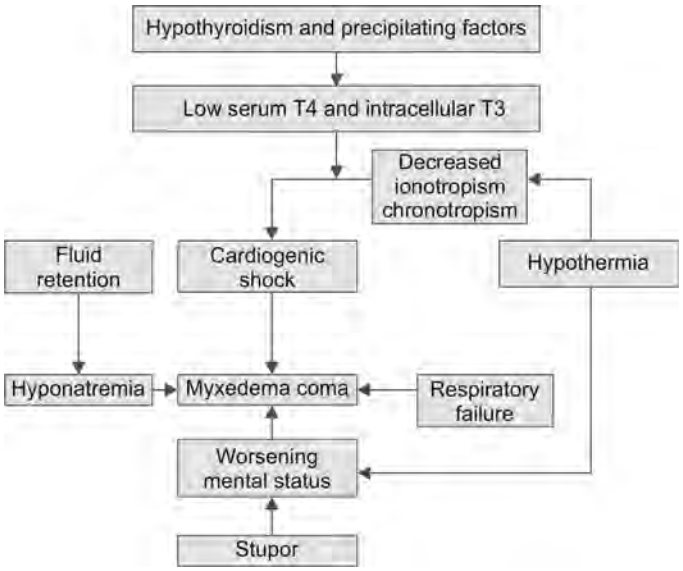
TABLE 1: Clinical presentation of myxedema coma.

System	*Clinical presentation*
Central nervous system (CNS)	• Decreased mental status—may be due to decreased cerebral blood flow and cerebral glucose metabolism • Confusion, apathy, lethargy, obtundation, and coma • Cognitive impairment and psychiatric disorders can also be seen • Hyponatremia • Hypoglycemia (~25% patients)
Respiratory system	• Respiratory depression • Fluid accumulation—pleural effusion • Obstructive sleep apnea—obesity and weight gain • Myxedematous infiltration of the pharynx and tongue requiring mechanical ventilation
Cardiovascular system (CVS)	• Bradycardia, low cardiac output, and decreased blood volume • Increased systemic peripheral resistance and pericardial effusion
Renal system	• Severe renal impairment—reduced blood flow and low glomerular filtration rate (GFR) • Elevated creatinine • Decreased sodium reabsorption leading to hyponatremia
Gastrointestinal tract (GIT)	Decreased intestinal mobility—constipation, anorexia, nausea, abdominal pain, and distension
Skin and hair	• Myxedematous facies—generalized puffiness, ptosis, macroglossia, coarse and sparse hair, and periorbital edema • Dry, pale, and thickened skin with nonpitting edema (myxedema) • Dry and brittle hair • Hoarseness in voice

Continued

Continued

System	Clinical presentation
Metabolic	Hypothermia (up to 75°F)
Laboratory and others	• Reduced T4 and T3 • Elevated thyroid-stimulating hormone (TSH)—primary hypothyroidism; normal/low TSH—central/secondary hypothyroidism • Respiratory acidosis • Electrocardiogram (ECG)—bradycardia, decreased voltage, prolonged QT interval, nonspecific ST-T changes and Osborn waves in cases of hypothermia • Chest radiograph—pleural effusions and cardiomegaly



FLOWCHART 3: Pathogenesis of myxedema coma.

myxedema coma. Overall, altered mental status, hypothermia, and the presence of precipitating events are the three key features for differential diagnosis of myxedema coma. *Chiong and Mariash* developed a tool as diagnostic criteria for myxedema coma based on six common parameters of the disease, which is used by intensive care units (ICUs) of several hospitals (**Table 2**).

TREATMENT

Treatment of Hypothyroidism

Life-long hormone therapy is required in most patients with hypothyroidism. The American Thyroid Association (ATA) recommends levothyroxine monotherapy as the standard of care for hypothyroidism. Levothyroxine should be started at 1.6 μg/kg/day in young and healthy adults for complete replacement. The detailed treatment algorithm for hypothyroidism is presented in **Flowchart 4**.

Treatment of Myxedema Coma

Myxedema coma is a metabolic thyroid emergency condition, and the suspected patients should be administrated intensive care therapy for vital pulmonary, respiratory, and cardiovascular support. The mortality rate could be from 25 to 60% in myxedema coma patients despite the best treatment. Hence, the treatment for suspected myxedema coma should be initiated immediately rather than waiting for laboratory confirmation. Due to lack of studies comparing the efficacy of different treatment regimens, deciding the optimal treatment is challenging. Successful treatment depends upon the timely diagnosis, prompt treatment with thyroid hormones (intravenous levothyroxine is preferred over oral), supportive therapy (appropriate fluid management and correction of hypotension and dyselectrolytemia), and administration of steroid supplement (hydrocortisone) until coexisting adrenal insufficiency is ruled out, along with the aggressive treatment of precipitating factors. The treatment of myxedema coma is detailed in **Flowchart 5**.

A push syringe should be used for the administration of intravenous levothyroxine in myxedema coma cases instead of the infusion tubes due to the risk of drug adherence to the polypropylene tubes resulting in ~40% decreased initial drug concentration. Thyroid function testing (T4 and T3) should be done every 1–2 days to check that T3 levels are not too high and therapy is working. Serum T3 and T4 levels can be improved prior to TSH normalization. Improvements can be observed in pulmonary, cardiovascular, renal and metabolic parameters within a week, and later the patient can be managed with oral T4 therapy alone.

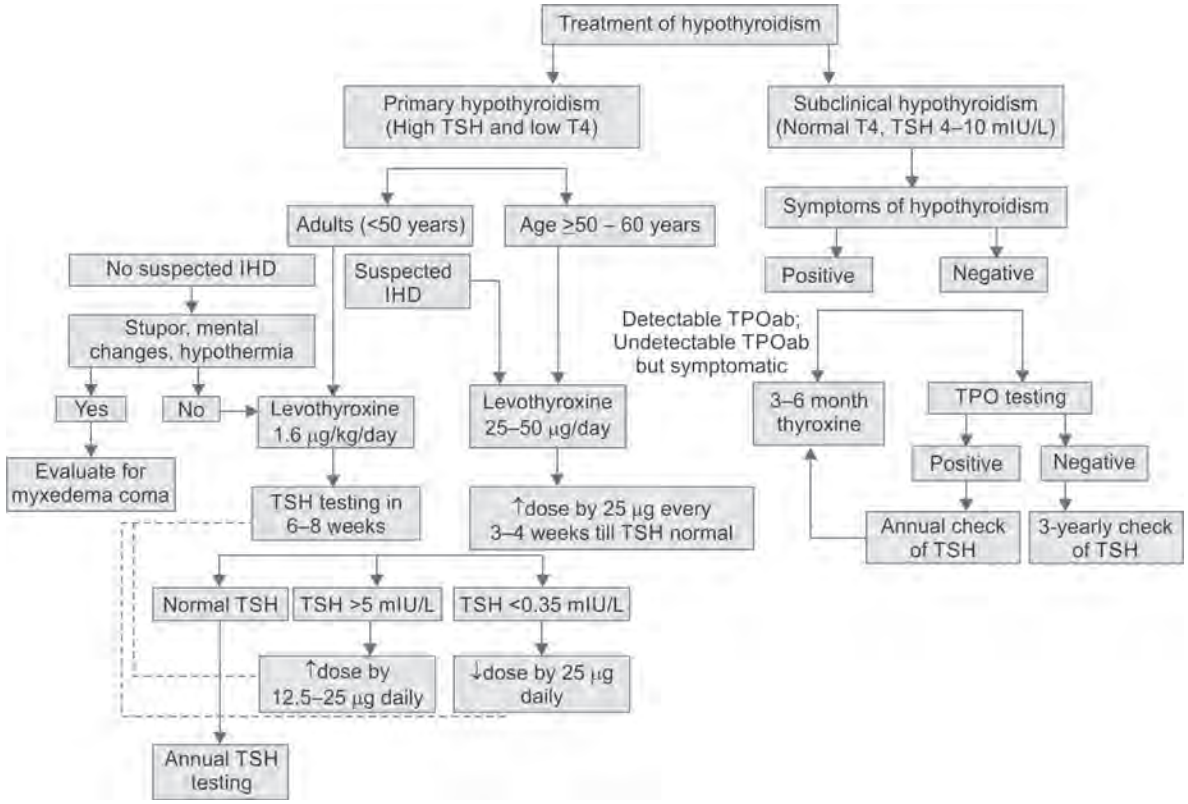
SUMMARY

Hypothyroidism, if not treated for prolonged duration, may lead to a potentially fatal disease condition myxedema coma, which is a rare but serious medical emergency. It is characterized by decreased mental status, hypothermia, hypotension, bradycardia, hyponatremia, hypoglycemia, and hypoventilation. In the case of suspected myxedema coma, serum thyroxine (T4) levels are generally low; TSH may be high for primary hypothyroidism or may be low, normal, or slightly high for central/secondary hypothyroidism. Determination of serum T4, TSH, and cortisol levels is recommended, however, the treatment of myxedema coma should be aggressively initiated in the ICU irrespective of the laboratory confirmation on thyroid levels. The treatment of myxedema coma comprises thyroid hormone therapy, supportive measures (mechanical ventilation, appropriate fluid replacement, correction of hypocortisolemia, hyponatremia, and hypothermia), and treatment of precipitating events (such as infections and gastrointestinal bleeding, etc.).

TABLE 2: Diagnostic criteria for myxedema coma.

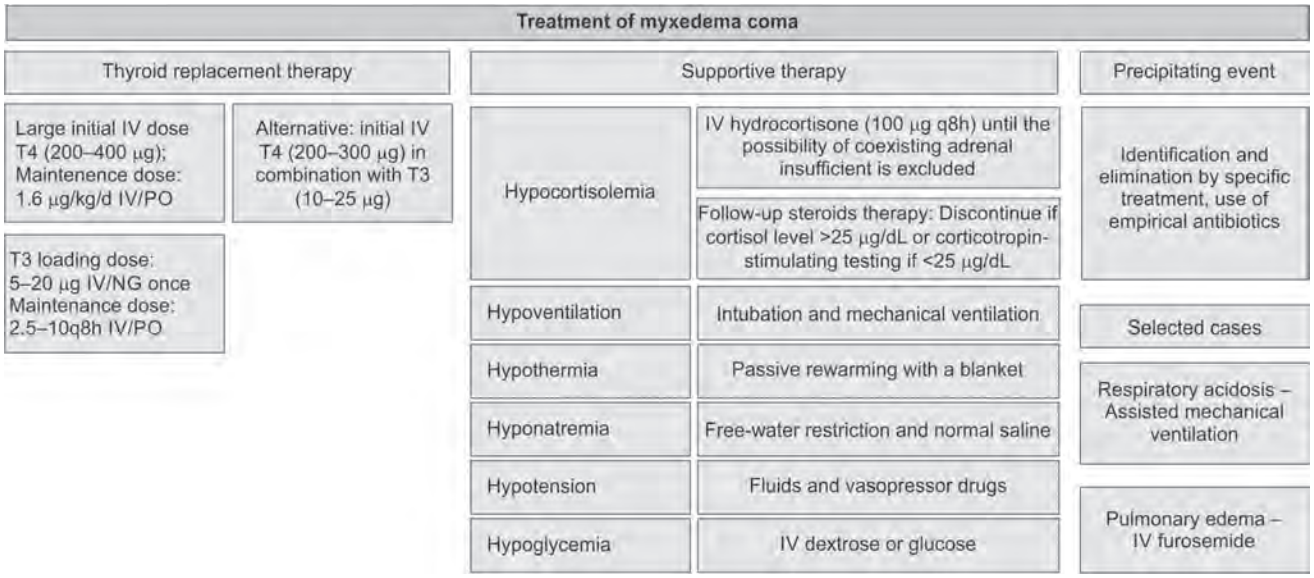
Parameter	1. Glasgow Coma Scale score				2. Thyroid-stimulating hormone (TSH) (mU/L)		3. Free T4 levels <0.6 ng/dL	4. Body temperature <95°F	5. Heart rate <60 beats/min	6. Precipitating event*
	0–10	11–13	14	15	>30	15–30				
Point	4	3	2	0	2	1	1	1	1	1
Scoring	Myxedema coma ≥7 points, likely 5–7 points, and unlikely <5 points									

*Burns, carbon monoxide retention, gastrointestinal hemorrhage, infection, sepsis, medications, stroke, surgery, trauma, etc.



(IHD: ischemic heart disease; TSH: thyroid-stimulating hormone; TPO: thyroid peroxidase; T4: thyroxine)

FLOWCHART 4: Treatment algorithm for hypothyroidism.


Treatment of myxedema coma
Thyroid replacement therapy
Supportive therapy
Precipitating event
Large initial IV dose T4 (200–400 µg); Maintenence dose: 1.6 µg/kg/d IV/PO
Alternative: initial IV T4 (200–300 µg) in combination with T3 (10–25 µg)
T3 loading dose: 5–20 µg IV/NG once Maintenance dose: 2.5–10q8h IV/PO
Hypocortisolemia
IV hydrocortisone (100 µg q8h) until the possibility of coexisting adrenal insufficient is excluded
Follow-up steroids therapy: Discontinue if cortisol level >25 µg/dL or corticotropin-stimulating testing if <25 µg/dL
Identification and elimination by specific treatment, use of empirical antibiotics
Hypoventilation
Intubation and mechanical ventilation
Selected cases
Hypothermia
Passive rewarming with a blanket
Hyponatremia
Free-water restriction and normal saline
Respiratory acidosis – Assisted mechanical ventilation
Hypotension
Fluids and vasopressor drugs
Hypoglycemia
IV dextrose or glucose
Pulmonary edema – IV furosemide

(IV: intravenous; PO: enteral)

FLOWCHART 5: Treatment of myxedema coma.

MULTIPLE CHOICE QUESTIONS

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131 CHAPTER

Hyperthyroidism—Graves' Disease and Thyroid Storm

Dheeraj Kapoor, Abhishek Goyal

INTRODUCTION

Graves' disease (the most common form of hyperthyroidism) is an autoimmune disorder of the thyroid gland leading to an overproduction of thyroid hormones. As a result of elevated levels of thyroid hormones T3 and T4, spectrum of disease varies from subclinical hyperthyroidism to thyrotoxicosis (hypermetabolic and life-threatening condition). Graves' disease was initially called "exophthalmic goiter", but later renamed after an Irish doctor Sir Robert Graves' who first described this condition in 1835. The autoimmune nature of the disease depends upon the complex interplay of both, the environmental and the genetic factors. Graves' disease has significant somatic and psychiatric symptoms which affect the overall quality of life with a significant increase in morbidity and mortality. The myriad of attributes of Graves' disease is an outcome of raised thyroid hormone levels. Thyrotropin receptors are activated by thyrotropin-stimulating immunoglobulins (TSIs) which leads to an over production of thyroid hormones and thus the symptoms. Treatment comprises of mitigation of symptom and amelioration of thyrotoxicosis.

EPIDEMIOLOGY

This is the most common cause of hyperthyroidism over the world with a peak incidence in the 3rd to 5th decade of life and a higher risk in women as compared to men. Annual incidence of Graves' ophthalmopathy is also more common in women as compared to men with a higher predominance in whites as compared to Asians. Associated morbidity advances with age. Graves'-associated ophthalmopathy typically occurs within a year of development of hyperthyroidism, but can occur even after a decade of the diagnosis of hyperthyroidism.

CLINICAL PRESENTATION

Since Graves' disease is an autoimmune disorder, signs and symptoms depend upon the prevailing autoimmunity and the degree of thyrotoxicosis. Presentation of Graves' disease rests mainly on the age at the onset of hyperthyroidism along with the severity and duration of thyrotoxicosis (**Table 1**). Generalized weakness, fatigue, listlessness, weight loss, intolerance to heat, and palpitations are the most common symptoms occurring in the majority of subjects. Cardiac symptoms occur more common in the elderly, who present with tachycardia and atrial fibrillation. Goiter can develop at any age but is more common in patients below the age of 60 years. Orbital signs indicate the presence of an active autoimmunity. Ophthalmopathy is disfiguring and may also endanger vision. Its clinical course follows a typical pattern from an active phase lasting up to 3 years to an inactive phase in which the symptoms stabilize. The combination of activity score and the severity of symptoms direct the treatment protocol.

Dermopathy occurs in only a small subset of patients with Graves' disease and is typically seen in those with orbitopathy. It is localized mainly to the pretibial area, but may also occur in areas with repeated trauma. Thyroid acropachy almost always occurs in patients with dermopathy and resembles clubbing of fingers and toes.

PATHOGENESIS

Secretion of thyroid hormones is a complex interplay of various stimulatory and inhibitory factors. thyrotropin-releasing hormone (TRH) produced by the hypothalamus stimulates the pituitary to release thyroid-stimulating hormone (TSH). This TSH then acts upon the thyroid follicles to secrete thyroxine (T4) and to some extent triiodothyronine (T3). Both T4 and T3 have an inhibitory effect on hypothalamus and pituitary. Synthesis of thyroid hormones is dependent upon dietary inorganic iodide absorbed by the intestine. This iodide is transported into the thyroid gland by iodine transporter where it is converted to iodine and gets bound to thyroglobulin by the enzyme thyroid peroxidase (TPO). This process results in the formation of monoiodotyrosine and diiodotyrosine which are coupled to form T3 and T4. These are stored along with thyroglobulin in thyroid follicles. Any process that leads to an increase in peripheral secretion of unbound thyroid hormone leads to signs and symptoms of thyrotoxicosis. Disturbance of this normal homeostatic mechanism can occur at the level of hypothalamus, pituitary, or the thyroid gland itself. TSIs stimulate the thyrotropin receptors leading to an

TABLE 1: Clinical features of hyperthyroidism (Graves' disease).

Signs of Graves' disease	*Symptoms of Graves' disease*	*Extrathyroidal physical signs*
• Loss of weight • Tachycardia and atrial fibrillation • Isolated systolic hypertension and wide pulse pressure • Heart failure • Moist warm skin, palmar erythema, and onycholysis • Loss of hair • Muscle weakness • Fine tremors, hyperreflexia, and hyperkinesia • Palpable goiter and thyroid bruit • Mood disorders (mania or depression)	• *General*: Fatigue, generalized weakness, weight loss, heat intolerance, and neck fullness • *Cardiovascular*: Palpitations and dyspnea • *Respiratory*: Dyspnea • *Neuromuscular*: Tremor, tiredness, fatigue, and muscle weakness • *Skeletal*: Pain in back • *Dermatological*: Warm moist skin, increased sweating, and pruritus • *Gastrointestinal*: Increased bowel frequency • *Eye*: Tearing, gritty eyes, pain, redness, and double vision • *Renal*: Increased thirst and polyuria • *Reproductive*: Menstrual irregularities in women and loss of libido • *Psychiatric*: Anxiety, nervousness, hyperactivity, irritability, and insomnia	• Ophthalmopathy: ○ Lid lag and lid retraction ○ Exophthalmos ○ Double vision ○ Periorbital chemosis, edema, and infection ○ Exposure keratitis ○ Orbital neuropathy • Localized dermopathy acropachy

overproduction of thyroid hormones, thereby abolishing the natural regulatory pathway of thyrotropin. To add to this insult immune cells such as T and B cells and antigen presenting cells produce interferon γ, interleukin (IL)-1β, 6, and 12, tumor necrosis factor-α (TNF-α), CD40 ligand, and other cytokines. Antithyroid drugs mitigate the effect of thyroid hormones thereby reducing the cytokine effect and thus attenuating the autoimmune process.

During the active phase of ophthalmopathy the orbit is impregnated with T and B cells along with CD34 + fibrocytes. These fibrocytes further transform into fibroblasts which in turn produce cytokines. These include IL-1β, 6, 8, and 16, TNF-α, regulated on activation, normal T-cell expressed and secreted (RANTES), and CD40 ligand; which consecutively activate orbital fibroblasts. TSI stimulate thyrotropin and insulin-like growth factor-1 (IGF-1) receptor complex, thereby presenting the inflammatory molecules and promoting glycosaminoglycan synthesis. Cytokine-activated fibroblast manufactures hyaluronan and other glycosaminoglycans, which augment the orbital tissue leading to proptosis and orbital nerve compression. In addition to this, the orbital fat also expands as an after effect of adipogenesis.

DIAGNOSIS

Serum TSH is usually the test of choice and when suppressed to unmeasurable levels (<0.05 μIU/mL) is a sensitive marker for the suspicion of thyrotoxicosis. Thorough history and clinical examination often provide valuable clues for the diagnosis of thyrotoxicosis which can be further confirmed by FT3 and FT4 levels. Diagnosis can be confirmed by the presence of TSH receptor antibodies, measured by enzyme-linked immunosorbent assay (ELISA), which has a high sensitivity and specificity of 98% and 99%, respectively as compared to anti-TPO antibodies, which are present in only 75% cases of Graves' disease. If antibody levels are inconclusive, radioactive iodine uptake (RAIU) can be helpful in differentiating various causes of thyrotoxicosis (**Flowchart 1**). In cases of subacute thyroiditis measurement of C-reactive protein (CRP) and erythrocyte sedimentation rate ESR are helpful. These are usually elevated. Electrocardiogram (ECG) is usually recommended to rule out arrhythmias. Interpretation of thyroid function test is given in **Table 2**.

Thyroid-associated Ophthalmopathy

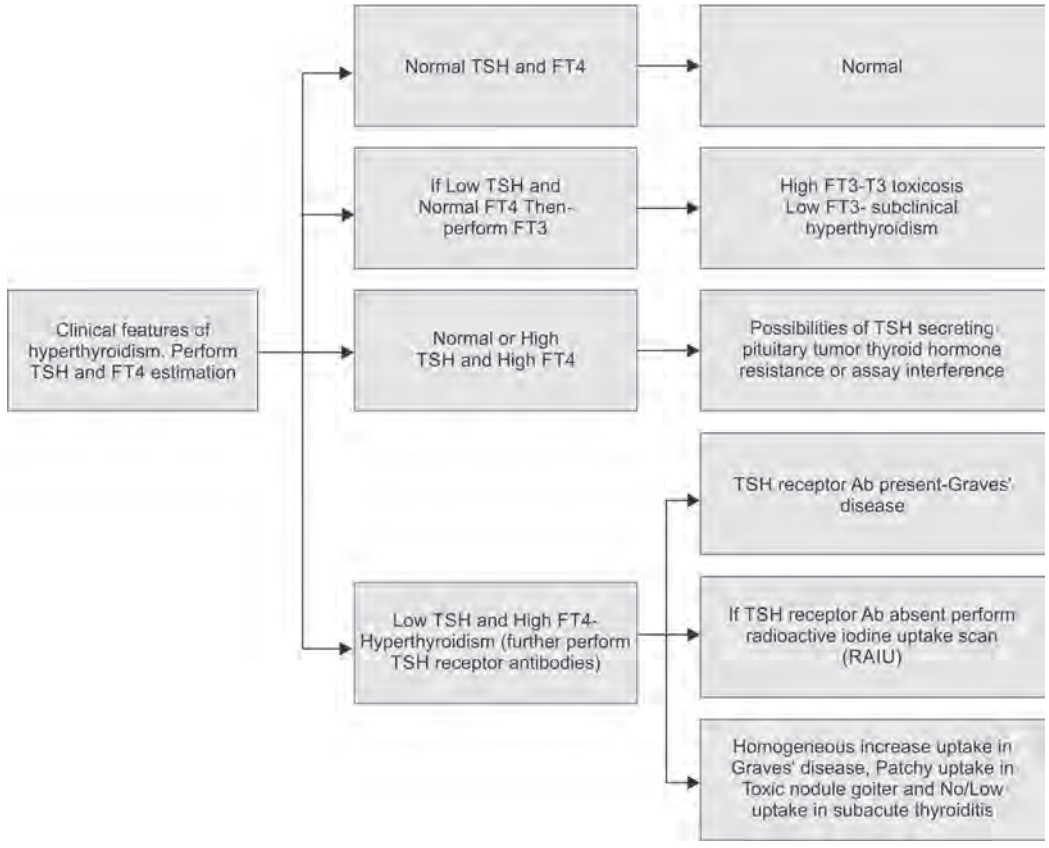
Imaging studies help in differentiating extraocular muscle enlargement from fat enlargement. CT and MRI imaging of orbit is advised when the cause of ocular presentation remains ambiguous. Orbital ultrasound, thermal imaging, scintigraphy with radiolabeled octreotide, and gallium scan may be a practical approach in accurately delineating the disease. Notably in cases of asymmetrical proptosis, excluding an orbital tumor or an artery venous malformation is critical. Estimation of activity and severity of ophthalmopathy by clinical evaluation is the corner stone in guiding treatment.

TREATMENT

Spontaneous remission has been reported in a small subset of patients. About 10–20% patients of Graves' disease develop auto immune hypothyroidism. Antithyroid drugs remain the therapies of choice in uncomplicated cases. Ablative therapy by way of radioiodine use or postsurgical thyroidectomy leads to hypothyroidism and which needs lifelong thyroxine replacement. Thus, each treatment approach has its own advantages and disadvantages which should be discussed in detail with the patient and the therapy be started only after proper counseling.

Symptomatic Relief

Beta-adrenergic blockers are advocated in most patients with symptomatic thyrotoxicosis, especially the elderly and those with a resting heart rate of >90 beats per minute or with another coexistent cardiovascular compromise. These drugs should preferably be avoided in patients with asthma. Alternatively, calcium channel blockers (e.g., verapamil and


Clinical features of hyperthyroidism. Perform TSH and FT4 estimation
Normal TSH and FT4
Normal
If Low TSH and Normal FT4 Then- perform FT3
High FT3-T3 toxicosis
Low FT3- subclinical hyperthyroidism
Normal or High TSH and High FT4
Possibilities of TSH secreting pituitary tumor thyroid hormone resistance or assay interference
Low TSH and High FT4- Hyperthyroidism (further perform TSH receptor antibodies)
TSH receptor Ab present-Graves' disease
If TSH receptor Ab absent perform radioactive iodine uptake scan (RAIU)
Homogeneous increase uptake in Graves' disease, Patchy uptake in Toxic nodule goiter and No/Low uptake in subacute thyroiditis

(FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone)

FLOWCHART 1: Evaluation of patient with hyperthyroid features.

TABLE 2: Interpretation of thyroid function test.

TSH	*Free T4*	*Free T3*	*Interpretation*
Normal	Normal	Normal	None
Low	High	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Low	Normal	High	T3 toxicosis
Low	High	Normal	Thyroiditis, T4, ingestion, and hyperthyroidism in older adults or in comorbid conditions
Low	Low	Low	Euthyroid sick syndrome and central hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism recovery from euthyroid sick syndrome

(T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone)

TABLE 3: Thyroid inhibitors.

Inhibit hormone synthesis (antithyroid drugs)	Propylthiouracil, carbimazole, and methimazole
Inhibit iodide trapping (ionic inhibitors)	Thiocyanates (–SCN), perchlorates ($–ClO_4$), and nitrates ($–NO_3$)
Inhibit hormone release	Iodine, iodides of Na and K, and organic iodide
Destroy thyroid tissue	Radioactive iodine (I131, I125, and I123)

diltiazem) can also be used in such cases. Anticoagulation is also recommended in patients with thyrotoxicosis presenting with atrial fibrillation.

Therapy

Antithyroid drugs (**Table 3**), surgery, and radioactive iodine have been used over the world by endocrinologists as per their preference and local guidelines while suiting their patient's profile.

Carbimazole and its active metabolite methimazole are the most preferred antithyroid drugs due to ease of once daily usage and a long half-life which leads to a rapid control of symptoms. These drugs act by inhibiting the synthesis of thyroid hormone by blocking oxidation of iodine in the thyroid gland. They are metabolized by the liver and excreted in urine. These are category D drugs and hence not recommended for use in pregnancy; because of secretion in breast milk it is advisable to use these with caution while nursing.

However the American Academy of Pediatrics and the American Academy of Family Physicians consider it to be safe. Methimazole is usually started at 5–15 mg twice daily, going up to 30 mg BID in patients who are toxic and has a maintenance dose of 5–10 mg daily as per the requirement.

Propylthiouracil also inhibits the synthesis of thyroid hormones by blocking oxidation, and when given in high doses, also blocks the 5' deiodinase enzyme which converts

thyroxine to triiodothyronine. It is metabolized by the liver and excreted in urine (35%) and is to be administered 8–12 hourly. It is marked Category D in pregnancy and distributed in breast milk; hence is believed to be contraindicated by some authorities. It is the treatment of choice just before and during the first trimester of pregnancy because methimazole administration during first trimester has been associated with congenital malformations.

This drug is usually initiated at doses of 100–150 mg every 8 hourly which can later be reduced to 50 mg twice or thrice daily as per clinical and biochemical response.

Most patients with Graves' disease achieve euthyroid status within 6–8 weeks of treatment. But some patients with a large goiter, severe hyperthyroidism or with a recent exposure with radioiodine may need to be treated for longer with higher doses. Once euthyroid is achieved, either of the two regimens may be followed. The first is the "block and replace" regimen in which the dose of thionamide is kept constant and later levothyroxine is added to maintain euthyroid. In the second, "titration" regimen, the dose of thionamide is progressively lowered till euthyroid is achieved. Approximately 50% patients treated for 6–18 months go into remission, after which these drugs can be safely stopped with a close monitoring of thyroid function at 4–6 weeks to detect early relapse. In case of relapse where surgery or radioiodine is not an acceptable option, a long-term small dose of thioamide should be considered.

The most common side effect encountered with thionamide use is a pruritic rash which is usually transient. Another rare but important side effect is agranulocytosis which presents with fever, cough, sore throat, or mouth ulcers. All patients being started on these medications should be explained in detail by both written and oral communication that in case of these symptoms they should immediately report to their physician.

Radioactive Iodine Treatment

Radioiodine is administered in a capsule or liquid form which is quickly absorbed by the thyroid gland resulting in thyroid-specific inflammatory response resulting in fibrosis and destruction of the gland over a period of 6 sweeks to 6 months. Iodine 131 is used in doses of 370–550 MBq; now the trend is towards giving a fixed dose which is effective in rendering 70–90% patients euthyroid or hypothyroid rather than individualizing each patient. It is the treatment of choice in patients with toxic multinodular goiter, solitary toxic nodule, Graves' disease, or side effects of antithyroid medication. Pregnancy and breastfeeding are absolute contraindications and it is advisable not to use it in patients with thyroid ophthalmopathy because of the risk of worsening. Post treatment patients are warned not to conceive for at least 6 months after radio ablation and avoid close contact with pregnant females and young children for at least 3 weeks.

Thyroid Surgery

Total or near total thyroidectomy is the treatment of choice in patients who have relapsed after medical management, having large goiter (for cosmetic reasons), women who want to conceive shortly after completion of treatment, and in patients who want to avoid antithyroid drugs or radiation exposure. Women who undergo surgery should wait for stabilization of TSH levels and replacement thyroxine therapy should be started before they attempt conception.

Treatment of ophthalmopathy depends upon the phase and severity of the disease. Most patients require only conservative measures for maintenance of ocular surface moisture and enhancement of tear film. But a small subset who has a symptomatic eye-threatening disease benefit from intravenous pulse glucocorticoid therapy. External beam radiotherapy in combination with intravenous pulse glucocorticoid therapy has better effects than when used alone. Orbital decompression is reserved for patients who have developed optic nerve neuropathy.

THYROID STORM

Thyroid storm is unrecognized, undertreated, and life-threatening form of severe thyrotoxicosis. Thyroid storm is rare and mostly acute reaction to thyroid and nonthyroid surgery, trauma infections, contrast media, amiodarone, and after delivery in preexisting hyperthyroidism. Other risk factors are acute coronary syndrome, pulmonary embolism, and diabetic ketoacidosis. Prompt recognitions and treatment is warranted as mortality is almost 100%. Causes of mortality in patient of thyroid storm are sepsis, multiorgan failure, congestive heart failure, arrhythmias, and disseminated intravascular coagulation. Clinical features of thyroid storm are typical and include hyperpyrexia, out of proportion tachycardia, altered mental status (agitation and delirium coma) along with clinical picture of hyperthyroidism. Management of thyroid storm is summarized in **Table 4**.

TABLE 4: Management of thyroid storm.

Beta-adrenergic blockers	• Propranolol 60–80 mg orally every 4 h [intravenous (IV) 0.5–1.0 mg as test dose then repeat 1–2 mg every 15 min till desired effect then 1–2 mg every 3 h] or • Metoprolol 25–50 mg orally every 6 h or • Esmolol 50–100 µg/kg/min infusion
Inhibition of thyroid hormone synthesis	Propylthiouracil 500–1,000 mg loading then 250 mg every 4 h or methimazole 60–80 mg/day
Inhibition of thyroid hormone release	• Saturated potassium iodide solution (50 mg/drops) 1–2 drops orally or per rectally or • Lugol's solution (8 mg iodide/drops) 5–7 drops
Corticosteroid	Hydrocortisone 300 mg IV then 100 mg every 8 h
Treatment of underlying precipitant	Empirical antibiotics
Supportive measures	Volume resuscitation cooling blankets and fan ice packs/lavage
Others	Lorazepam and diazepam

SUMMARY

In Graves' disease, timely recognition of signs and symptoms followed by adequate supportive care and thyroid-specific therapy is necessary to alleviate the associated risk along with morbidity and mortality. This being the most common cause of hyperthyroidism and remains to be a hot topic for research and evidence-based recommendations. With the advent of newer diagnostic and genomic tools which help in understanding the pathophysiology better, scientists are now more focused on developing agents that block the thyrotropin and IGF-1 receptors, thereby improving the quality of life and at the same time improving the longevity as well. With the knowledge of the dominant antigen of Graves' disease, there stands a chance for antigen-specific therapy. Establishing better immune resilience against thyrotropin receptor is the eventual intention. Evaluation of patient with hyperthyroid features is summarized in **Flowchart 1**.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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132 CHAPTER

Acute Adrenal Crisis

Dheeraj Kapoor, Abhishek Goyal

INTRODUCTION

Acute adrenal crisis is a life-threatening medical emergency which responds to supra physiologic glucocorticoid doses. Its initial presentation can be in form of nausea, vomiting, and abdominal pain with unexplained refractory shock not responding to fluid and pressor support. This is a clinical presentation of glucocorticoid deficiency with or without deficiency of mineralocorticoid and adrenal androgens.

Adrenal crisis is the most accepted representation of adrenal insufficiency (AI) with infections being the major precipitating cause. Primary AI is most commonly caused by autoimmune adrenalitis whereas hypothalamic–pituitary tumors most commonly present as secondary AI.

In this chapter we discuss in detail about various aspects of acute adrenal crisis with emphasis on diagnosis and management of this disorder.

Thomas Addison in 1855 described the classical symptoms of AI as fatigue, anorexia, generalized weakness, weight loss, orthostatic hypotension, and salt craving with hyperpigmentation as the primary symptoms. It was considered fatal till 1949 when cortisone was found and glucocorticoid replacement started. Still so many years passed by but this disorder has always been a challenge in diagnosis and treatment. Acute adrenal crisis mimics to several emergencies due to its nonspecific presentation so emergency physician should consider this entity as important differential diagnosis if high index of suspicion on the basis of history, physical examination, and laboratory findings. For effective management of acute adrenal crisis understanding about basic physiology of adrenal gland, pathophysiology, etiology, and therapy are described in this chapter.

BASIC ANATOMY AND PHYSIOLOGY OF THE ADRENAL GLAND

Adrenal gland is capsulated retroperitoneal organ divided *into two zones; (i) outer part known as adrenal cortex, and (ii) outer adrenal medulla.* Adrenal cortex further subdivided in to three zones: (1) *Zona fasciculata* which secretes glucocorticoid (cortisol), (2) *Zona reticularis* secretes the dehydroepiandrosterone acetate (DHEA) which is the intermediate metabolite for sex steroids androgen and estrogen. *Zona glomerulosa* secretes mineralocorticoids (aldosterone), and (3) *Adrenal medulla* secretes catecholamines, epinephrine, and norepinephrine. Important functions of adrenal hormone are summarized in **Table 1**.

Glucocorticoid (Cortisol)

Cortisol is important for normal functioning of all tissues. Cortisol gives cardiovascular stability by maintaining adequate circulatory volume, cardiac contractility, and vascular tone thus stimulate cardiac function. Cortisol enhances the action of catecholamines, epinephrine, and norepinephrine. Release of vasodilators from endothelium is also reduced by cortisol. Thus, cortisol deficient patient present with circulatory collapse/shock which is the hallmark of acute adrenal crisis. Glucocorticoid are important for glucose lipid and protein metabolism and regulate energy storage and utilization. Thus, in glucocorticoid deficient patient loss of appetite weight loss and cachexia are present. Glucocorticoid also facilitate healing of damaged tissue due to its anti-inflammatory action and its absence or deficiency results

TABLE 1: Important functions of adrenal hormone.

System	*Physiological response*
Cardiovascular	Maintain cardiac contractility cardiac function and vascular tone thus provide cardiovascular stability
Endocrine	Inhibit insulin secretion and epinephrine synthesis
Inflammatory	Maintain inflammatory homeostasis, anti-inflammatory action of cortisol, reduce circulating leukocyte and cytokines response, eosinophils, and lymphocytes
Metabolic	Gluconeogenesis lipolysis, muscle protein catabolism, and raise plasma glucose during stress
Renal	Increase in glomerular filtration rate (GFR)

in increase in inflammation and patient present with fever, arthralgia, myalgia, and lethargy. Cortisol release is controlled by hypothalamic–pituitary–adrenal axis (HPA axis) and released during trauma, infection, and stress (**Fig. 1**).

Mineralocorticoid (Aldosterone)

Main function of aldosterone is sodium reabsorption in exchange of potassium at the level of distal convoluted tubule and maintain sodium, potassium, and water balance. Thus, aldosterone deficiency cause sodium loss and potassium retention and rapid loss of salt and water during vomiting and diarrhea leads to coma or death. Aldosterone release is regulated by renin–angiotensin–aldosterone system. Hypotension, hemorrhage, low perfusion pressure, volume depletion, and sodium loss are the trigger factors for renin release (**Fig. 2**).

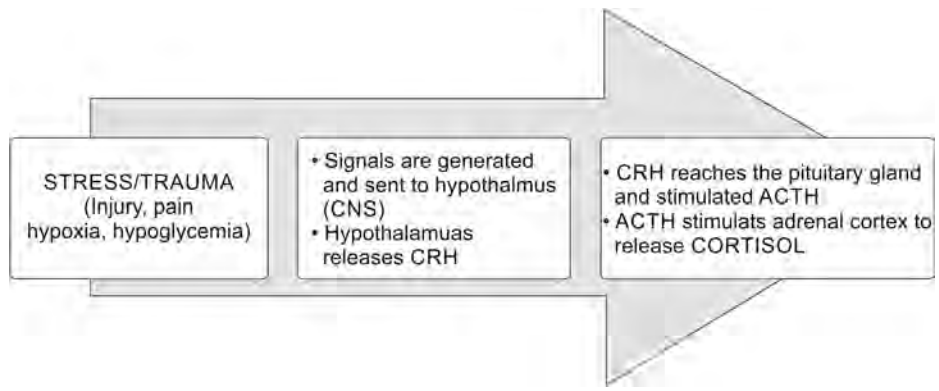
CLASSIFICATION

After understanding the basics about anatomy, physiology, and function of adrenal gland, the one point is clear that adrenocortical hormone deficiency results in reversal of these hormonal effect and produce acute adrenal crisis. Hormone of importance in acute adrenal crisis is cortisol. *AI can be classified on the basis of mechanism into primary, secondary, and tertiary*. Primary AI results from disease inherent to adrenal cortex. Central AI being the collective name for secondary and tertiary resulting due to defective production or action of corticotropin. Secondary AI is a result of pituitary disease that affect the release of corticotropin or prevent its action on adrenal cortex. Tertiary AI is a result of defective synthesis or action of corticotropin-releasing hormone (CRH) and/or vasopressin from hypothalamus which in turn affects the synthesis of corticotropin.

PATHOPHYSIOLOGY

Adrenal cortex is divided into three distinct zones which secrete hormones under the direct feedback control of pituitary and hypothalamus. Zona glomerulosa, the outermost zone secretes aldosterone which is primarily regulated by renin–angiotensin system and extracellular potassium concentration. Hence, the secretion of aldosterone is not affected in secondary and tertiary AI. Zona fasciculata secretes cortisol under the feedback control of anterior pituitary, which produces corticotropin, which in turn is regulated by hypothalamic CRH and vasopressin. The innermost zone, zone reticularis produces androgens, dehydroepiandrosterone, and androstenedione.

The pathophysiology of adrenal crisis has till now only been deciphered to a limited extent. Development of hypotension can be elucidated to lack of permissive action of glucocorticoid on adrenergic receptors and by volume


STRESS/TRAUMA
(Injury, pain
hypoxia, hypoglycemia)
• Signals are generated and sent to hypothalmus (CNS)
• Hypothalamuas releases CRH
• CRH reaches the pituitary gland and stimulated ACTH
• ACTH stimulats adrenal cortex to release CORTISOL

(ACTH: adrenocorticotropic hormone; CNS: central nervous system; CRH: corticotropin-releasing hormone)

FIG. 1: Response of hypothalamic–pituitary–adrenal axis to stress and trauma.

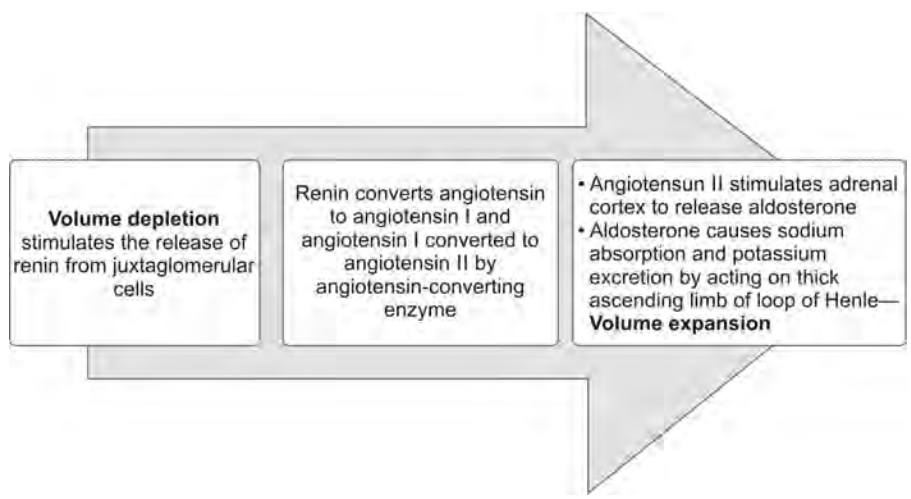

Volume depletion
stimulates the release of renin from juxtaglomerular cells
Renin converts angiotensin to angiotensin I and angiotensin I converted to angiotensin II by angiotensin-converting enzyme
• Angiotensun II stimulates adrenal cortex to release aldosterone
• Aldosterone causes sodium absorption and potassium excretion by acting on thick ascending limb of loop of Henle—**Volume expansion**

FIG. 2: Response of renin–angiotensin–aldosterone system to volume depletion.

loss due to paucity of sodium and water retention because of missing mineralocorticoid activity. Vomiting and diarrhea aggravate the situation further. Reduced cortisol surge during infection leads to a mismatch between the permissive and suppressive action of glucocorticoids, thereby enhancing the release of proinflammatory cytokines and increased sensitivity to harmful outcome of cytokines [e.g., tumor necrosis factor (TNF) alpha]. Moreover, glucocorticoid receptor function is impaired by proinflammatory cytokines thereby aggravating glucocorticoid deficiency. In cases of adrenal crisis precipitated by surgery or emotion stress, the basic process of execution remains same with the release of cytokines and TNF alpha and glucocorticoid resistance.

CAUSES

After understanding the basics about anatomy, physiology, and function of adrenal gland the one point is clear that adrenocortical hormone deficiency results in reversal of normal physiologic hormonal effect and which in response produces acute adrenal crisis. Hormone of importance in acute adrenal crisis is cortisol. Causes of AI are summarized in **Box 1**.

BOX 1: Causes of adrenal insufficiency.

Causes of primary adrenal insufficiency

- Autoimmune adrenalitis: Isolated or associated with autoimmune polyendocrinopathy syndrome type 1, 2, and 4
- Infections (tuberculosis, human immunodeficiency virus, syphilis, and histoplasmosis)
- Bilateral adrenal hemorrhage/metastasis/infiltration
- Bilateral adrenalectomy
- Drug induced (anticoagulants, ketoconazole, phenytoin, rifampicin, and phenobarbital)
- Genetic disorders: Adrenoleukodystrophy, congenital adrenal hyperplasia, and adrenal hypoplasia congenita
- Familial glucocorticoid deficiency

Causes of secondary adrenal insufficiency

- Pituitary tumor or trauma (adenomas, cysts, meningiomas, and rarely carcinomas)
- Pituitary surgery or irradiation
- Pituitary infiltration or infection (tuberculosis, meningitis, sarcoidosis, and actinomycosis)
- Pituitary apoplexy
- Genetic disorders: Congenital proopiomelanocortin deficiency and Prader–Willi syndrome

Causes of tertiary adrenal insufficiency

- Hypothalamic tumor (craniopharyngiomas or metastasis from breast or lung cancer)
- Hypothalamic surgery or irradiation
- Infection or infiltration (tuberculosis, meningitis, sarcoidosis, and actinomycosis)
- Trauma and injury (skull base fracture)
- Chronic endogenous glucocorticoid hypersecretion (Cushing's syndrome)
- Drugs (glucocorticoids, mifepristone, antipsychotics, and antidepressants)

Tuberculosis

Tuberculosis had been the leading cause of primary AI during the early part of 20th century, but now for past 50 years and more it is autoimmune AI which has become more common. Primary AI can affect all age groups with 30–50 years being most commonly affected and a predisposition for female gender. Secondary AI being more common than primary also has a predisposition for women with the peak age of diagnosis in sixth decade of life. Tertiary AI is a result of long-term exposure to glucocorticoids which leads to sustained suppression of hypothalamic secretion of CRH. Various studies in patients of AI on chronic replacement therapy have reported an incidence of 5–10 adrenal crisis/100 patient years with a proposed mortality from adrenal crisis to an extent of 0.5/100 patient years. Strikingly it has been observed that there is a huge variation in the occurrence of crisis, as some do not experience it for decades while other patients have reported recurrent adrenal crisis, the reason for same is still unknown.

Adrenal Hemorrhage and Infarction

Adrenal glands do not have direct arterial blood supply so they are more prone for infarction and damage during systemic hypotension. Adrenal cortex receives the blood supply from subcapsular arteriolar plexus. Bilateral massive adrenal hemorrhage (BMAH) occurs under severe stressful conditions such as myocardial infarction, severe sepsis with shock, trauma, burn, surgery, and complicated pregnancy. Coagulopathy, thrombocytopenia, and anticoagulants are also responsible for adrenal hemorrhage. Adrenal infarction is common in sepsis by meningococcemia, *Pseudomonas*, *Escherichia coli*, and *Staphylococcus* infections.

Sudden Discontinuation of Long-term Glucocorticoid Therapy

Risk of acute adrenal crisis is more in patient who is on long-term glucocorticoid therapy due to underlying adrenal atrophy and adrenocorticotropic hormone (ACTH) suppression. Adrenal crisis can occur with single use, topical preparation, and even with inhaled steroid.

CLINICAL PRESENTATION

The clinical features in AI depend on the rate of outset and severity of adrenal deficiency, with the preclinical course sometimes ranging up to years even in presence of metabolic derangements, high antibody titers, and raised corticotropin. In patients with undiagnosed AI, there is a typical history of declining health over weeks to months with increasing exhaustion in day-to-day activities, anorexia, and weight loss.

Symptoms in patients with primary AI is due to deficiency of all adrenocortical hormones (glucocorticoid, mineralocorticoid, and androgens), this being in contrast to those with secondary AI who have an intact renin–angiotensin–aldosterone system. This explains the difference in clinical presentation of these conditions due difference in salt and water balance. A specific sign of primary AI, seen in chronic cases, not acute which differentiates it from secondary AI is the presence of hyperpigmentation on pressure points (elbows and knuckles), palmar creases, axillae, nipples, and mucous membranes (buccal, vaginal, and anal). This is caused due

to increase stimulation of melanocortin 2 receptor by ACTH itself. Sign and symptoms of secondary and tertiary AI is due to deficiency of glucocorticoids only along with the underlying primary disorder causing it. Hyponatremia and volume expansion is usually secondary to disproportionate increase in vasopressin release. Clinical manifestation of other anterior pituitary hormones may also persist.

Acute adrenal crisis is usually triggered by a stressful episode (e.g., infection, physiological stress, surgery, or trauma). Customarily a patient presents with nausea, vomiting, abdominal pain, severe hypotension, and hypovolemic shock. They are exhausted, lack on energy and are depressed, these symptoms being frequently misdiagnosed as gastroenteritis. Fever is usual as most of the cases are triggered by an infection. This being a life-threatening medical emergency requires immediate management, and in cases of undiagnosed crisis treatment comes first rather than going for biochemical confirmation of disease. It is imperative to differentiate between Addison's disease and acute adrenal crisis in which the latter presents as vomiting, abdominal pain, and hypovolemic shock. This is a rare disease but can be life-threatening when overlooked. Clinical and laboratory features of the AI and acute adrenal crisis are summarized in **Table 2**.

DIAGNOSIS

Adrenal crisis is endocrine emergency and should be considered in acutely unwell patient with profound unexplained circulatory shock. Severity is depend on level of defect, primary or secondary etiology (HPA axis). Initial diagnosis is completely based on clinical evaluation. Detailed history, physical examination, and investigation are helpful in evaluating the patient (subacute and chronic symptoms) in outpatient department, but not very helpful in emergency department. High index of suspicious is important for diagnosis of adrenal crisis in emergency department. Emergency physician should start the empiric treatment immediately even before receiving the confirmatory laboratory results. One may not get classic laboratory results in acute adrenal failure like adrenal hemorrhage.

CONFIRMATORY DIAGNOSTIC TESTING

Patient with all form of adrenal deficiency have low cortisol level. Low serum cortisol level and inadequate response to stimulation test confirm the diagnosis.

- First step is early morning serum cortisol <3 μg/dL confirm the adrenal deficiency while diagnosis is doubtful when cortisol level >15 μg/dL.
- Second step is to find out if cortisol deficiency is due to ACTH or CRH deficiency, give 250 μg of synthetic ACTH (cosyntropin) and measure the serum cortisol if serum cortisol >8 μg within 30 minutes, considered normal response, and exclude primary adrenal deficiency, but basal corticotropin level are required to differentiate between primary and secondary adrenal deficiency. Corticotropin level are high in primary and low or normal in secondary adrenal deficiency. Insulin tolerance test is test of choice for suspected secondary adrenal failure.
- But in emergency department and in crisis situation both above method of diagnosis, early morning cortisol level and stimulation test are not practical, random serum cortisol level >34 μg/dL exclude the adrenal deficiency while random cortisol level below 15 μg/dL in patient with severe sepsis or shock suggestive of acute adrenal crisis.

Other Investigations

Few more laboratory test, radiology is required to identify the treatable cause (sepsis) of acute adrenal failure. CT abdomen can be done to find out tuberculosis-associated calcification, adrenal hemorrhage, and infiltration while CT head may give clue to destruction of pituitary gland (empty sells syndrome).

TABLE 2: Clinical and laboratory features of adrenal insufficiency.

	Primary adrenal insufficiency	***Secondary adrenal insufficiency***
Clinical features	• Hyperpigmentation, vitiligo, weight loss, hypotension, postural dizziness, and syncope shock • Weakness, fatigue, myalgia, arthralgia, anorexia, vomiting, constipation, abdominal pain, and diarrhea • Amenorrhea infertility salt craving • Depression psychosis	• Weight gain, thin axillary and pubic hair, decreased libido, infertility, and amenorrhea • Weakness fatigue • Headache visual disturbances, anorexia, vomiting, constipation, abdominal pain, diarrhea, myalgia, arthralgia • Depression and psychosis
Laboratory features	Hyponatremia, hyperkalemia, hypochloremia, and acidosis mildly elevated BUN, mild hypoglycemia, anemia, B12 deficiency, and type 1 diabetes mellitus	Hypernatremia or hyponatremia, hypokalemia or normal potassium, normal serum chloride, normal BUN, and marked hypoglycemia
Risk of acute adrenal crisis	Very high	Low
• Clinical features of acute adrenal crisis • Circulatory shock is the hallmark of acute adrenal crisis (hypotension shock tachycardia) • Fever, fatigue, dehydration, arthralgia, myalgia, nausea, anorexia, vomiting, poor concentration, depression, disorientation, abdominal pain (rebound tenderness and rigidity), flank pain, back pain, and lower chest pain		

(BUN: blood urea nitrogen)

EVALUATION AND MANAGEMENT IN EMERGENCY DEPARTMENT

Upon presentation of a patient in emergency room with a suspicion of having adrenal crisis, collecting a comprehensive history is the first step towards assessments of the condition. A brief analysis of his previous medical and surgical history with an emphasis on present medication and steroid use with sudden withdrawal is indispensable. Determining any triggering factors and gathering history about other autoimmune disease is imperative. Classical laboratory abnormalities may affirm the diagnosis to some extent. The findings reveal hyponatremia, hyperkalemia, and hypoglycemia. An electrocardiogram may have abnormalities with an indication of cardiomyopathy. At this point of time empiric treatment for adrenal crisis can be started consists of following points.

Empiric Treatment for Adrenal Crisis before Confirm Laboratory Results

- Hydrocortisone is drug of choice, it has both glucocorticoid and mineralocorticoid properties
- Empiric antibiotics can be started depending on underlying conditions
- Fresh frozen plasm to reverse coagulopathy
- Hyperkalemia should be corrected
- Thyroxine supplementation requirement in primary HPA axis failure (clinical hypothyroidism)
- Correction of dehydration and hypoglycemia
- Vasopressors

Treatment of adrenal crisis condition is straight forward with parenteral administration of 100 mg of hydrocortisone intravenously as bolus along with correction of hypovolemia with 1,000 mL of isotonic saline within first 1 hour, followed by 50–100 mg hydrocortisone in 5% dextrose every 6 hourly intravenously or intramuscularly depending on age and body surface area. In case hydrocortisone is not at disposal, then any other synthetic glucocorticoid like prednisolone can be used in proportionate doses. Baseline blood samples such as cortisol, ACTH, and blood cultures should be drawn before initiation of therapy. In addition to this, aggressive fluid and vasopressor support should be started under continuous cardiac monitoring. Basis the intercurrent condition which triggered the crisis antibiotics and antithrombotic are initiated. Depending upon severity of condition patient should be admitted then to intensive care setting for further workup and management. Serum electrolytes and blood glucose levels should be watchfully checked every 4–6 hours until stabilized. Once patient is stable intravenous glucocorticoid can be tapered and oral maintenance dose started.

Long-term hormone replacement therapy should be initiated once patient is recovered from crisis, intravenous steroid should be changed to oral preparation and prednisolone with longer half-life is required only once daily. Fludrocortisone (mineralocorticoid) is usually given in patient with primary adrenal failure. Androgen transdermal DHEA 25–50 mg is also added for primary adrenal failure.

This treatment regimen to treat hypotension with correction of electrolyte and cortisol imbalance is essentially constant leading to improvement in symptoms within 24 hours. In case recovery in not as progressive as anticipated then other causes of illness (severe sepsis with shock) should be reconsidered. Treatment guidelines for acute adrenal crisis are summarized in **Table 3**.

PREVENTION AND PATIENT EDUCATION

A sizeable morbidity and mortality associated with adrenal crisis can be averted by befitting physician and patient education. As most clinicians rarely see adrenal crisis, they fail to act satisfactorily. Education should emphasize on the endogenous cortisol rhythm and its swift acclimatization to unforeseen demands, limitations of parenteral cortisol administration and its constraint in imitating the natural response. Though it is difficult to predict the oncoming episode of crisis every time still it is wise to be prepared in stressful medical conditions events such as illnesses and elective surgeries with adequate dose adjustments. Suggested dose modifications intent to have a ceiling effect as should happen during a natural deviation in case of a euadrenal patient during the similar episode. This approach to cortisol overload is momentary and does not carry major adverse effects. Corticosteroid dose adjustment guidelines in nonsurgical and surgical situation are summarized in **Tables 4** and **5**.

TABLE 3: Treatment guidelines for acute adrenal crisis.

Fluid resuscitation	At least 2–3 L of normal saline to restore volume and normal sodium balance
Intravenous steroids	Intravenous hydrocortisone 100 mg bolus followed by 100 mg two or three times per day (300–400 mg daily is initial regimen)
Antibiotics	Broad-spectrum antibiotics for febrile patients
Vasopressors	In case of refractory shock
Glucose	50% dextrose may be used, if required
In stabilized patient	• Oral prednisolone fludrocortisone and androgen replacement • Patient education regarding steroid management during acute febrile illness (double the dose of steroid for 3 days) and regular follow-up with physician

TABLE 4: Dose adjustment during nonsurgical procedures in patients of adrenal insufficient for prevention of crisis.

Episode	*Dose adjustment*
Acute febrile illness	Double or triple the daily oral glucocorticoid dose basis the temperature surge, higher the temperature higher the dose adjustment
Significant emotional stress (e.g., major examination)	Add 10–20 mg hydrocortisone or steroid equivalent to regular replacement dosage
Significant physical stress (e.g., intense exercise)	Add 10–20 mg hydrocortisone 30 min before exercise
Acute gastroenteritis/ serious infection (e.g., pneumonia)	Early parenteral hydrocortisone 100 mg then repeat every 6–12 hourly until recovery

TABLE 5: Dose adjustment during surgical procedures in patients of adrenal insufficient for prevention of crisis.

Episode	*Dose adjustment*
Minor outpatient department (OPD) procedure	No adjustment needed, can add extra 20 mg of oral hydrocortisone postprocedure if symptoms suspected
Dental procedure under local anesthesia	Repeat morning dose 1 h before procedure, then continue with double the oral dose for 24 h, thereafter return to normal dose
Minor surgery or major dental surgery under general anesthesia	100 mg hydrocortisone administered parenterally before anesthesia or as infusion during the surgery, postoperatively then continue with double the oral dose for 24 h, thereafter return to normal dose
Major surgery	Start with infusion of hydrocortisone (100 mg over 12 h) just before anesthesia and continue till nil per os, postoperatively then continue with double the oral dose for 48 h, thereafter return to normal dose
Labor and vaginal delivery	Start with infusion of hydrocortisone (100 mg over 12 h) just at the onset of labor and continue till delivery of child, postoperatively then continue with double the oral dose for 48 h, thereafter return to normal dose
Invasive bowel procedure requiring bowel preparation with laxatives	Admit in hospital overnight and start hydrocortisone 100 mg parenterally at the time of bowel preparation along with intravenous fluids, repeat hydrocortisone just before the procedure. Postprocedure continue with double the oral dose for 24 h, thereafter return to normal dose

Every patient should be educated for compliance to hydrocortisone therapy and to carry an emergency card with an emergency set containing 100 mg of hydrocortisone injection for parenteral administration. Patient and their relatives should be well trained about the use of injection in case of emergency. The treating physician should emphasize that in case of crisis sometimes the physical and cognitive impairment can act as a barrier for self-intramuscular injection hence a subcutaneous route can be preferred then. Though it has been observed in clinical practice that most patients prefer a subcutaneous route considering the ease. This change of conventional route is backed by literature which clearly states that even though there is a lag of 11 minutes in case of subcutaneous injection as compared to intramuscular in reaching therapeutic levels, but still this can be a life savior in case of crisis than reaching out to an emergency and getting the injection done. Looking towards future the need of hour is development of a subcutaneous pen device for hydrocortisone injection which will ease the administration and avert a crisis episode.

SUMMARY

Adrenal crisis is a life-threatening medical emergency which requires immediate medical attention. High suspicion for the condition should be reserved for patients presenting with undiagnosed and refractory shock not responding to fluid and vasopressors. Though it can affect all age groups, but elderly and patients with altered mental status at presentation along with concomitant endocrine disorders have higher morbidity and mortality. Hyponatremia, hyperkalemia, and hypoglycemia are usually the presenting symptoms along with hypovolemia. Treatment is unequivocal with parenteral administration of 100 mg hydrocortisone at presentation. Every patient of AI should be educated about the possible crisis and technique of self-administration of hydrocortisone to prevent any uneventful episode.

MULTIPLE CHOICE QUESTIONS

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Section 13: Eye, Ear, Nose, Throat, and Oral Emergencies

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CHAPTER

Eye Emergencies

Carreen Pakrasi, Sudipto Pakrasi

INTRODUCTION

The eye is a small but essential part of the body. It is the one thing that adds quality to life. Hence, care of the eyes is as important as of any other part of the human body. Most often, the emergencies related to the eye will be obvious, with the cause related to either injuries such as trauma and chemicals and presenting with suggestive history and complaints of severe pain and visual loss of varying degrees from 6/6 to no perception of light. Sometimes, pain is the only presenting complaint in potentially debilitating conditions that must be detected early so as to prevent late visual complications, such as optic neuritis, temporal arteritis, and sometimes herpes zoster. A high index of suspicion and an acute clinical sense is important in early diagnosis. Ocular emergencies are those conditions that may or may not present with ocular pain and redness and are potentially blinding. These have to be recognized and treated swiftly so as to preserve the visual functions of the eye.

The World Health Organization (WHO) studies quote the incidence of ocular injuries causing loss of work hours as 55 million. Epidemiological studies by Vats et al. has found the mean age of ocular trauma to be 24.2 years. The prevalence of ocular trauma is reported to 2.4% of the population in an urban setting in India. We are going to try to present the various scenarios in a logical progression so that they are easily identifiable by first responders in an emergency setting. The Ocular Trauma Score has been presented according to various standard systems, of which the Birmingham Eye Trauma Terminology (BETT) is one of the most widely accepted. The terminology and classification is mostly to differentiate between penetrating and nonpenetrating ocular trauma due to mechanical cause.

Causes of Ocular Emergencies

Of the patients presenting in the emergency, the cause of symptoms can be any of the following. Most classifications of ocular emergencies will focus on ocular trauma. However, in a multispecialty hospital, patients walk in with any of the following presentations:

- *Infections*:
  - *Viral conjunctivitis*: Herpes simplex conjunctivitis or epidemic keratoconjunctivitis
  - Mucopurulent conjunctivitis
  - Ocular involvement due to herpes zoster
- *Trauma*: This will be discussed in detail.
- Ocular presentations of systemic diseases
- Diplopia and sudden loss of vision due to vascular or neurological causes

  Culturally, in India, there are a few festivities that have a high incidence of ocular emergencies. These may be infective or there may be chemical injuries to the cornea or emergency as a result from ocular trauma. All emergencies are usually on high alert around these festivities.
- *Holi*: Injury during the festival of Holi can be any of the following:
  - Infections due to contaminated color or water going into the eye
  - Chemical injuries due to reactions to adulterated and artificial colors
  - Closed or open globe injuries due to blunt trauma with balloons willed with water hitting the eye at high velocity
- *Dussehra*: Bow and arrow injuries

ANATOMY

The eye has a unique function, which requires clarity of its surface. It is soft, therefore susceptible to traumatic injuries. However, it also has a unique setting. It is placed inside a bony socket, which is designed to protect the eye, which by its nature of being closed on all sides except the front, serves as a buffer against direct impact. The front of the eye is protected by the eyelids, which are very sensitive to light, wind, and are served by a highly reactive nervous system, which closes the lids whenever there is a threat to them. Any loss of function of the lids will therefore increase the risk of injury to the eye itself.

The entire body is protected by skin, which is tough and capable of protecting the underlying tissue from direct injury. The eye, however, has skin that is soft, transparent, and susceptible to injury. This is because of its function of gathering light rays and transmitting them to the retina, so that an image can be generated. The cornea, the most anterior part of the eye, has to be as clear as any clear glass. Disturbance in this clarity will result in an alteration in the visual acuity.

In the same way, the arrangement of cells in the minutest way is very crucial to the proper functioning of the central part of the eye in the visual axis, which is responsible for good vision. The cornea, lens, the chambers of the eye, the retinal layers, and the optic nerve are all part of this visual pathway which culminate in the visual cortex, in the brain which is ultimately the seat of vision perception. There are conditions, which present as ocular emergencies with loss of vision or doubling of vision, which have nothing to do with the eye, but instead have diseases of the brain and the nerves that originate there, the cranial nerves. With this minimalistic overview of the relevant anatomy, we will approach the various cause of ocular anatomy by first dividing them into three major categories, which are:

1. *Traumatic ocular emergencies*: Those related to injury. Penetrating and nonpenetrating injuries and blunt injuries.
2. *Nontraumatic ocular emergencies*: Causes not arising from injury. Infections, inflammations, vascular, and neurological.
3. Chemical injuries

PENETRATING OCULAR INJURIES

History

The maintenance of the integrity of the globe is the most natural instinct served by vision to protect the eye and it has an inbuilt protective mechanism in the following ways.

The orbit serves to protect the globe from injuries by serving as a physical block against any oncoming projectiles unless they are directly approaching it from the front.

The eyelids also protect the globe with their ability to respond to sudden external insult by shutting the lids to cover the cornea. The lids themselves are soft so it is common for penetrating injuries of severe nature to go through the lid into the globe.

In penetrating injuries, there will be a history of any of the following projectiles entering the eye: stone, bullet, sharp object, finger with great force, pencil, and crackers.

The scenarios in which these injuries happen are school—in the classroom as well as in the playgrounds and laboratories, road traffic injuries, factories, construction sites, Diwali and Dusshera celebrations because of the crackers and swords used for play, and sports, especially those that involve sharp implements and speed. Any situation can result is eye injuries of varying levels if they involve implements that are sharp or pointed, hence, preventive measures are always to be followed as per protocols. The signs/symptoms that indicate an ocular emergency can be any of the following: Sudden and acute pain, sudden drop in vision, bleeding from the eye or around it, swelling, doubling of vision, flashes/floaters, and history of injury/intraocular foreign body.

Examination

The clinical signs will vary according to the severity of the injury, associated injuries, head and neck injuries, facial injuries, orbital fractures, neurological damage, and multiple injuries. The BETT is the most widely accepted classification of ocular trauma (**Box 1**).

The BETT provides a logical key to understanding of all injuries to allow better understanding of the extent and prognosis. It is desirable that it becomes the language for everyday clinical practice. We are further simplifying the signs and symptoms so that all physicians may be able to grade and treat presenting ocular emergencies more efficiently.

A key consideration is the kinetic energy of the bow as it makes impact with the eyeball. $E = ½\ mv^2$ or (Energy) = ½ (mass) × $(\text{velocity})^2$. A sharp object will easily penetrate the eye,on the other hand blunt objects need higher kinetic energy to cause rupture of the globe. They can cause extensive damage to the intraocular structure without globe rupture.

The original classification stressed on mechanical trauma. The following is the adapted terminology of the BETT, which includes nonmechanical injuries, which has been proposed by Shukla et al. (**Table 1**).

The following are the injuries depending on which part of the eye is involved:

- *Lid lacerations*: There can be tears of the eyelids and the skin around the eye. Often, in the presence of a penetrating injury, it would be wise to look for a track, which may point to the site of penetration of the eyeball.

BOX 1: Eye trauma.

- *Closed globe injuries:*
  - Contusion
  - Lamellar laceration
- *Open globe injuries:*
  - Laceration penetrating
  - Intraocular foreign body (IOFB)
  - Perforating

TABLE 1: New classification for ocular trauma (Shukla et al.).

Local	*Associated injuries*	*Cause of injuries*
Mechanical: • Globe • Destructive • Adnexal	• Head injury • Facial injury • Multiple injury	• Industrial • Sports related • Road traffic • Assault • Agricultural • Orbital • Daily activities
Nonmechanical: • Chemical • Thermal • Radiation • Electrical		

- *Conjunctival tears*: These can be accompanied by hemorrhage in the affected area. If any hemorrhage is seen, it is wise to look for an injury in the sclera under the hemorrhage.
- *Penetrating scleral injury* will often be found if there is a local contusion in the conjunctiva.
- *Penetrating corneal injuries:* The extent of the corneal tear will determine the extent of the injury.
- *Closed penetrating corneal injury*: If the injury is small it may be self-sealed or partial and the integrity of the globe will be maintained, this may be still a closed globe injury because the injury is partial thickness or sealed. The iris may seal the wound. If there is a knuckle of the iris in the wound, it is imperative for the iris to be repositioned in order to avoid the dreaded complication of sympathetic ophthalmia in the other eye. There may be blood in the anterior chamber of the eye known as hyphema. In the process of the blood been mobilized out of the anterior chamber, there may be blood cells which block the anterior chamber angle from where drainage from the anterior chamber takes place. This will lead to a rise in the intraocular pressure. It is imperative to look for a retained intraocular foreign body, which may be imbedded in any of the intraocular structures, that is, the cornea, the iris, the lens, or the retina. There can also be blood in the vitreous cavity of the back of the eye, which makes it difficult to see the retina. In these cases, if an iron foreign body causes the penetrating injury, a simple X-ray of the orbit will reveal the embedded foreign body. It is important to remove these foreign bodies because these are toxic to the eye. If there is an accompanying retina injury, the retina may be detached or may have a hemorrhage. Direct optic nerve injuries are rare but penetrating injuries have been known to sever the optic nerve completely causing optic avulsion.
- *Open globe injury*: When there is full thickness corneal wound and open globe.

NONPENETRATING OCULAR INJURIES

Blunt/Closed Globe Injury

The eye is a finely balanced instrument of vision and in order to achieve its perfect functionality, all the anatomical arrangements in the path of the light has to be in perfect alignment. Any injury, which leads to misalignment or alteration of the normal anatomy of these anatomical structures, will cause an aberration in its function, which results in loss of vision to varying extents.

Symptomatic Presentation

The patient may have any of the following complaints following blunt trauma to the eye:

- Watering
- Foreign body sensation
- Inability to keep the eye open
- Photophobia
- Loss of vision
- Pain
- Doubling of vision

Clinical Findings

Again, the approach to localizing the diagnosis must be logical and methodical, examining the eyeball and noting the findings from the outer part of the eye and progressing inward.

Contusions (Nonpenetrating Injury)

In contusion injuries, there may be injury to the eye wall, i.e., the sclera and the cornea. Look for any swelling in the supraorbital margins, the eyebrows or the eyelids. The discoloration of the lids will be evident if there is a localized hemorrhage anywhere on the forehead or eyebrows. Pooling of fluid will follow the gravitational pull and swelling will usually extend downward toward the cheekbones presenting as a *black eye*.

Supraorbital Injuries

Injuries in the area of the eyebrow line with a swelling over the lateral one-third of the eyebrow must be looked at carefully. Very often there will be an indirect optic nerve compression injury. In such cases the pupillary reaction must be closely evaluated to indicate any afferent pupillary defect. These are often overlooked in the face of other seemingly more serious injuries and can result in permanent loos of function of the optic nerve and visual loss. The only indicator will be an afferent pupillary defect in the presence of the supraorbital injury because the optic atrophy will not be apparent in the initial stages. A timely course of systemic steroids can save the optic nerve from damage due to local inflammation and edema and need to be given immediately, on detection.

Subconjuctival Hemorrhage

These are alarming to look at but will be harmless and easily treated by local cold compresses alone with lubricating eye drops to ease any foreign body sensation (**Fig. 1**). The important possible underlying injury to look for is that of a scleral rupture which can be hidden by the hemorrhage. There may also be an involvement of the ocular muscles with accompanying diplopia.

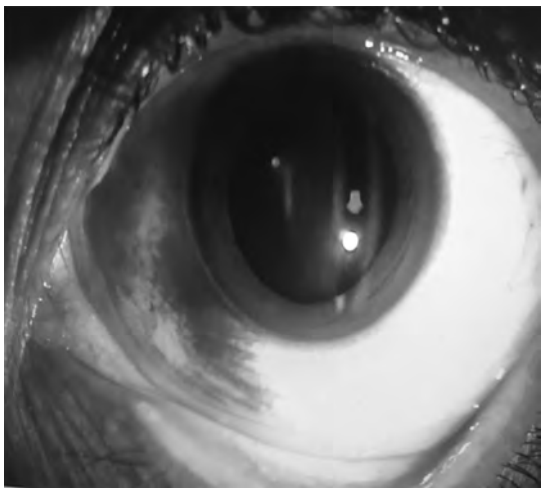

FIG. 1: Subconjunctival hemorrhage. ***(For color version, see plate 14)***

Corneal Abrasions

These are the most common injuries after any impact (**Fig. 2**). The cornea is intact but the continuity of the surface is compromised. The presence of corneal injury will typically give rise to acute and copious watering accompanied by unbearable foreign body sensation. This is a protective response, which help to protect the cornea from drying and infection when the surface is abraded. The eye remains closed and the pain is acute. On staining the cornea with fluorescein dye a tell-tale fluorescence will be clearly detected indicating a breach in the corneal epithelium. These require pad and bandage with an antibiotic ointment to assist resurfacing for as long as the corneal epithelium takes to heal completely. Examination must be done every 24 hours with a repeat pad and bandage every day until the epithelium is resurfaced and the cornea no longer registers staining. Healing can sometimes result in various levels of scarring. Depending on the site of the initial injury, the vision can be variously affected with central scars obviously causing the maximum loss.

Hyphema

It is defined as blood in the anterior chamber. The presence of blood in the anterior chamber of the eye can follow open (penetrating) as well as closed (nonpenetrating) injuries of the eye. Whenever there is a history of significantly severe force, any blunt injury of the eye can cause blood to collect in the anterior chamber. This occurs due to direct force on the iris causing it to bleed.

Associated Injuries

There can be various nonobvious effects that can accompany a bleed into the anterior chamber. These have to be detected early to prevent future vision loss. Angel recession must be ruled out with a good gonioscopic examination of the anterior chamber angle. The incidence of angle recession can be anywhere between 20% and 90% of all ocular trauma and of these 5–20% will develop angle recession glaucoma. Angle recession of the angle of >180° has a high risk of raised intraocular pressure. Raised intraocular pressure will also result due to the hyphema itself, concomitant uveitis or anterior dislocation of the lens. All or any of these can cause blockage of the trabecular meshwork. The patient must be given a pad and bandage to rest the eye and speed the mobilization of heme from the anterior chamber. The patient is also encouraged to lie in a semi-reclined position as the resolving hyphema can result in deposition of heme pigments on the anterior surface of the lens. In case the hyphemia is increasing over the first few days, look for iris injury.

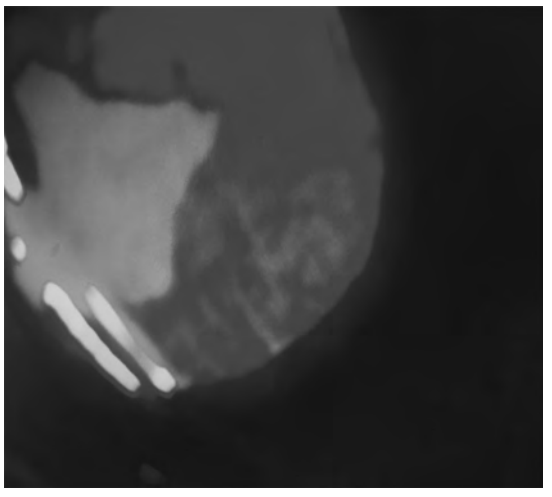

FIG. 2: Corneal abrasion. ***(For color version, see plate 14)***

Iris Injuries

Injuries to the iris will give a good indication of the presence of an angle recession. The iris sphincter damage will result in a dilated nonreacting pupil with no loss of a consensual response to light.

Vitreous Hemorrhage

Retinal hemorrhage, retinal tears, or posterior vitreous avulsion can also result in a bleed into the vitreous cavity. This will result in severe loss of vision. The fundus glow will be lost on distant direct. Ultrasound examination (preferably B-scan) will reveal the extent of the injury and can identify any retinal detachment, which significantly decreases the visual prognosis.

Retinal Injuries

Injuries to the retina may or may not result in immediate loss of vision. If the injury is sparing the macula and is not in the visual axis, the vision may not be affected on primary examination. Floaters are a good indicator of the presence of vitreous liquefaction and maybe a retinal tear. Flashes will most certainly accompany a tear in the peripheral retina. Careful history taking is a must to determine this. In case there are any complaints of floaters or flashes, the peripheral retina must be screened repeatedly over the following weeks to make sure that small tears in the retina is not missed. These are potentially preventive with timely treatment. Retinal hemorrhages can be present without symptoms and can be easily detected by careful examination of the retina with a 90D lens as well as careful indirect ophthalmoscopy. They need no treatment except observation and follow-up.

Berlin Edema

This is caused by countercoup injury to the macular due to impact over the anterior part of the globe. It is also called commotio retinae in keeping with the pathophysiology, where the injury is indirect, due to the transmission of the force across the tissues causing damage across the point of impact. There is retinal swelling, which can cause a significant drop in the visual acuity, which usually resolves spontaneously in a couple of weeks.

Extraocular Muscle Involvement

Any involvement of the extraocular muscles will give rise to diplopia. Any complaint of diplopia demands a thorough evaluation of the surrounding orbital spaces and bony structures for any inflammation or fracture and trapping of any of the ocular muscles within the fracture. The diplopia will usually resolve spontaneously with anti-inflammatory medication and requires observation till healing is complete before contemplating surgical management. Blow out fractures involve fracture of the inferior wall and may sometimes need surgical correction without which the diplopia will not resolve.

CHEMICAL INJURIES

As far as ocular injuries go, chemical injuries are the most dreaded and difficult to contain. It is absolutely essential that they be recognized immediately and managed efficiently as this will determine the visual prognosis. The load of contaminant, the response time, and type of contaminant determines the success of treatment. The goal is to eliminate the causative substance and restore the conjunctival spaces to the normal PH level as soon as possible so as to limit the seepage of the contaminant into the deeper layers of the ocular surface tissues.

Alkali Burns

In this respect, alkali burns continue to be the most challenging situations because of the nature of alkali. They can saponify the cell membrane and penetrate the cornea rapidly into the anterior chamber causing the PH of the aqueous to rise thereby damaging the iris and ciliary body. The vascular supply can be affected causing ischemic damage to the cornea leading to rapid deterioration of the integrity of the ocular surface.

Acid Injuries

On the contrary, the nature of acid burns is to coagulate and fix the ocular tissues so that there is limited penetration to the deeper structures. They may cause expensive immediate damage but will contain themselves after the initial insult.

Management

Immediate and copious irrigation of the affected eye should be carried out and continued until PH testing of the conjunctival sac returns to normal. This helps the offending substance to leech out gradually, thereby limiting the extent of penetration into the deeper tissues.

After sufficient irrigation has been carried out, a detailed history of the type of chemical involved in the injury. In case there is evidence of any solid particles, these must be carefully removed from the conjunctival sac so that there is no risk of continued penetration.

The presence of limbal ischemia is an indicator of the extent of injury and will determine the prognosis. Corneal epithelium integrity has to be determined by fluorescein staining of the cornea. In the presence of alkali burns, 10% potassium ascorbate drops have been seen to be useful in limiting damage to the ocular tissue by scavenging free radicals released by degranulating polymorphs. Further management will best be done by an ophthalmologist and will involve prevention of scarring with the use of antibiotic steroid combinations, ointment, and pad and bandage. Further surgical treatment may be required to treat any scarring that is bound to occur if the injury is extensive.

CONTACT LENS-RELATED EMERGENCIES

Displaced or Broken Contact Lenses

This is a common complaint. The patient may or may not be aware of the contact lens inside the eye. Patient may present with pain, foreign body sensation and red eye. A careful history will determine that the patient is a contact lens user. Detailed examination of the eye must be done to detect the presence of a contact lens in the conjunctival sulcus. Removal of the lens and antibiotic along with lubricating eye drops will suffice as treatment. Sometimes, the patient would have tried unsuccessfully to extract the contact lens and may have abrasion on the cornea. This will require a pad and bandage with antibiotic ointment for 24 hours.

CONJUNCTIVITIS

These will sometimes report to the emergency room and working knowledge is useful even though they are rarely sight-threatening and have very few complications apart from superficial corneal scarring. Allergic or infective inflammation of the conjunctiva can occur suddenly and without warning making it an ocular emergency. Allergic conjunctivitis will most often be accompanied by edema of the surrounding adnexa. The eyelids will be swollen without much inflammation and increased local temperature. The conjunctiva will reveal typical papillary response with causing acute dry eyes and foreign body sensation. The discharge will be watery if there is not accompanying infection. Bacterial conjunctivitis will by typically accompanied by mucopurulent discharge and matting of the lashes. A conjunctival swab from the lower fornix for Giemsa stains and culture sensitivity before treatment would be prudent to allow specific antibiotic therapy according to the sensitivity pattern.

Viral conjunctivitis will be accompanied by decreased corneal sensations and this simple test can prevent unnecessary antibiotic exposure. The symptoms will vary little except for the lack of mucopurulent discharge. Epidemic keratoconjunctivitis must be treated with close follow-up and will usually not require topical antibiotic unless the picture is of a mixed infection with superadded infection. Prevention of transmission of this highly contagious disease is as important as the treatment of the disease itself in order to limit the proportion of the epidemic. Personal hygiene lessons must be given along with other management.

CORNEAL ULCERS

Corneal ulcers are a dreaded condition, which unless treated immediately and well, can lead to nonhealing and chronically debilitating complications that are potentially blinding.

They can be of bacterial or viral infective origin and can also be degenerative. These will all present with similar symptoms of red eye accompanied by extreme pain and photophobia.

Bacterial Corneal Ulcers: Examination will reveal a staining ulcer on the cornea of varying depth and extent depending on the severity of the condition. If caught early, a course of broad-spectrum oral antibiotics along with local fortified antibiotic drops will prevent further deterioration and promote restoration of the normal epithelial integrity. Mydriatic eye drops will alleviate pain and redness and relieve the photophobia.

Viral corneal ulcers can be identified by the classical dendritic pattern on staining. Topical and systemic antiviral medication will be required to promote healing. Mydriatic eye drops will alleviate pain and redness and relieve the photophobia in these conditions as well.

UVEITIS

This potentially debilitating condition can present as an anterior, posterior, or panuveitis, involving both the anterior as well as the posterior chambers of the eye. The patient will present with complaints of a varying degree of pain and photophobia depending on the severity of the inflammation. If caught early, the treatment will prevent deterioration otherwise the inflammation progresses to create keratic precipitates (KPs) on the endothelium with outpouring of cells into the anterior chamber resulting in an increased stickiness of the iris. Unless the ciliary muscles are kept in motion by the prescription of a medium long-acting mydriatic eye drop, the sticky iris will form posterior synechiae with the anterior lens surface.

Management

Immediate management of uveitis aims to decrease the inflammation by the administration of topical and if severe enough, oral corticosteroids to control the inflammatory response. The prescription of mydriatic eye drops is necessary in order to prevent synechiae and also to relax the ciliary muscles thereby decreasing the pain. Long-term management must include all tests for the detection of an underlying cause. Pointers toward possible cause are the type of KPs (fine KPs in nongranulomatous uveitis and thick mutton fat KPs in granulomatous uveitis). These are not in the purview of emergency management.

GLAUCOMA EMERGENCIES

High intraocular pressure in the eye will result in the following: Pain due to stretching of the ocular structures, blurring of the vision, and haloes due to corneal edema. The pupillary reactions will be sluggish. If the patient has angle-closure glaucoma, the anterior chamber will be flat with possible iris bombe, if there is a pupillary block.

Angle-closure Glaucoma

This is a very typical presentation with a patient complaining of headache accompanied by generalized congestion of the conjunctiva with blurring of vision. Bringing the intraocular pressure down is immediately rewarding with alleviation of symptoms. Further management on follow-up will require preventive yttrium aluminum garnet (YAG) laser peripheral iridotomy. Angle-closure glaucoma will cause most glaucoma emergencies but the intraocular pressure can also be high in untreated open angle glaucoma, secondary glaucoma, or steroid induced glaucoma, resulting in similar symptoms without flattening of the anterior chamber.

NEURO-OPHTHALMOLOGY EMERGENCIES

Ocular emergencies of neurology origin will bring the patient into the emergency room with any of the following complaints:

- *Sudden loss of vision*: The most ominous and urgent complaint that can result from optic neuritis, temporal arteritis, and intracranial lesions affecting the optic tract or papilledema.
- *Diplopia*: This is a very debilitating condition that can arise from loss of innervation to any of the muscles groups or isolated muscles.
- *Ptosis*: Usually resulting from under action of the third nerve alone or in conjunction with other nerves.
- *Proptosis or periorbital swelling* in case of thyroid ophthalmopathies and orbital tumors. Management will involve investigation to isolate the cause and treatment of the cause itself if one is found.

OPTIC NEURITIS

Inflammation of the optic nerve will result in swelling of the optic nerve head with loss of vision to varying degrees. The pupil will show afferent pupillary defect in the side involved. Management with intravenous (IV) methylprednisolone or a short course of oral steroids is indicated and visual outcome is dependent on early initiation of treatment. If systemic steroids are not instituted early, they have questionable efficacy in the late stage. Central vision may be maintained with a significant peripheral field loss so a visual field analysis (VFA) test and an optical coherence tomography (OCT) to demonstrate optic nerve abnormality is highly indicated.

PAPILLEDEMA

Routine evaluation of hypertensive patients may reveal the presence of papilledema, which then becomes an emergency. On evaluation, the blood pressure may be found to be dangerously high. Neurological emergency patients may present with papilledema, in which case, the pupils may be sluggish and the visual fields indicative of the pathology.

VASCULAR EMERGENCIES

Sudden loss of vision may be a complaint in patients with vascular abnormalities resulting in hemorrhages in the retina or the vitreous cavity. Dilation of the pupil will reveal the pathology.

Venous Occlusion: Central Retinal Vein Occlusion and Branch Retinal Vein Occlusion: Semi-emergencies

Symptoms

Sudden onset of floaters and varying degrees of visual loss depending on the volume of hemorrhage. Venous occlusions are the most common causes of visual loss in diabetic retinopathy. Central retinal vein occlusion (CRVO) at the optic nerve is one of the causes of sudden visual loss. 90% of these occur in people over 80 years. Branch retinal vein occlusion (BRVO) or branch vein occlusion will also cause visual loss but occurs in the branch veins.

Central Retinal Artery Occlusion

It is an acute emergency. Sudden and complete loss of vision, which may or may not be accompanied by history of acute, transient, pain, or headache. This is one of the most dreaded causes of sudden loss of vision. It involves blockage of the central retinal artery resulting in acute ischemia. The treatment requires quick diagnosis and lowering of the eye pressure with ocular massage and medication. Only one out of four patients will retain good vision on recovery.

VITREOUS HEMORRHAGE

Symptoms

Sudden and painless loss of vision to varying degrees depending on the extent of the hemorrhage. Examination in all these cases will reveal loss of vision with abnormal fundus glow. The eye will be quiet and there is usually no pain unless the intraocular pressure is high. The intraocular pressure must be checked, as it can be associated with abnormal vasculature that can be the cause of both the hemorrhage as well a rise in the intraocular pressure.

Management

Vitreous hemorrhage is not an acute emergency. The symptoms are very mild, apart from the vision loss. The patient needs to be thoroughly examined to rule out the presence of a retinal detachment. Manage any comorbidity like hypertension or cardiac disease, which may be the pathogenesis of the condition. If patient is on any anticoagulants, either stop them or modify them according to INR. The immediate management of central retinal artery occlusion (CRAO) is directed at bringing down the intraocular pressure to facilitate greater perfusion. This is done by undertaking anterior chamber paracentesis and with the help of medical management to bring down the intraocular pressure. Efforts must be then made to isolate possible causes with full blood work and cardiology workup.

SUMMARY

Successful patient outcomes in the setting of ocular emergencies depends on correct recognition and assessment as well as appropriate initial management and referral. Assessment involves a concise history, observation, pupil examination, and ocular movements should be tested in patients with a suspected orbital wall fracture. Documentation of visual acuity or subjective vision is vital. Important conditions to recognize include penetrating injuries, nonpenetrating injuries, chemical burns, acute angle-closure glaucoma, orbital cellulitis, and retinal detachment. Common presenting complaints in emergency department, their evaluation, and interventions are summarized in (**Table 2**).

TABLE 2: Common eye problem presentation in emergency department and their evaluation and treatment.

Presentation	***Possible causes to look for***	***Investigations***	***Treatment***
Acute foreign body sensation accompanied by watering and conjunctival congestion	• Corneal or conjunctival foreign body • Conjunctivitis	Fluorescein staining/evert the upper lid and check the palpebral conjunctiva/check the conjunctival fornices	• Antibiotic eye drops and ointment • Moisturizing eye drops • Removal of foreign body and pad and bandage with antibiotic ointment for 24 h and close follow-up
Acute foreign body sensation accompanied by watering	History of injury: Paper edge/blunt trauma/pointed substances/finger/eye pencil	Fluorescein staining	Pad and bandage with antibiotic ointment for 24 h and repeat if there is residual staining with fluorescein under observation in cobalt blue filter
Acute pain with circumciliary congestion of the conjunctiva	Flare and cells in the anterior chamber/presence of posterior synechiae	CBC with ESR/ACE/ANA/ tubercular antibodies	Topical corticosteroids in high frequency initially depending on the grade of cells and flare in the anterior chamber, in tapering dosage. In the presence of severe or pan uveitis, systemic corticosteroids are advised
Acute pain with congestion, photophobia, and haloes	Flattening/shallowing of the anterior chamber accompanied by high intraocular pressure	Check the intraocular pressure and do a gonioscopy to determine the presence and grade of angle-closure	Antiglaucoma agents, specifically pilocarpine eye drops to induce miosis causing the intraocular pressure to drop. If insufficient, injection mannitol can be given in IV bolus over 20 min after checking the blood pressure
Sudden painless loss of vision	Optic disk edema or hyperemia/ disk hemorrhages/optic disk pallor/retinal ischemia (CRAO, CRVO, and BRVO)	OCT and fluorescein angiography/visual field test/ check pupillary reaction	Refer to ophthalmologist for OCT/VFA and fluorescein angiography before starting any treatment. In case of CRAO, immediate paracentesis and ocular massage is very essential
Sudden painless loss of vision/floaters and flashes	Gray fundus reflex/retinal detachment on indirect ophthalmoscopy	Screening of the peripheral retina to rule out any holes/ tears or retinal detachment	Refer to ophthalmologist for treatment of retinal detachment
Sudden blurring of vision with history of mild pain or painful movements	Afferent pupillary defect/field defect and blurring of the disk margins to suggest optic neuritis	Visual field test/OCT	Systemic steroids have a role if started early otherwise their role is debatable

Continued

Continued

Presentation	*Possible causes to look for*	*Investigations*	*Treatment*
History of injury/dog bite/ RTA/blunt injuries	Look for penetrating injuries or orbital fracture/history of abuse/ look for supraorbital injury	X-ray orbit to rule out retained intraocular foreign body/diplopia charting/ pupillary reaction	Dog bite protocol has to be followed according to guidelines. The face is a very sensitive area. May need repair/ refer to ophthalmologist. Seidel sign test: Put fluorescein in the eye and check for aqueous leak on the slit lamp
History of splash or contact with chemical agents/sprays	Detailed history is required to determine the agent and classify it as an acid or alkali. The treatment is specific and must be instituted immediately		Wash the eye from the medial to the lateral side for at least 30 min with normal saline or water if none is available. Find and remove all crystals. Irrigate till the pH reading returns to 7–7.3. In alkali injuries, 10% potassium ascorbate has been shown to decrease morbidity

(ACE: angiotensin-converting enzyme; ANA: antinuclear antibody; BRVO: branch retinal vein occlusion; CBC: complete blood count; CRAO: central retinal artery occlusion; CRVO: central retinal vein occlusion; ESR: erythrocyte sedimentation rate; OCT: optical coherence tomography; RTA: road traffic accident; VFA: visual field analysis)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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134 CHAPTER

Ear Emergencies

Shaarang Sachdev, Salil Malik

INTRODUCTION

A variety of emergency conditions related to ear problems; emergency physician may need to handle in emergency department (ED). Common ear emergencies are related to infections either related to outer middle or inner ear. It is important for the emergency physician to aware about the anatomy of the ear to effectively manage the ear emergencies. Other emergencies like trauma to ear are also needs to manage effectively. This chapter describes infections, trauma, and procedures related to ear.

ANATOMY OF EAR

External Ear

The auricle or the pinna of the external ear is a protruding structure prone to traumatic lacerations. It consists of an elastic cartilage with tightly attached overlying skin, receiving its blood supply from the underlying perichondrium. Exposure of the cartilage after an injury may lead to infections, erosive chondritis, and necrosis. The outer one-third of the external auditory canal (EAC) has an incomplete cartilage whereas the inner two-thirds is composed of bone with a tight overlying skin attachment that easily injured due to a minute trauma.

The blood supply is from the superior temporal vessels in the anterior part and the posterior auricular vessels in its posterior part. The connection of the posterior auricular vein to the sigmoid sinus is a source of the intracranial spread of infections.

The nerve supply is via the auriculotemporal nerve, greater auricular nerve, lesser occipital nerve, and the vagus nerve. The posterior wall of the EAC is supplied by the vagus nerve and so it would not be anesthetized with an auricular nerve block if any repair is required. Anatomy of ear is described in **Figure 1** and normal otoscopic examination shown in **Figure 2**.

Middle Ear

The middle ear is an air-filled cavity in the petrous bone that extends from the tympanic membrane (TM) laterally to the oval

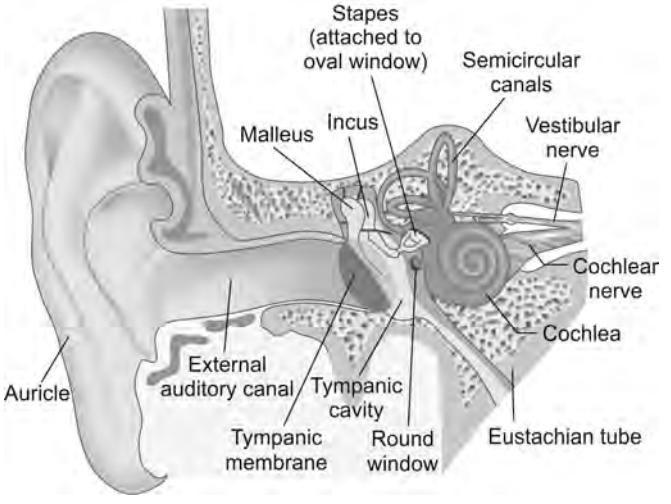


FIG. 1: Anatomy of the ear.

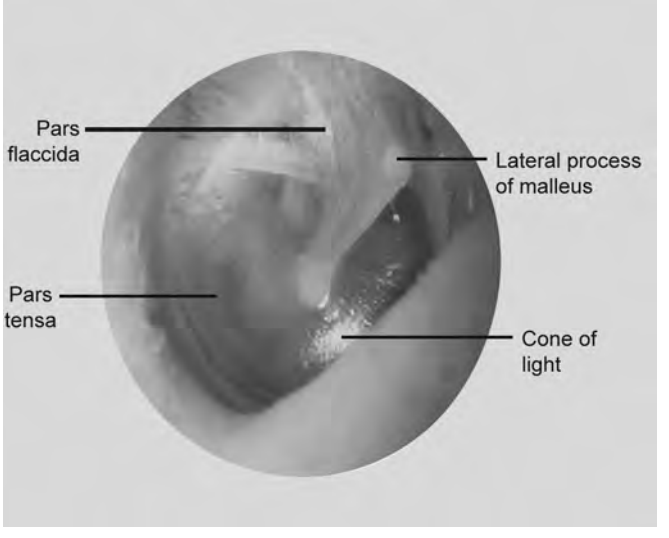


FIG. 2: Normal ear on otoscopic examination. ***(For color version, see plate 14)***

window medially and contains the three auditory ossicles—malleus, incus, and stapes.

Anteriorly, it communicates with the nasopharynx via the eustachian tube, and posteriorly, to the mastoid. Superiorly is the attic or the epitympanum. Most of the infections and barotrauma to the middle ear is due to the dysfunction of the eustachian tube due to inflammation, obstruction, or direct trauma. The relative horizontal and short nature of the eustachian tube in the pediatric population accounts for higher incidence of otitis media (OM) as it hinders its drainage via gravity with increased transmission of infections from the nasopharynx.

The TM is an oblique fibrous membrane attached medially to the malleus at the umbo forming the *cone of light* [as visualized via the otoscope (**Fig. 2**)]. Superiorly, the *pars flaccid* is a thicker part of the TM. The remainder of the membrane is thin, known as the *pars tensa* and is prone to perforation.

The facial nerve transverses through the posterior wall of the middle ear. The innervations of the middle ear are via the tympanic nerve (CN IX), auriculotemporal nerve (CN V), and the auricular nerve (CN X).

Inner Ear

The inner ear consists of the bony and the membranous labyrinth.

- The bony labyrinth is part of the temporal bone and contains the cochlea, the vestibule and the three semicircular canals and is filled with perilymph.
- The membranous labyrinth consists of the cochlear duct (hearing organ), the vestibule (utricle and saccule), and the semicircular ducts (balance organs).

Vestibular afferent nerves passing to the brainstem help modulate body balance, tone, body, and eye movements. Blood supply is from the vertebrobasilar system. Since the anterior vestibular artery supplies the semicircular canals and not the cochlea, its isolated occlusion leads to vestibular syndrome without auditory defects.

COMMON SYMPTOMS OF EAR PROBLEMS

Common symptoms related to ear pathology are otalgia tinnitus and hearing loss and their causes are summarized in **Table 1**.

Otalgia

Otalgia or earache can be classified as primary otalgia and referred otalgia. Primary otalgia is caused by diseases of the auricular and periauricular structures, whereas referred otalgia is caused by diseases originating from distant structures. Causes of *primary otalgia* include infections of the ear (otitis externa, OM, etc.), cerumen impaction, otic foreign bodies, trauma to the ear, and facial neuralgias. Causes of *referred otalgia* include eustachian tube dysfunction, pathology of the temporomandibular joint, dental pathology, infections, and abscesses in and around the pharynx, nasal cavity pathology, foreign body in the throat or neck, and thyroid disorders.

Tinnitus

It is defined as perception of sound without external stimulation. Tinnitus can be divided into *objective* (which can be heard by the examiner) and *subjective. Objective tinnitus* is caused by conditions such as arteriovenous (AV) malformations and arterial bruits. Some of the conditions which cause *subjective tinnitus* include hearing loss (sensorineural or conductive), head trauma, side effects of medications (aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, loop diuretics, and chemotherapeutics), psychiatric disorders (depression and anxiety), hypertension, multiple sclerosis, and Ménière's disease. Consider antidepressants for patients presenting to ED with tinnitus and who have been advised discharge with ear, nose, and throat (ENT) follow-up. It is often difficult to elicit the cause of tinnitus in a busy emergency room. Referral to an otolaryngologist is warranted in such cases.

TABLE 1: Causes of otalgia tinnitus and hearing loss.

Causes of otalgia	*Causes of tinnitus*	*Causes of hearing loss*	*Ototoxic agents (causing tinnitus and hearing loss)*
• *Infections*: Otitis externa, otitis media, mastoiditis, myringitis, labyrinthitis, and perichondritis • Trauma • Foreign bodies of ear • *Neuralgias*: Trigeminal, herpetic, and great auricular neuralgias • *Dental*: Dental caries and abscess • *Retropharyngeal/oropharyngeal problems*: Tonsillitis and abscess • *Nasal problems*: Sinusitis and deviated nasal septum • Cerumen impaction • *Referred pain*: Temporomandibular joint problems	• *Objective causes*: Arteriovascular malformation, arterial bruit, eustachian tube enlargement, and stapedial muscle spasm • *Subjective causes*: Sensorineural hearing loss, conductive hearing loss, head injury, hypertension, depression, anxiety, acoustic neuroma, multiple sclerosis, Ménière's disease, and Cogan's syndrome	• Idiopathic • *Infections*: Mumps, Epstein–Barr virus, herpes simplex virus, and meningitis • *Ear disease*: Ménière's disease and ear surgery • *Trauma*: Head injury, barotrauma, and acoustic trauma • *Systemic disease*: Cardiovascular/ neurovascular disease, and intracranial hemorrhage	• *Antibiotics*: Aminoglycosides, vancomycin, erythromycin, neomycin, and polymyxin B • *Salicylates*: NSAIDs and quinine • *Diuretics*: Furosemide and bumetanide • *Chemotherapeutic drugs*: Carboplatin, cisplatin, vinblastine, and vincristine • *Others*: Ethanol, sildenafil, and tadalafil

(NSAIDs: nonsteroidal anti-inflammatory drugs)

Hearing Loss

Sudden hearing loss can be divided into *sensorineural* (cochlea, auditory nerve, or central auditory processing) and *conductive* (external ear, TM, and ossicles).

Conductive hearing loss generally occurs in reversible conditions such as otitis externa, OM, or cerumen impaction. Causes of sudden hearing loss are varied and may be idiopathic (most common), infectious, vascular, hematologic, metabolic, rheumatologic, or conductive. Evaluate the medication history of the patient for possible toxic side effects.

Prior history of trauma or a pop heard preceding the hearing loss may indicate perforation of the TM or ossicular dislocation. Ménière's disease usually presents with a triad of hearing loss, vertigo, and nystagmus. If the physical examination is unremarkable (perhaps a conductive hearing loss ruled out), consider urgent otolaryngology consultation. Consider glucocorticoids (60 mg of prednisone OD for 7–14 days or dexamethasone 300 mg OD for 3 days) with ENT follow-up for suspected idiopathic sensorineural hearing loss.

Weber Test

Weber test is performed by placing a vibrating tuning fork on the forehead of the patient. Normally, the sound is heard equally on both sides. Lateralization of sound to either side implicates either a conductive hearing loss on that side or a sensorineural hearing loss of the other ear.

Rinne Test

Rinne test is performed by placing the tuning fork over the mastoid bone, and then moving it towards the entrance of the ear canal. The sound is usually heard better though the air conduction than the bone conduction. A conductive hearing loss of the ear can be established if the sound is heard better over the mastoid bone on that side.

OUTER EAR INFECTIONS

Acute Diffuse Otitis Externa

Otitis externa is the infection and inflammation of the EAC. Predisposing factors for the development of otitis externa include disruption of the skin integrity of the EAC, secondary to scratching or overzealous disimpaction of cerumen (**Fig. 3**). It occurs mostly in summers and in tropical climates. It is often referred to as swimmer's ear. Diabetic patients have a higher cerumen pH, therefore, a higher incidence of otitis externa in this population.

Microbiology: Pseudomonas aeruginosa, *Staphylococcus aureus, Staphylococcus epidermidis*, and Enterobacteriaceae are the common microbes involved. Fungal otitis externa (otomycosis) occurs in tropical climates and in the immunocompromised individuals or in individuals who have been previously on long-term antibiotic therapy. Most cases are caused by *Aspergillus* or *Candida.* Topical medications and hearing aids are implicated in causing noninfective otitis externa.

Clinical features are pruritus, otalgia, erythema, and edema of the EAC (**Fig. 4**). Otorrhea, crusting of the ear canal, mastication, or periauricular skin movement triggers the pain and hearing loss in severe cases.

Emergency department treatment includes analgesia, keep the ear dry and advise against inserting anything in the ear, nonototoxic ototopical antimicrobials with or without steroids (aminoglycoside is contraindicated in cases of TM perforation), cleansing of the EAC (irrigation with *hydrogen peroxide* in a 1:1 dilution with warm saline or water or a gentle suction under direct visualization), acidifying agents (acetic acid), aural toilet ± ear wick insertion in case significant canal edema or extensive debris, and ENT specialist review, if needed.

The following are commonly used antibiotic/steroid regimens:

- Ofloxacin otic five drops BD
- Acetic acid/hydrocortisone otic five drops thrice daily (do not use with perforated TM)
- Ciprofloxacin/hydrocortisone otic three drops BD
- The above antibiotics are commonly used for 7 days to treat otitis externa. Oral antibiotics indicated in febrile patients and those with periauricular spread of the disease. If fungal infection is suspected, treat with topical *clotrimazole* 1% solution. Alternatively, systemically treat with an antifungal agent such as *fluconazole.*

Malignant Otitis Externa

Malignant otitis externa is a potentially life-threatening infection of the external ear/canal/soft tissue with possible spread to the skull base. Malignant otitis externa begins as a simple otitis externa which then spreads to the deep tissues of the external ear/canal.

FIG. 3: External ear appearance in otitis externa. ***(For color version, see plate 14)***

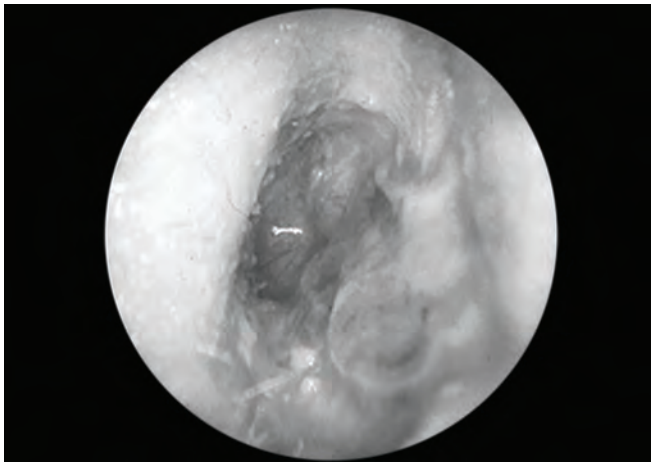


FIG. 4: External auditory canal erythema and edema. ***(For color version, see plate 14)***

Suspect in individuals with persistent otitis externa despite 2–3 weeks of topical antimicrobial therapy. Elderly, diabetic, and immunocompromised patients are most affected.

Microbiology: Pseudomonas aeruginosa and methicillin-resistant *Staphylococcus aureus* (MRSA).

Clinical features: Severe otalgia, otorrhea, edema of the EAC, granulation tissue on the floor of the EAC. Parotitis, trismus, and assess for the seventh cranial nerve function which may be affected secondary to cranial extension.

Complications: Lateral or sigmoid sinus thrombosis and meningitis.

CT or MRI of the head used to diagnose the infection. ED treatment includes analgesia, emergent otolaryngology (ENT) consultation, and admission to hospital for intravenous (IV) antibiotics. Commonly used antibiotic regimens are:

- Tobramycin 2 mg/kg IV and piperacillin 3.375–4.5 g IV
- Ceftriaxone 1 g IV
- Ciprofloxacin 400 mg IV

Perichondritis

Perichondritis is infection of cartilage of outer ear. Ear piercing, ear trauma, and burn skin infection are common risk factors while diabetes and immunodeficiency can aggravate it. Problem stars with pain, redness and swelling around the auricle and later pus develops, and fluctuation can be palpated. Any foreign body like piercing must be removed and pus should be drained to control the infection. Common causative organism is *Pseudomonas aeruginosa*. Antibiotic fluoroquinolones-ciprofloxacin orally should be started. Parenteral antibiotics may be required as SPACE (*Serratia, P. aeruginosa, Acinetobacter Citrobacter, Enterobacter*) organism develops resistance to fluoroquinolones very quickly and reaccumulation of abscess may occur. Single ED visit is not sufficient for complete treatment so patient should be referred to specialist in early stages to avoid reaccumulation of abscess or permanent disfigurement (cartilaginous destruction of auricle of the ear "cauliflower ear").

MIDDLE EAR INFECTION

Otitis Media

Otitis media primarily affects infants and children with incidences peaking in the preschool years (6–18 months of age) and declining with advancing age. Acute OM is much less common in adults than children. The most common bacterial pathogens recovered in adults with *acute OM* are *Streptococcus pneumoniae*, *Haemophilus influenzae*, Methicillin-sensitive *S. aureus*, and *P. aeruginosa*. Young adults remain protected from all *Haemophilus* strains as they have received the *H. influenzae* type b vaccine. The predominant organisms involved in *chronic OM* are *S. aureus, P. aeruginosa*, *Aspergillus*, and anaerobic bacteria (less common). *Viral OM* caused predominantly by respiratory syncytial virus and rhinovirus occur in those under the age of 10.

Clinical features: Otalgia, otorrhea, hearing loss, deafness (older children), nonspecific symptoms such as fever, lethargy, irritability, and poor feeding (younger children), prodrome of an upper respiratory infection (younger children), *and* bulging or retracted TM which may be red in color, with associated loss of light reflex may be present on otoscopic examination (**Fig. 5**). Pneumatic otoscopy almost uniformly demonstrates impaired mobility. Assess facial nerve function in view of its proximity to the middle ear.

Treatment measures include analgesia, oral antibiotics, and urgent specialist consultation for patients appearing septic or for those who present with complications of acute OM. Strongly consider IV antibiotics in such cases. The preferred initial antibiotic treatment includes:

- Amoxicillin 250–500 mg PO three times daily for 7–10 days
- Azithromycin 500 mg PO daily for 1 day then 250 mg PO daily for 4 days
- Cefuroxime 500 mg PO two times daily for 10 days

Complications of OM are TM perforation, hearing loss, acute serous labyrinthitis, facial nerve paralysis, acute mastoiditis, lateral sinus thrombosis, cholesteatoma, and intracranial complications (meningitis and brain abscess).

Acute Mastoiditis

Mastoiditis is an infection of the mastoid process of the temporal bone (**Fig. 6**). *Microbiology: S. pneumonia*e, *S. pyogenes*, and *P. aeruginosa* are common causative organism.

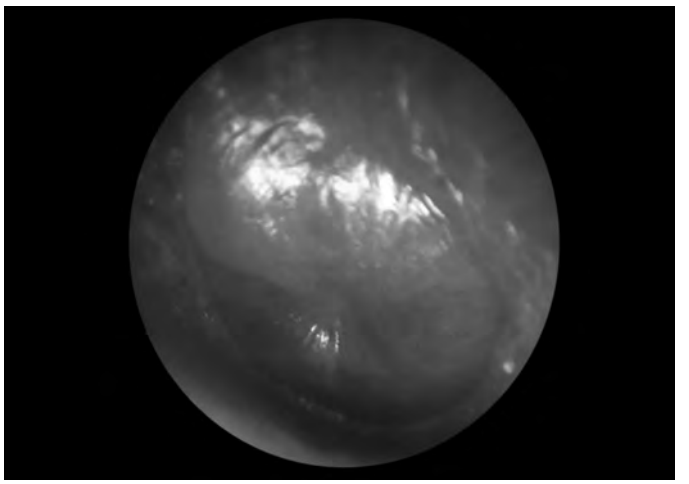


FIG. 5: Otoscopic appearance of external auditory canal and tympanic membrane in otitis media. ***(For color version, see plate 14)***

FIG. 6: Postauricular erythema and swelling in acute mastoiditis. ***(For color version, see plate 15)***

Clinical features of acute mastoiditis are otalgia, fever, otorrhea, postauricular erythema, swelling, and tenderness.

Diagnosis is by history, physical examination, and by contrast CT.

Treatment includes IV antibiotics, ceftriaxone 2 g IV, or levofloxacin 750 mg IV. Refractory cases may require irrigation and debridement with possible mastoidectomy.

Bullous Myringitis

Bullous myringitis is a form of acute OM characterized by painful fluid-filled vesicles on the TM (**Fig. 7**). Blisters may be blood filled, serous, or serosanguineous. Most commonly caused by *S. pneumoniae*, numerous other pathogens have been implicated including viruses, *Mycoplasma pneumonia,* and *Chlamydia psittaci. Clinical features* include otorrhea and hearing loss.

Treatment measures are pain control, warm compresses, and antibiotics can be given for concomitant OM.

Lateral Sinus Thrombosis

A complication of acute OM arising from spread of infection/inflammation from the mastoid to the adjacent lateral or sigmoid sinus.

Microbiology: Staphylococcus, Streptococcus, and upper respiratory anaerobes (*Bacteroides fragilis*).

Clinical features include headache (most common symptom), papilledema, sixth-nerve palsy, and vertigo.

Diagnosis by angiography with venous phase and MRI.

Treatment by IV antibiotics (a combination of cefepime 2 g IV, metronidazole 500 mg IV, and vancomycin 1 g IV), and urgent ENT specialist consultation for possible mastoidectomy.

INNER EAR INFECTIONS

Inner ear consists of two structures, *vestibular system* (semicircular canal and vestibule) which is responsible for balance and *cochlea* which converts mechanical vibration to electrical signals to brain and possible for a person to perceive and hear sound. Labyrinthitis and vestibular neuronitis are the two most common infections of the inner ear.

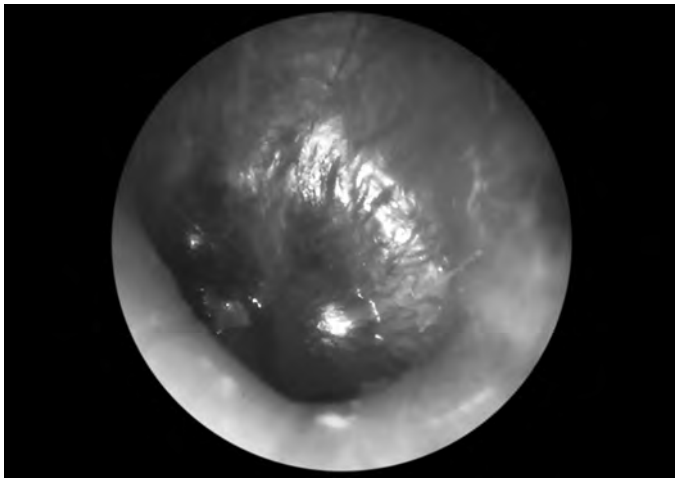


FIG. 7: Otoscopic appearance of tympanic membrane in a bullous myringitis. ***(For color version, see plate 15)***

Labyrinthitis

Labyrinthitis is infection of labyrinth and most commonly secondary to acute OM. Other conditions which give rise to seeding of infections in inner ear are meningitis, mastoiditis, cholesteatoma, and traumatic fracture of labyrinth. Vertigo, nystagmus, tinnitus, hearing loss, otalgia, nausea, vomiting with history of OM are common presentations of labyrinthitis. For diagnosing and evaluation of complication of labyrinthitis CT/MRI is best modalities. Proximity to brain and to avoid serious complication, admission specialist consultation, and parenteral antibiotics (ceftriaxone 50–100 mg/kg/day maximum 2 g IV are often prescribed. Myringotomy and mastoidectomy is recommended in severe cases.

Vestibular Neuronitis

Often considered synonym of labyrinthitis but vestibular neuronitis associated with ongoing upper respiratory tract infection and sudden and severe vertigo is common presentation. Nausea, vomiting, and horizontal nystagmus are additional features. Unlike labyrinthitis these patients do not have tinnitus or hearing loss. Diagnosis is clinical and based on history and physical examination. Though condition is primarily considered as viral cause and self-limiting, symptomatic treatment with antiemetics antihistamines and benzodiazepine is advised.

TRAUMA TO EAR

Ear Barotrauma

Ear barotrauma is caused by the difference of pressure between the atmosphere and the middle ear. The most common cause is flying. Diving, decompression sickness, hyperbaric O_2 therapy, and ballistic injuries account for more serious but less common causes.

The most common manifestation is ear fullness. However, if pressure difference is large, bleeding may occur due to rupture of TM or the oval window leading to severe conductive hearing loss. Vertigo and sensorineural hearing loss should alert the physician to investigate for perilymphatic fistula between the inner and middle ear. Tinnitus can be caused due to any of the above causes and may be pulsatile or constant.

A good history and detailed examination are the keys to a good diagnosis. Advice the patient to avoid triggers as much as possible. Oral antihistamines and nasal decongestants reduce edema around the eustachian tube. Swallowing, yawning, chewing gum, and Valsalva maneuver equalize the pressure in the middle ear with that of the atmosphere. Ventilatory tubes may be useful for patients undergoing hyperbaric therapy.

Most mild injuries heal spontaneously. Antibiotics have a little role, whereas glucocorticoids have not shown any benefit. Otolaryngologist consult would be required in cases of vertigo or sensorineural hearing loss when perilymphatic fistula is suspected. Tympanoplasty may be warranted in injuries to the ossicles. Myringotomies with or without tube have limited preventive and therapeutic values as they spontaneously close within a few days. This is especially not useful in scuba divers.

Tympanic Membrane Perforation

Tympanic membrane perforations (**Fig. 8**) may occur due to middle ear infections, barotrauma, blunt/penetrating trauma,

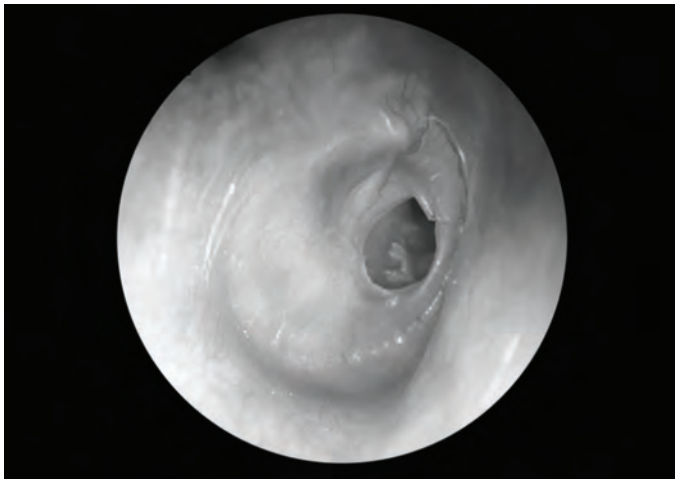


FIG. 8: Perforated tympanic membrane. ***(For color version, see plate 15)***

acoustic trauma, lightning strikes, ballistic injuries, foreign bodies in the ear canal, skull fracture, and self-injury with an ear bud. Iatrogenic, it may persist after myringotomy or with dislodgement of the drainage tube.

Perforations secondary to barotraumas are in the pars tensa involving the anterior or inferior part of the TM. *Clinical features* include otalgia, hearing loss, otorrhea (hemorrhagic or serous), tinnitus, and vertigo.

Treatment

Most TM perforations heal spontaneously. Caution should be taken; avoid liquid entering the ear canal. Topical or systemic antibiotics may be warranted for infections of the ear or otic foreign body debris. Perforations secondary to blunt or noise trauma can safely be discharged with ENT follow-up. Posterosuperior or traumatic perforations such as in penetrating injuries warrant urgent otolaryngologist consult due to a high likelihood of ossicular disruption. At times, surgical intervention with paper or a biofilm patch may be required.

PROCEDURES RELATED TO EAR

Auricular Hematoma Evacuation

Auricular hematoma is the collection of blood between the auricular cartilage and the perichondrium resulting mostly from blunt traumatic injuries seen in contact sports. As the underlying cartilage gets hypoperfused, eventually necrosis followed by fibrosis and neocartilage formation occurs. This leads to a disorganized chronic fibro cartilage overgrowth of the pinna typically known as the *cauliflower ear*. Acute hematomas are painful, tender, and tense and should be differentiated from auricular abscess, perichondritis, and chondritis. Auricular abscess will have pus rather than hemorrhagic fluid on aspiration and would be fluctuant. A skin avulsion followed by erythema indicates perichondritis or chondritis.

All auricular hematomas need to be drained either by aspiration, incision-drainage, or catheter insertion as soon as possible (**Fig. 9**). *The aim is to remove the hemorrhage and put regional pressure for days to prevent reaccumulation*. More than 7 days old hematoma may require surgical subspecialty consult. Up to 1–2% lidocaine with epinephrine may be used for regional auricular block but should be avoided for perilesional field block. Needle aspiration may be useful for small acute hematomas which are ≤ 2 cm and <48 hours old.

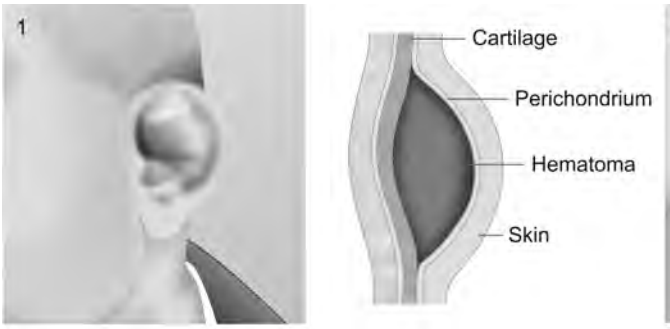
For larger and older hematomas, incise along the inner curvature of the helix and do gentle suction at the dependent part. After suturing the incision, use a petroleum jelly dipped gauze or a saline gauze to carefully pack into all the convolutions of the auricle to apply a uniform pressure at the suture site. Alternatively, a dental roll can be bolstered with a through and through suture to hold it against a similar bolster behind the auricle. After applying dry gauze to both sides of the auricle, wrap a compression bandage around the head to maintain pressure over the incision site. Revaluate the dressing daily for fluid reaccumulation for at least 5 days. Empirical antibiotics against *Pseudomonas* and *Staphylococcus aureus* should be given to all patients post treatment.

Foreign Body Removal

Cerumen or ear wax is one of the most common reasons for a person to come to the ED with complains of otalgia, fullness in the ear, dizziness, or a ringing sound. Other foreign bodies in the external ear may include small beads, button batteries, or insects.

Direct inspection can be done by pulling the pinna and tragus outwards and visualization aided by an otoscope. Most common sites for foreign body impaction are the junction of cartilaginous and bony segments followed by the isthmus of the bony segment.

- Mineral oil and preferably 2% lidocaine/benzocaine may be used to drown live objects before removal.
- Organic matter like vegetable or cellulose may expand due to irrigation with saline and hence it is advisable to follow caution in such cases.
- Irrigating from the superior part of the canal with 20 mL of saline via an IV catheter usually helps in most of the cases. Pressure should be minimum to prevent TM perforations. Use room temperature saline and direct the pressure towards the wall of the canal. Perforated TM or myringotomy tubes are contraindications for saline irrigation.
- Small alligator forceps, loops, or right-angle hooks may be used (**Fig. 10**) to pull out soft or live objects under direct visualization taking care not to erode the skin.
- Cyanoacrylate (super glue) may be applied to the end of an ear bud and stuck to the inorganic foreign body for 30–60 seconds before pulling it out.
- Suction with a thin plastic tube may be attempted to pull out smooth objects or remnants of live objects.
- Impacted button batteries may lead to necrosis of the canal and warrant immediate intervention.
- Softening of hard and dried cerumen may be done before removal. This is achieved with diluted hydrogen peroxide, mineral oil, sodium bicarbonate, or docusate sodium left in place for 30 minutes.



Auricular hematomas manifest after trauma with anterior auricular swelling. The hematoma forms between the cartilage and perichondrium and will lead to permanent deformity if not treated.

Anesthetize the pinna via local infiltration of 1% lidocaine without epinephrine or via an auricular block.

Use a scalpel to incise the skin along the natural skin folds at the edge of the hematoma. Follow the natural curve of the pinna.

Gently peel the skin and perichondrium off the hematoma and underlying cartilage. Completely evacuate the hematoma and irrigate the pocket with normal saline.

A compression dressing must be placed to prevent reaccumulation of the hematoma. Place dry cotton into the EAC and fill all external auricular crevices with saline-soaked or Vaseline gauze.

Carefully conform the material into all the convolutions of the auricle. Vaseline gauze, saline-soaked 1/4-inch packing gauze, or saline-soaked cotton may be used. Place gauze behind the ear.

Place three to four layers of gauze behind the ear as a posterior pack, and then cover the entire ear with multiple layers of fluffed gauze.

Secure the dressing to the head with Kerlix or an elastic wrap.

FIG. 9: Steps in aspiration of auricular hematoma.

FIG. 10: Different-shaped ear scoops and loops are useful to remove cerumen from an impacted ear. Miniature alligator forceps can be used to extricate foreign bodies from the external ear canal.

An otolaryngologist consult may be necessitated in cases of failed extraction, advanced infections, or glue stuck to the TM. In cases of an uncooperative patient, procedural sedation with ketamine may be needed.

Complications of Cochlear Implantation

Cochlear implants are prosthetic devices (**Fig. 11**) installed surgically and consists of a battery-operated external processor with electrodes inserted into the cochlea to stimulate the auditory nerves. Cochlear implants are commonly used in patients with moderate/severe bilateral sensorineural hearing loss. Common complications include vestibular complaints (occurs in 4% of patients), device failure, and infections (skin infections, OM, acute mastoiditis, and meningitis).

MRI compatibility should be checked before conducting the same on any patient with a cochlear implant. CT with or without contrast and device testing is usually required to diagnose the complications of cochlear implants.

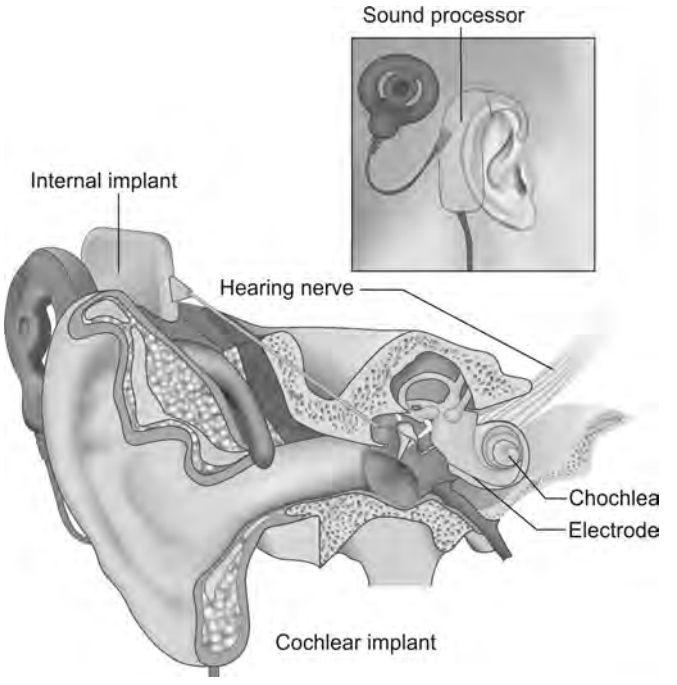


FIG. 11: A cochlear implant.

SUMMARY

It is important for the emergency physician to aware about the gross anatomy of the ear, common symptomatology of ear problem, and their causes to effectively manage the mild to serious problem of ear emergencies. Common emergencies differentiated into infections (outer and middle inner ear infections), trauma (barotrauma and traumatic rupture of TM), and complications of various ear surgery like cochlear implant. Emergency physician should have knowledge of procedures related to ear like aspiration of auricular hematoma and removal of foreign body of the ear in ED. Timely referral to specialist is important for effective management.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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ONLINE REFERENCES

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CHAPTER

Nasal Emergencies

Harshil Mehta

INTRODUCTION

Nasal emergencies are a common presentation to emergency departments and also in primary care settings. Trauma is the main cause of acute nasal injury and can present as epistaxis, nasal fracture, or even nasal septal hematoma. Epistaxis accounts for majority of all admissions to emergency ear, nose, and throat (ENT) departments and head and neck surgery facilities, and it can require cautery or packing. In some cases, surgical intervention is required. Nasal fractures are considered as most common type of facial fracture. Nasal fractures predominantly seen in the adult population because nasal spine begins to ossify at around 3 years of age, completing its growth and ossification during puberty. The incidence of nasal fractures is rising most commonly caused by blunt trauma to nose or assault. Sporting injury is also an important cause of nasal emergencies. Nasal septal hematomas require urgent evaluation to prevent nasal deformity.

EPISTAXIS

Epistaxis is one of the most common nasal emergencies that hardly turns into life-threatening (<6%). 1 in 200 emergency visits is related to epistaxis and hospitalization rate is <0.2%. It is seen more commonly with males and observed more in bimodal age distribution (2–10 years and >50 years of age). Causes of epistaxis (**Table 1**) can be divided in three categories—local, systemic, and idiopathic.

Applied Anatomy and Pathophysiology

Nasal mucosa has a very rich blood supply from internal carotid artery (ICA) and external carotid artery (ECA). Kiesselbach's plexus (Little's area) is situated anteriorly and formed by anterior and posterior ethmoidal arteries (branches of ICA), sphenopalatine, and branches of internal maxillary artery (branches of ECA). Posteriorly nasal mucosa gets blood supply from posterior branched of sphenopalatine artery (**Fig. 1**). Pathology behind epistaxis is erosion of mucosa and rupture of superficial arteries or veins. Nearly 90% of patients presents with anterior epistaxis from Little's area. Rest 10% patients presents with posterior epistaxis that is more serious than anterior and more commonly seen in old age patients with comorbidities.

Clinical Presentation

Patient presents with acute onset nasal bleed. Bleeding may be active or clotted blood is visible on examination. Sometimes complains of posterior pharyngeal trickling of blood or hematemesis is also present. Patients may have high blood pressure on presentation.

TABLE 1: Causes of epistaxis.

Local causes	*Systemic*
• Nasal trauma	• Anticoagulant therapy
• Facial trauma	• Accelerated hypertension
• Nose picking	• Pregnancy
• Nasal polyp	• Hepatic disease
• Foreign body in nose	• Blood dyscrasia
• Allergies	• Diabetes mellitus
• Dry weather	• Alcoholism
• Neoplasm	• Vitamin K deficiency
• Septal deviation	• Blood transfusion therapy
• Nasal mucormycosis	• Chronic use of nasal vasoconstrictor
• Postoperative epistaxis	• Cocaine use
	• Drug-induced thrombocytopenia

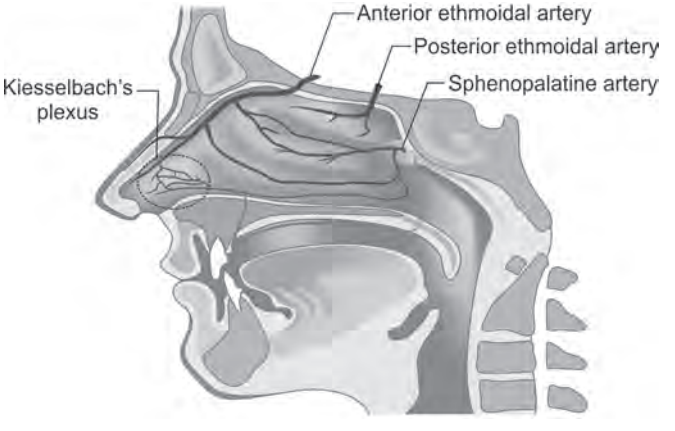


FIG. 1: Nasal anatomy.

Red Flags

Be careful as an emergency physician while treating patients with epistaxis with following signs: Bleeding not stopped by direct pressure, suspected sock, recurrent unilateral bleed, associated symptoms such as facial pain, numbness or diplopia, anticoagulants, or anything to suggest blood disorder.

Evaluation

History

For stable patients, nasal and systemic histories are important. Specific questions regarding duration, severity, frequency, location, laterality, precipitating factors of epistaxis, and methods used to stop need to be asked. Nose picking or local trauma to nose along with spontaneous nose bleed is frequently reported. History regarding other symptoms should be asked to suspect systemic causes. Headache, hematemesis, melena, easy bruising, or other bleeding episodes should make clinical suspicious of a systemic cause and prompt a hematologic workup. Past medical history, use of medication [especially aspirin, warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), heparin, ticlopidine, and dipyridamole), and family history should be documented.

Physical Examination

Check vitals of patient. Make patient stable if any abnormality observed. Nasal examination requires nasal examination instruments including nasal speculum (**Figs. 2** and **3**), adequate illumination, proper suction, and required topical medicines, cauterization, and packing material ready. External nasal examination for any trauma is the initial step in examination. Remove previous nasal packs and watch for active bleeding. Topical vasoconstrictor (0.05% oxymetazoline) is beneficial in hemorrhage control and localizing bleeding point. Clots should be suctioned out for better examination. The nasal floor should be parallel to room floor. Tilted head would restrict visualization to anterior and upper part of nasal cavity only. Nasal speculum is used for internal examination. Hold the nasal speculum with special technique (**Fig. 4**). Spread it vertically to determine place of bleeding in cases of anterior epistaxis. Such exposure (**Fig. 5**) is needed for packing as well as cauterization.

Posterior epistaxis should be suspected in constant posterior pharyngeal trickling even after placing anterior packing; epistaxis from both nares and location of bleed cannot be visualized from anterior examination. Fiberoptic endoscopy by experienced consultant is an advanced option for better visualization of nasal cavity and nasopharynx. Throat examination would complete examination in patients with epistaxis. Trickling of blood on posterior pharyngeal wall would indicate posterior epistaxis and on-going bleeding.

Investigations

Blood investigations are not routinely indicated in single infrequent cases. For recurrent bleeding or patient with other comorbidities, few routing blood tests can be done, i.e., complete blood count (CBC), prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT), liver function tests, etc. CT scan or MRI is indicated to evaluate surgical anatomy or local pathology. Angiography is rarely required.

FIG. 3: Nasal speculum.

FIG. 2: Nasal examination instruments.

FIG. 4: Nasal speculum holding technique.

FIG. 5: Nasal cavity examination. ***(For color version, see plate 15)***

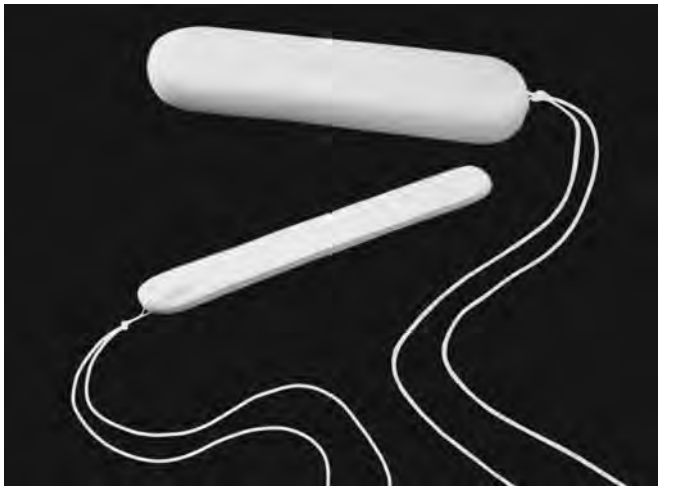


FIG. 6: Merocel.

Treatment

First stage of treatment is to maintain hemodynamic instability. Hypotension or hypertension should be managed accordingly. Local treatment of epistaxis is divided into *surgical or nonsurgical management*. Aim of management is to identify and control source of bleeding. There are various methods to control bleeding.

Manual Hemostasis

First of hemostasis is manual direct pressure of nostrils for 5–30 minutes. Ask patient to keep head elevated but not hyperextended. If this hemostasis maneuver is unsuccessful then a gauze piece soaked with 1:10,000 epinephrine/phenylephrine can be placed in nostril to get vasoconstriction and hemostasis.

Cauterization

When bleeding persists further to two attempts at direct pressure, this is the next appropriate step. Chemical cauterization with silver nitrate is done. Preanesthetize the nasal mucosa with cotton soaked in 0.05% oxymetazoline and 4% lidocaine solution in equal concentration. Visualize the bleeding site after anterior rhinoscopy and the silver nitrate stick can be placed proximal to the bleeding source. Once a blood less field is obtained apply silver nitrate directly to the bleeding site briefly. This should not be attempted on both sides of the septum as it can increase the chances of perforation. Silver nitrate is a strong oxidizing agent and on interaction with liquids it precipitates and leads to release of free radicals. This process oxidizes mucosa and destroys mucosal structures which later heal with scar tissue with decreased vascularity. Application of this cautery for 4–5 seconds after hemostasis coagulates tissue. It should never be maintained for >15 seconds. It should be in direction of above to downward and peripheral to center. Following cauterization local ointment application with saline gel is recommended to avoid crusting and rebleeding. Complete recovery can take 2–3 weeks period. Silver nitrate cauterization has a success rate of 75–85%.

Nasal Packing

Anterior and posterior packing are used in cases where direct pressure, vasoconstrictor, and cauterization are unresponsive and if thrombotic gel or foams are not available.

Anterior nasal packing is done by anterior epistaxis balloons or preformed sponges or layered stripped gauze. Anterior nasal balloons (Rapid Rhino) are of different sizes and covered with cellulose or other material that promote platelet aggregation. Water soaked balloon should be inserted along the floor of nasal cavity and inflate slowly with air until bleeding is stopped. Do not use saline to inflate as on rupture of saline filed balloon as chances of aspiration are there. If unilateral balloon is not successful, a second balloon in opposite side is required.

Preformed nasal sponge *(Merocel)* is made of synthetic material that expands after hydration (**Fig. 6**). It should be coated with antibiotic ointment or lubrication jelly and inserted along floor of nose. Irrigate it after insertion with normal saline for proper expansion. Second sponge can be inserted into opposite nostril for desired result. Tap down string to face to avoid aspiration. It is more effective but causes more pain than balloon on removal. Ribbon gauze packing can be placed if sponge/balloons are not available. Antibiotics are not preferred prophylactically for toxic shock syndrome. Pain management with NSAIDs or opioids is required in emergency room (ER) and at home. Packing should be removed in 2 days to avoid pressure-related necrosis.

Posterior Nasal Packing

Failure to control bleeding by any of the above measures suggests posterior bleeding. For its control, routing Foley's catheter is useful. Commercially available devices can be used too. Obtain ENT consultation before doing any further intervention. Foley's catheter should be inserted lubricated with lidocaine jelly parallel to nasal floor while keeping patient in sniffing position. Tip of catheter beyond balloon should be cut to avoid gag reflex. As tip of catheter is visible in posterior oropharynx, inflate balloon with 7 mL of air and retract it anteriorly till it gets fixed at choanal arch. Avoid using water for inflation to avoid chance of aspiration on rupture of balloon. If balloon slides further into nasal cavity, then deflate balloon and reinsert it and inflate with 10 mL of air and again retract it. This procedure is associated with higher complication rates. Early ENT consultation is required in cases of posterior epistaxis or uncontrolled anterior epistaxis. Around 10% of patients require invasive therapy.

Surgical Treatment

If clinically significant bleeding starts after pack removal then there is a need for surgical treatment. The bleeding will need evaluation in operating room under general anesthesia and possible bleeding vessel will need ligation or cauterization. Endoscopic clipping or coagulation of sphenopalatine artery may be necessary. The ligation of ethmoidal artery, facial artery, sphenopalatine artery, or internal maxillary artery as required may be done by endoscopic method. Interventional radiologist doing an angiography and selected arterial embolization may be necessary in intractable epistaxis. The complications involved in these procedures can include stroke and blindness which should be discussed with the patient and informed consent must be obtained before proceeding with it.

Management of Epistaxis in Patients on Anticoagulants

Anticoagulation can be continued in minor epistaxis episodes which can be controlled by minor interventions. Only in episodes of massive uncontrollable bleeding adjustment of doses should be considered in consultation with hematologist and cardiologist. When anticoagulant overdose is suspected then reversal of anticoagulation is deemed necessary.

- *Antiplatelets therapy*: Normal hemostasis will be restored after a week of discontinuing antiplatelet therapy. Platelet transfusion can be considered.
- *Unfractionated heparin*: Administer protamine sulfate with a dose guided by aPTT.
- *Vitamin K antagonists*: Administer vitamin K and fresh frozen plasma, if overdose is suspected.
- *Direct oral anticoagulation*: Adjustment of doses with expert consultation. Antidote for use is available only in the case of dabigatran.

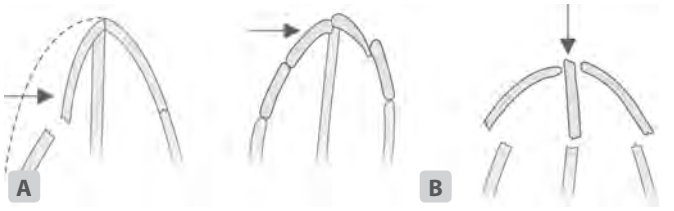
Disposition of Epistaxis Patient

If hemorrhage is controlled then patient may be discharged after 1–2 hours observation in ER. Follow-up with ENT consultation and pack removal after 48 hours. Patent should be explained regarding simple methods to control bleeding at home. NSAIDs should be avoided for 3–4 days. Antibiotics are not advisable as prophylactic measure of *Staphylococcus aureus* infection or toxic shock syndrome. Patients with uncontrolled anterior epistaxis or posterior epistaxis should be admitted for further observation.

NASAL FRACTURE

The nasal bone fractures are most common among maxillo-facial complex. Nasal fractures should prompt emergency physician to search other facial injuries because of its central location and proximity to other important structures. Most common is direct trauma over nasal bones during road traffic accidents or sport related injuries.

Injury results mainly due to transfer of kinetic injury above tolerance power to underlying structure, i.e., nasal bones and cartilages. Two patterns of biomechanism are well-known; one is lateral impact caused lateral displacement and second is head-on impact causes posterior displacement of bone structure (**Figs. 7A** and **B**).



FIGS. 7A AND B: Mechanism of nasal injury. (A) Lateral impact; (B) Direct impact.

FIG. 8: Nasal fracture.

Clinical Presentation

Clinical presentation includes epistaxis, abnormal nasal contour, external nasal wound (abrasion/bruise/laceration), and any other facial injuries. Other complaints are headache, paresthesia, weakness, and numbness.

Red Flags

Patients with associated basal skull fractures of other facial injuries, septal hematoma, and severe traumatic epistaxis.

Evaluation

History

History regarding mechanism of injury and force and event of trauma should be obtained. Questions regarding above mentioned symptoms and red flags are to be asked. These details allow estimation of injury severity.

Physical Examination

Nasal examination should always be preceded by general examination. Nasal injuries can be identified by simple inspection by deformity (**Fig. 8**), edema, bruise, abrasions, laceration, or periorbital ecchymosis in absence of any other facial injuries and profuse epistaxis.

On palpation, tenderness, crepitus, or movement of nasal bridge by grasping it between thumb and index finger are diagnostic of nasal fracture. Pinch one nostril alternatively and see whether patient can breathe from either side. Anterior rhinoscopy should be done to examine for mucosal laceration, septal fracture, or hematoma (**Fig. 9**).

FIG. 9: Nasal septal hematoma. ***(For color version, see plate 15)***

Investigations

It is mainly clinical but radiology investigations aid into accurate diagnosis. The result of plain radiography can miss nasal fracture in 50% of patients and rarely change course of management. Ultrasonography has similar sensitivity and specificity in this condition. CT scan is not required in diagnosing isolated nasal bone fracture.

Treatment

The main priority is to exclude any other life-threatening injuries, nasal septal hematoma, and vitals management. Nasal fractures with laceration should be managed as good as open fracture. After excluding all serious injuries, most simple nasal fractures should be asked to follow up with ENT surgeon. Closed reduction of nasal fracture should be done by ENT specialist only in view of cosmetic and facial features concern.

NASAL SEPTAL HEMATOMA

The nose is the commonly injured facial structure. Isolated nasal injuries does not require immediate intervention except septal hematoma. It is a serious but rare complication. Nasal septal hematoma mostly occurs secondary to trauma. It can be seen spontaneously in cases of bleeding diathesis or iatrogenic to nasal surgeries such as septal correction and turbinate surgeries. Child abuse should be suspected if history does not get matched with clinical examination. A hematoma is collection of blood mucoperichondrial or mucoperiosteum of nasal septal cartilage or bone. It lifts perichondrium and disrupting blood supply to cartilage and causing septal necrosis.

Clinical Presentation

Patient presents with nasal septal hematoma within 24–72 hours of trauma. Presenting symptoms are nasal obstruction (unilateral or bilateral), pain, rhinorrhea, fever, and nasal deformity.

Red Flags

Nasal septal hematoma itself is a red flag for nasal trauma. Whenever it is detected it should be removed immediately. Nasal septal hematoma can lead to septal necrosis and saddle deformity and nasal obstruction. Hematoma may get converted into abscess by colonizing bacteria within 72 hours. Untreated hematoma can complicate into osteomyelitis, cavernous sinus thrombosis, meningitis, and intracranial abscess.

Evaluation

History

History of mechanism of injury and mentioned clinical symptoms are important. Duration of hematoma decides further complications. For nontraumatic hematoma, past medical history and medication history play a significant role. Also, if a nasal obstruction does not get resolved with vasoconstrictor drops and removal of clot, it strongly suggests nasal septal hematoma.

Physical Examination

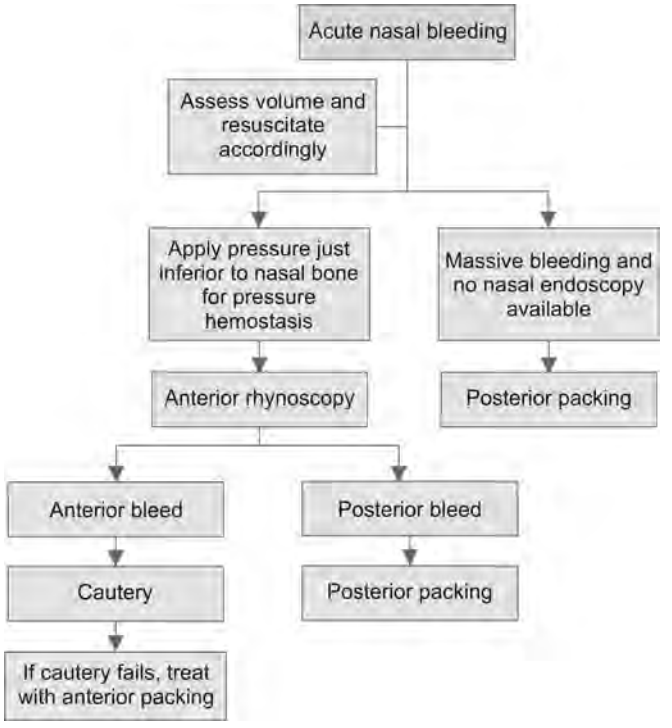
Examination generally confirms diagnosis. Inspection can be done with nasal speculum. Asymmetrical septum with bluish or reddish discoloration usually suggests hematoma. Newly developed hematoma can only be confirmed with palpation as does not show discoloration. Palpation can be done by gently inserting little finger. Hematoma is soft and fluctuant in palpation in contrast to hard nasal septal bone/cartilage. Hematoma does not get reduced on application of decongestant spray. Clinical examination is diagnostic. CT/MRI may add to clinical examination.

Treatment

Nasal septal hematoma must be drained urgently with ENT specialist. Prophylactic antibiotics should be prescribed against *S. aureus*, *Haemophilus influenzae*, and *S. pneumoniae*. Strict follow-up with ENT specialist is must to avoid further complications.

SUMMARY

Nasal emergencies are of both types; medical and surgical. They are nonlife-threatening; however, it required urgent attention to avoid deadly complications. Epistaxis is very frequently encountered in emergency department. Trauma to nose can give rise to all the above three scenarios. Urgent ENT consultation should not be avoided. This is very important to for emergency physician to know the management of epistaxis (**Flowchart 1**).



FLOWCHART 1: Management of epistaxis in emergency department.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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136 CHAPTER

Face and Jaw Emergencies

Devendra Richhariya, Harshil Mehta

INTRODUCTION

Patient may present to emergency department with various facial and jaw-related problem. Facial swelling in focal or generalized form may be the presentation. Emergency physician should be able to differentiate various causes of focal and generalized facial swelling. Facial cellulitis is another important presentation which needs immediate attention and antibiotic therapy. Jaw dislocation is another presentation in emergency department which can be managed by emergency physician.

FACIAL SWELLING

Facial swelling is defined as the term which involves the localized or generalized swelling over the face. This may involve neck or throat region also. Facial swelling can present as a chronic case in the outpatient department (OPD) or as catastrophic event in emergency. To treat the facial swelling, one must have a deep insight into the anatomy, physiological features involving face so that the etiology can be identified promptly and clearly. This necessitates appropriate and timely treatment. As face is the mirror of body, any small or large swelling can be seen very early and hence, the treatment is never delayed. The facial swelling, etiologically, can be grouped into two types; localized and generalized (**Table 1**).

LOCALIZED FACIAL SWELLING

Ocular Congestion

Causes include allergic conjunctivitis, infective conjunctivitis, endophthalmitis, or orbital bone infections. Treatment includes antibiotics, decongestants, cold compresses, and intraocular steroids (endophthalmitis).

Angioedema

There is a swelling below the eyes. Normally a drug or food-induced allergic reaction or insect bites, accompanied with urticaria and itching. Additionally, may have urticarial and itching on hands, legs, or other areas of body. Patient may

TABLE 1: Causes of facial swelling.

Causes of localized facial swelling	***Causes of generalized facial swelling***
Trauma including fracture of facial bones and nasal bones	*Cardiac related*: Heart failure
Ocular infections such as stye, conjunctivitis, endophthalmitis, etc.	*Hepatic*: Cirrhosis and portal hypertension
Abscesses including actinomycosis	*Renal*: Nephrotic-nephritic syndrome and CKD
Sinusitis (frontal and maxillary)	*Endocrine*: Cushing syndrome and hypothyroidism
Allergic reactions: Drug induced, food allergy, and insect bite	*Nutritional*: Hypoproteinemia
Parotid swellings including inflammatory tumors	*Pregnancy related*: Preeclampsia
Lymphadenopathy: Preauricular, supraclavicular, and submandibular	Mediastinal tumors
Thyroid disorders such as goiter and tumors	*Respiratory*: Acute and chronic bronchial asthma Bronchial compression due to lymphadenopathy or tumor
CVA; cavernous sinus thrombosis	*Drug-induced*: Steroids, NSAIDs, contrasts-induced AKI
Dental infections	*Angioedema*: Anaphylaxis or acute drug reaction

(AKI: acute kidney injury; CKD: chronic kidney disease; CVA: cerebrovascular accident; NSAIDs: nonsteroidal anti-inflammatory drugs)

have abdominal cramps also. If severe, may cause emergency situation. Diagnosis can be done on physical examination and eosinophilia, C1 esterase inhibitor test, and complement components C2 and C4. Treatment includes cold compresses and antiallergic drugs (oral or injectable depending on the situation—antiallergic, steroids, and subcutaneous adrenaline in anaphylaxis).

Sinusitis

It is the infected inflammation of facial sinuses mainly frontal and maxillary. If not treated, may lead to chronic suppurative otitis media (SOM) or thrombosis, which may migrate to cavernous sinus in the mid brain. Treatment is antibiotics, decongestants, and surgical drainage.

Abscess

Local nasal or facial abscess or abscess in the dental or gum area. Treatment includes cold compresses, antibiotics, anti-inflammatory, and finally surgical drainage.

Goiter

A goiter is a swelling caused by enlarged thyroid gland, which is not functioning properly. Worldwide, over 90% of goiter cases are caused by iodine deficiency. It may be associated with hypothyroidism or hyperthyroidism. Goiter may be uninodular, multinodular, or diffuse. These nodules may be just inactive or toxic. Causes may include iodine deficiency, autoimmune (Hashimoto's), Graves' disease, and congenital or neoplastic in origin. It may be a part of systemic disease or drug induced also. Look for the cause very carefully and order investigations according to the list of differential diagnosis made, based on clinical examination. Treatment depends upon hypo or hyper or euthyroid status. Broadly includes iodine solution, L-thyroxine replacements, steroids (in autoimmune diseases), radioactive iodine, surgery, etc.

Parotitis

Parotitis is an inflammation of one or both parotid glands. Parotids are the major salivary glands located on either side of the face and mostly affected by inflammation. Infectious parotitis can be acute bacterial parotitis (patient reports progressive painful swelling of the gland and fever; chewing aggravates the pain); acute viral parotitis-mumps (patient presents with pain and swelling of the gland lasting for 5–9 days, moderate malaise, anorexia, and fever, mostly seen as bilateral involvement); human immunodeficiency virus (HIV) parotitis (patient present with nonpainful swelling of the gland and mostly patient is asymptomatic); and parotitis in tuberculosis (patient present with chronic nontender swelling of one parotid gland or a lump within the gland with clinical evidence of tuberculosis).

Treatment includes local heat in chronic and cold compresses in acute, gentle massage of the gland from posterior to anterior, and hydration and sialagogues. If pus is expressed from the Stensen duct, culture and sensitivity studies guide antibiotic selection. Intermittent irrigation of the ductal system with saline, steroid solution, and/or an antibiotic and mechanical removal of inspissated mucus or pus from the ducts can also be done. Treatment of the primary disease (e. g., HIV and rheumatoid arthritis) is advocated. Intravenous (IV) antibiotics in severe acute bacterial infections [for methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin, linezolid, tigecycline, and colistin] may be required.

Lymphadenopathy

Enlargement of lymph nodes, essentially is a result of infection somewhere else, the area from where the lymph is drained. Lymphadenopathy of face and neck is an important marker for metastasis of malignancy on any part of the body. Lymphadenopathy can be infective, inflammatory (secondary to chronic diseases like Koch's/HIV/sarcoidosis, etc.) or neoplastic (part of lymphoma, metastatic of nearby organs like lungs/bronchus/thyroid, etc., or from far away primary). The lymphadenopathy needs to be investigated thoroughly and treatment depends on the primary cause. Important thing is to examine and identify the small lymphadenopathy in submaxillary/submandibular or supraclavicular area which gives you a clue to the early diagnosis of systemic diseases such as Koch's, lymphoma, or metastasis. Early diagnosis is the key to good treatment.

Cushingoid

Cushing syndrome or features like Cushing syndrome also called hypercortisolism. High production of cortisol can produce some of the hallmark signs of Cushing syndrome—a fatty hump between your shoulders, a rounded face, and pink or purple stretch marks on your skin. Cushing syndrome can also result in high blood pressure (BP), bone loss, and, occasionally, type 2 diabetes mellitus. It can also cause thinning, fragile skin that bruises easily with slow healing of cuts, insect bites, and infections. It may also cause acne, decreased libido, erectile dysfunction, fatigue, muscle weakness, depression, and cognitive difficulties. Causes include pituitary gland tumors (adenoma), ectopic adrenocorticotropic hormone (ACTH) producing tumors (carcinoma of lung, pancreas, thyroid, or thymus), primary diseases of adrenals or drug-induced (steroid therapy, chronic, or overdose). Patient presents with moon-like face with hypertension. Treatment depends on removal of primary cause and medications to control excessive production of cortisol at the adrenal gland such as ketoconazole, mitotane, and metyrapone.

GENERALIZED FACIAL SWELLING

Preeclampsia

Preeclampsia is gestational hypertension plus proteinuria (>300 mg of protein in a 24-hour urine sample). Severe preeclampsia involves a BP >160/110 mm Hg, with additional medical signs and symptoms. Hemolysis, elevated liver enzymes, and low platelets count (HELLP) syndrome is a type of preeclampsia. It is a combination of three medical conditions: Hemolytic anemia, elevated liver enzymes, and low platelet count. It is a medical emergency.

Treatment

Intravenous magnesium sulfate—loading dose of 4–6 g in 100 mL saline to give in 30–40 minutes, followed by infusion of 2 g/h (Magpie Trial). It reduces the risk of eclampsia by 50%. In women who already have seizures, magnesium sulfate is a better choice than phenytoin. Aspirin (enteric coated)—

if administered early in pregnancy, prevents development of preeclampsia in high-risk patients. It showed 17% reduction. Recommended dose—75–100 mg daily. Calcium supplementation also helps.

Anasarca

Generally referred to as edema, which is generalized and present all over the body. As Claude Bernard said "edema is merely a result of expansion of milieu interieur—the extracellular fluid of the body". So it is defined as abnormal accumulation of extravascular extracellular (interstitial fluid) over the body. All edema comes from the circulating blood; hence, its composition is similar to plasma and contains electrolytes, glucose, urea amino acids, and many more crystalloids. The protein contents depend on the cause of edema. Edema of the face is a sign common to a variety of disorders and recognized very early.

Commonly the causes of anasarca include nutritional (hypoproteinemia, anemia, cachexia, and beriberi), cardiac disorders (heart failure, pericardial effusion, and constrictive pericarditis), renal disorders [nephritic-nephrotic syndromes—chronic kidney diseases (CKDs)], hepatic disorders (cirrhosis—portal hypertension), drug-induced (vasodilators), blood malignancies (leukemia, etc.), infections (filaria and chronic malaria), autoimmune (Raynaud's disease and vasculitis), endocrine disorders (hypo/hyperthyroidism), and edema of pregnancy.

Management depends on the cause. Treatment of the cause in emergency room depends on the sickness of the patient.

Anaphylaxis

It is usually an emergency which can be a life-threatening condition and hence, timely and adequately critical care is required. It is an allergic reaction with rapid onset of sign and symptoms on exposure to allergen. The clinical features usually include urticarial, rashes, and itching over the body swelling over the face. If exposure to allergen is large (in case of drugs) or hypersensitivity of patient is enhanced [as in glucose-6-phosphate dehydrogenase (G6PD) deficiency], there can be fall in BP, respiratory distress, mental confusion, and shock.

Treatment includes IV fluids, antihistaminic drugs, steroids (preferably hydrocortisone or methylprednisolone), and subcutaneous adrenaline, if shock persisting. In advance cases patient may require ventilatory support, pacemaker (to cover bradycardia), vasopressor, or hemodialysis.

Evaluation and Management

In Emergency Department

A patient visiting emergency department evaluates the following:

- *History*: Whether swelling is acute, chronic, or acute on chronic. History of trauma fever, cough with expectoration, hemoptysis, severe headache, tremors, slurred speech, or seizure should be obtained. Drug intake or food ingested generalized diseases such as hepatic, cardiac, renal, and thyroid disorders; dyspnea; or orthopnea/paroxysmal nocturnal dyspnea (PND)/palpitations.
- *Physical examination*: Look for features of trauma on face such as bruises, reddish or bluish discoloration patches, hives, and insect bites. If trauma, feel for features of nasal, orbital, maxillary, or mandibular fractures. Look for acute ocular, dental, auricular, gum, and parotid infections; orthopnea; or normal respiration.
- *Systemic examination*: It includes pulse, BP, jugular venous pressure (JVP), cardiac, hepatic respiratory, or central nervous system (CNS) examination. If pregnancy is associated with hypertension then consider preeclampsia. If present, treat as described above.

Differential Diagnosis

Various infective causes of facial swelling must be rule out and appropriate antibiotics therapy should be prescribed.

- *Infectious causes*: Cellulitis, impetigo, erysipelas, viral exanthem, parotitis, necrotizing fasciitis, herpes zoster, and malignant otitis externa
- *Inflammatory causes*: Insect bite, apical abscess with buccal swelling, and contact dermatitis
- *Immunologic causes*: Systemic lupus erythematosus, angioneurotic edema, and vancomycin flushing reaction

Management

Maintain airway if the situation is life-threatening as in case of anaphylaxis due to insect/snake bite, food or drugs causing respiratory distress, or severe trauma obstructing airways. Ventilatory support should be provided in cases of severe respiratory distress

Take care of IV fluids, O_2 support, airways clearing, BP monitoring (vasopressor, if required), and fresh blood transfusion in case of severe bleed. Drainage of abscess is important step in managing the abscess along with antibiotic therapy. As the infection or infected thrombus may move to CNS and cause cavernous sinus thrombosis or CNS abscess. Look for underlying cause, in case of acute on chronic swellings. Treat it accordingly. Most of the infections of face need to be treated by antibiotics.

FACIAL CELLULITIS

Facial cellulitis must be treated more aggressively than cellulitis in other body areas because of the morbidity and mortality of complications, which include cavernous sinus thrombosis and possible extension of the cellulitis to the brain. Most patients with facial cellulitis are admitted for IV antibiotics, especially when there is significant facial involvement or systemic symptoms such as fever. Most facial cellulitis is caused by extension of infection from the oral cavity, whereas acute sinusitis accounts for most of the remainder of causes. Because each upper central incisor drains bilaterally, they are of more concern when they become infected, although the maxillary molars are the most common origin of facial cellulitis. In children, it is important to distinguish facial cellulitis from buccal cellulitis, but the era of systemic buccal cellulitis is almost gone with the advent of *Haemophilus influenzae* type b vaccine. The organisms responsible for facial cellulitis in adults are usually mixed flora. In a recent study of cultures taken at surgical drainage, 19% of the samples contained only aerobic organisms, 36% only anaerobic organisms, and 45% contained mixed aerobic and anaerobic flora. *Streptococcus* was the most frequently isolated aerobic bacteria, noted in 65% of infections. Anaerobic bacteria accounted for 62% of isolates and the most frequently isolated were *Prevotella* species, in 55% of cases. Facial cellulitis must be treated aggressively with antibiotic therapy (**Table 2**).

TABLE 2: Facial infection and recommended antibiotic therapy.

Infections	*Antibiotics*	*Duration of therapy*
Nonpurulent cellulitis	Oral—amoxicillin-clavulanate, clindamycin, and cephalexin Parenteral—cefazolin and nafcillin clindamycin	5–7 days
Purulent cellulitis	Oral—TMP-SMX, doxycycline, clindamycin, and linezolid Parenteral—vancomycin, linezolid, and daptomycin	5–7 days
Facial cellulitis of dental origin	Oral—amoxicillin-clavulanate, clindamycin, and β-lactam drug plus metronidazole Parenteral—ampicillin-sulbactam, piperacillin, tazobactam, and β-lactam drug plus metronidazole	5–7 days
Erysipelas	Oral—amoxicillin and amoxicillin-clavulanate Parenteral—vancomycin and clindamycin	5–7 days
Impetigo	Topical—mupirocin ointment ± oral therapy Oral therapy—amoxicillin-clavulanate and cephalexin Alternative—azithromycin MRSA suspected—clindamycin/TMP-SMX	5–7 days
Suppurative parotitis	Oral—amoxicillin-clavulanate, clindamycin, and cephalexin with metronidazole Parenteral—ampicillin-sulbactam or cephalexin with metronidazole if allergic to Penicillin Consider vancomycin if hospital acquired	10–14 days
Masticator space infection	Parenteral—clindamycin, ampicillin-sulbactam, piperacillin, tazobactam, or ampicillin with metronidazole	10–14 days
Antibiotic doses for facial infections		
Route	*Antibiotics*	*Doses*
Oral antibiotics	Amoxicillin-clavulanate	875/125 mg twice daily
	Azithromycin	500 mg first dose the 250 mg four times daily for 4 days
	Cephalexin	500 mg four times daily
	Clindamycin	300 mg three to four times per day
	Doxycycline	100 mg two times per daily
	Metronidazole	500 mg 8 hourly
	Trimethoprim-sulfamethoxazole	1 double strength (DS) tablet twice daily
Parenteral antibiotics	Ampicillin-sulbactam	1.5–3.0 g every 6 hourly
	Piperacillin tazobactam	3.375 g every 6 hourly
	Clindamycin	600 mg every 8 hourly
	Cefazolin	1 g every 8 hourly
	Linezolid	600 mg every 12 hourly
	Daptomycin	4 mg/kg IV every 24 hours
	Metronidazole	1 g loading then 500 mg every 8 hours
	Vancomycin	15 mg/kg every 12 hours adjusted with renal function

(TMP-SMX: trimethoprim-sulfamethoxazole)

JAW DISLOCATION

Jaw (mandible) dislocation results due to the displacement of mandibular condyles from articular groove in temporal bone. Most of the dislocations can be managed and reduced in emergency department. The temporomandibular joint (TMJ) is formed by articular surface between the mandibular condyles and the temporal bone. It is lined by synovial membrane and act by hinge as well as sliding mechanism. It is supported by various ligaments. Dislocation of mandible can happen in four positions: anterior, posterior, superior, and lateral. Risk factors for mandibular dislocations are as following:

- Shallow mandibular fossa
- Dystonia
- Convulsions
- Hypermotility syndrome
- Previous history of TMJ dislocation

Anterior Dislocation

This is the most common type of position amongst all and results in displacement of the condyle anterior to the articular eminence of the temporal bone. This condition is classified as acute, chronic recurrent, and chronic. Anterior dislocations happen due to dissociation between muscular actions of jaw muscles (masseter, temporalis, and lateral pterygoid). Etiologies of anterior dislocation are most often the result of low energy trauma (e.g., tooth extraction) or secondary to a medical condition that affects the stability of the joint (seizures, ligamentous laxity, degeneration of joint capsule, dystonia, and general anesthesia). Even after endoscopic procedure, anterior dislocation has been reported.

Posterior Dislocation

It usually occurs due to a blow directly to chin. Due to blow to mandible, its condyles are pushed backwards to toward mastoid.

Lateral Dislocation

The most common reason of such dislocation is mandibular fracture. The condylar head can be palpated in temporal space as it migrates laterally away from skull.

Superior Dislocation

It occurs due to direct blow to a half open mouth. It is also known as central dislocation. With such kind of injury, fracture of glenoid fossa can occur with mandibular condyle displacement into middle skull base.

Clinical Presentation

Jaw pain or trismus after extreme mouth opening or direct blow to the jaw are the most common presenting features of jaw dislocation. Immediately after dislocation, a loud crunch noise can be heard against the ear drum. Apart from these, other symptoms are not able to close mouth completely, drooling from mouth, difficulty with speaking, swallowing, and malocclusion. Previous history of similar kind of dislocation or hypermotility syndrome or any injury to TMJ should be elicited. Physical examination is needed to rule out other pathologies apart from jaw dislocation as pain and jaw movement difficulty is present in all patients with mandibular pathologies.

Anterior dislocation will have a palpable and/or visible periauricular depression from displacement of condyle. Deviation of jaw to any one side is evident in unilateral jaw dislocation of the opposite side. In bilateral anterior dislocations, patients generally show an underbite or prognathic with pain over both TMJ. Oral cavity examination is necessary to rule out any laceration that may suggest open injury. Examination of external auditory canal is also necessary to assess any injury. Thorough examination of V and VI cranial nerves are mandatory to rule damage to them while dislocation.

Differential Diagnoses

- Condylar fracture
- Trismus
- Mandible fracture
- Dystonic reaction
- TMJ dysfunction
- Traumatic hemarthrosis

Diagnosis

Before relocation of any joint, a plain X-ray must be done to rule out any fracture. Likewise, X-ray of mandible also must be done to rule out any mandible fracture, especially in traumatic dislocation. Orthopantomogram is the view of choice in case of jaw dislocation. It is a panoramic view that is acquired with camera planning around the patient. CT scan is more sensitive in diagnosing mandibular dislocations and other abnormality hence its use is increasing in traumatic dislocations. It is acceptable now a day to do CT scan as initial imaging modality in traumatic mandibular pathologies. Primarily, MRI is not ordered for acute management. However, it is a useful tool to detect soft tissue injury along with complications of mandibular injuries. It is informative for planning of long-term management in chronic recurrent dislocations. Laboratory tests are not required in healthy patients with isolated jaw injury.

Management

In emergency department, initially assessment of airway, breathing, and circulation (ABC) is to be done primarily. If every sign and investigation is suggestive of isolated acute mandibular dislocation, then it is to be decided whether close reduction in emergency is appropriate or not. Maxillofacial surgeon opinion is required in complicated as well as chronic mandibular dislocations. Close reduction can be done in emergency under proper analgesia and muscle relaxants. Local anesthesia can be five in TMJ as well as masseter and deep temporal nerve block. By reducing spasm and pain, it aids to successful reduction. Systemic benzodiazepine, i.e., IV midazolam also helps in reduction by pain relief and reducing muscle spasms. Various methods are used routinely to reduce anterior jaw dislocation. Eliciting gag reflex may be useful in reducing jaw dislocation according to some case reports.

Classical Technique

This is the most commonly used technique (**Fig. 1**). While doing this maneuver physician stands in front of sitting patient and

FIG. 1: Classic technique.

FIG. 2: Recumbent technique.

FIG. 3: Wrist pivot method.

places gloved thumbs on inferior molars a deep as possible and fingers are curved beneath the body and angle of mandible. Backward and downward pressure is to be given through thumb and fingers with slight mouth opening. This helps to reposition condyles back into fossa by disengaging them from anterior eminences. Sometimes it is difficult as the strength of masseter contractions has to be overcome. A risk of fingers bitten or disease transmission is involved in such procedures.

Recumbent Approach

Standing behind the recumbent patient, physician places both thumb on inferior molars and gives downward and backward pressure until condyles reaches back to normal position (**Fig. 2**).

Wrist Pivot Method

With same position as classical method, cephalad pressure on tip of mentum by thumb and caudal pressure on inferior molars by fingers as shown in **Figure 3** is to be given to reduce displaced mandible.

Postreduction Care

After successful relocation, no specific medicines are required. Sometimes soft collar may be prescribed to support TMJ. Patients must be advised not to open mouth very wide or yawn forcefully. Patients with history of recurrent dislocation or with other complications are requested to follow-up with specialists. Those patients who are suffering from chronic dislocations may get help initially from Barton bandage (elastic fabricated bandage that wraps around the top of the head and mandible). Further surgical management is required for permanent solution of chronic dislocation.

Complications

Complications due to dislocation are as follows:

- Degenerative disease of joint structures
- Injury to facial and external carotid nerve
- Injury to external auditory canal
- Deafness

Complications of reduction are as follows:

- Fracture of mandible
- Physician thumb may get injured

Jaw dislocation is not uncommon to treat for emergency physician. Prompt action and accurate maneuver can relocate mandible without much efforts to its normal location. Patients can be discharged on outpatient (OP) basis with follow-up with specialist, oral analgesics, and safety instructions.

SUMMARY

Facial emergencies are important to address at the right time. Emergency physician should aware of the relevant anatomy of the face-related illness. Facial infection needs immediate attention. As face is the mirror of body, any small or large swelling can be seen very early and hence, the treatment should never be delayed. The facial swelling, etiologically, can be grouped into two types; localized and generalized. Dislocation of TMJ is another condition which needs to be addressed in timely manner in emergency department.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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137 CHAPTER

Neck, Throat, Oral, and Dental Emergencies

Aman Sharma, Devendra Richhariya

INTRODUCTION

The oral cavity comprises of many structures with various functions and is also the gateway for the microbes to enter our body that may lead to different pathological conditions. The throat is the continuation of oral cavity anteriorly and comprises of epiglottis, pharynx, and larynx. The neck is among the most complex structures in the body which plays a vital role in head movement and mobility. This chapter will discuss the common emergency conditions associated with these structures. The common presentation of disease related to throat "sore throat" are pharyngitis, epiglottis, and peritonsillar abscess. Emergency physician must evaluate and manage sore throat manifestation and oral lesion carefully as these may be features of serious illness.

PHARYNGITIS

Pharyngitis and tonsillitis are among the most common presenting conditions to the emergency department (ED) worldwide. The affected population may range from infants to elderly with peaked visits during seasonal flu outbreaks. Causative organisms are both bacterial—*group A beta-hemolytic streptococci (GABHS), Fusobacterium necrophorum, Neisseria gonorrhoeae, Mycoplasma pneumonia, and Corynebacterium diphtheriae* and viral origin—*rhinovirus, influenza, parainfluenza, respiratory syncytial virus, and corona virus*. Causative organism invades the mucosa and release multiple toxins and give rise to variety of clinical manifestations (**Flowchart 1**).

Clinical Presentation

Viruses are most common pathogens for the cases of pharyngitis or tonsillitis; however, the clinical symptoms in both viral and bacterial causes may be similar. While the viral pharyngitis is self-limiting and most commonly affecting the adults, bacterial pharyngitis caused due to GABHS can have serious complications in children. Usually the symptoms are of rapid onset in nature with sore throat being the most common presenting complaint. Other symptoms include fever, malaise, body ache, headache, enlarged tonsils, dysphagia, and anorexia. Cough, coryza, and diarrhea are usually associated with viral pharyngitis. Red flags (serious) clinical features are (STD_4) stridor, tachypnea, drooling of saliva, dyspnea, dysphonia, and dehydration.

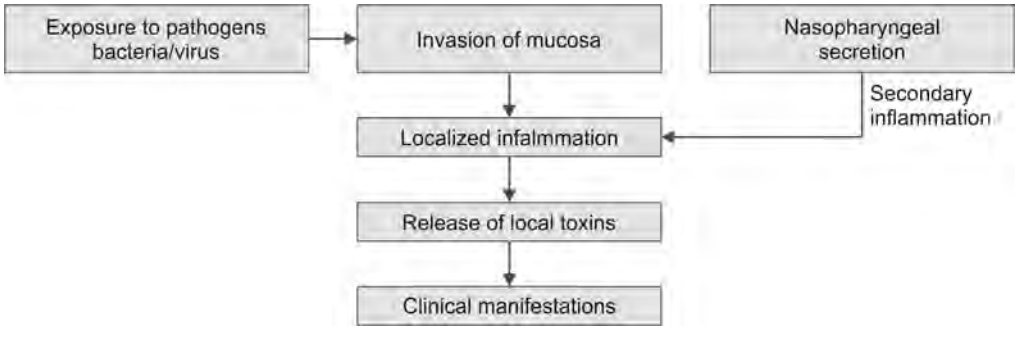
Evaluation

History

Contact with persons having similar clinical features and travel history.

Physical Examination

Bacterial infection—visual examination of oropharynx reveals exudative changes with tonsillar hypertrophy and erythema,



FLOWCHART 1: Pathophysiology of pharyngitis.

diffuse lymphoid hyperplasia of Waldeyer's ring, tender cervical lymph nodes, petechiae at junction of hard and soft palate, and rashes over torso (**Fig. 1**). Viral infection—whitish exudates covering erythematous pharynx and tonsils, cervical lymphadenopathy, and conjunctivitis. Pharyngitis due to GABHS bacteria is most common in children and spikes during seasonal transition from winters to spring.

Investigations

While the viral pharyngitis is self-limiting and does not require any specific investigation, bacterial pharyngitis requires laboratorial evaluation. To identify the likelihood of a bacterial infection in adult the Centor score may be used for patients presenting with sore throat. Throat swab and testing for GABHS pharyngitis by rapid antigen detection test (RADT) should be performed as the clinical features do not differentiate much between the viral and bacterial cause. RADT have a sensitivity and specificity of 95%. Throat cultures should be sent in children and adolescents with negative RADT tests. Antistreptococcal antibody titers are not recommended in the routine evaluation.

Treatment of Pharyngitis

Viral Pharyngitis

Only supportive treatment is recommended. Acetaminophen or a nonsteroidal anti-inflammatory agent (NSAID) may provide relief of sore throat pain. Lozenges, sipping warm beverages, eating soft foods, and warm saline gargles also provide relief from throat pain and soreness.

Group A Beta-hemolytic Streptococci Pharyngitis

Rapid antigen detection test positive and throat culture positive patients require antibiotic therapy for prevention of complications and better recovery. The Infectious Diseases Society of America (IDSA) recommends penicillin or amoxicillin as first-line antibiotics in treatment of GABHS. Single shot of intramuscular 1.2 million units of benzathine penicillin or oral penicillin V 500 mg twice daily for 10 days. For penicillin-allergic patients, the IDSA recommends first-generation cephalosporin, clindamycin or clarithromycin, and azithromycin as alternatives. The routine use of steroids is not recommended, but they may shorten the span of the illness and provide pain relief in adults. Oral prednisolone 40–60 mg per day for 1–5 days or single intramuscular dose of dexamethasone 10 mg may be prescribed. The irrational use of antibiotics worldwide is a growing concern as most of the patients with non-GABHS pharyngitis also receive antibiotics. Only symptomatic supportive treatment should be advised. Summary of treatment for pharyngitis is given in **Flowchart 2**. Since the condition is self-limiting, most of the cases can be treated on outpatient basis. However, the red flags should be always taken into account and in case patient develops any complications they should be advised for an otolaryngologist consultation and hospitalization.

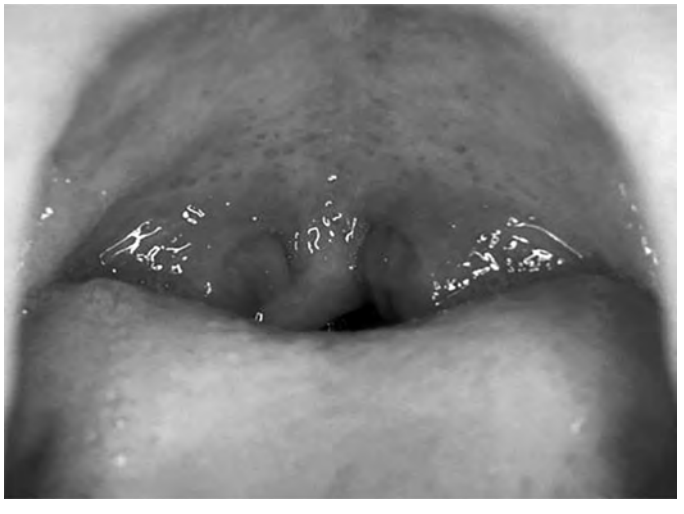


FIG. 1: Redness and edema of the oropharynx and petechiae on the soft palate. ***(For color version, see plate 15)***

EPIGLOTTITIS

It is characterized by inflammation and swelling of epiglottis, and is a potentially life-threatening condition which requires immediate attention. *Causative organism* and *conditions* responsible for epiglottitis are *bacterial—Haemophilus influenzae* type B (Hib), *Streptococcus pneumoniae, Streptococcus pyogenes, Pseudomonas aeruginosa,* and *Candida* in immunocompromised hosts; *burns*—thermal inhalational injury; and *trauma*—upper airway trauma, chemical irritants, and foreign body. Exposure to these pathogens, inhalational injury, and trauma leads to invasion of mucosa of epiglottis and aryepiglottic folds which causes local inflammation with edema and increased secretions. Obstruction of airway during inspiration occurs and leads to serious complications.

Clinical Presentation

Patients usually have symptoms of pharyngitis, i.e., sore throat, fever, and throat pain. The patient also typically has dysphagia and odynophagia along with the above-mentioned symptoms. Dysphonia may also be present; however, hoarseness is not commonly seen. Inspiratory stridor is a characteristic finding of epiglottitis. Emergency physician is expected to identify red flags (serious clinical features), *tripod posture* (**Fig. 2**), *cannot talk, cannot swallow, drooling of saliva, febrile toxic child, altered mental status, hypoxia, and compromised airway*.

Evaluation

History

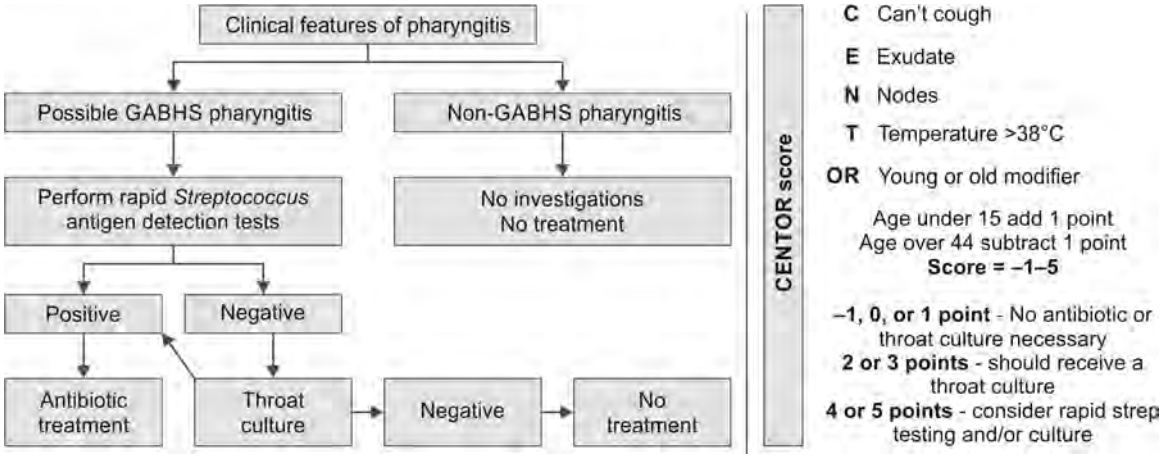
Smokers and persons having frequent upper respiratory infections have more risks for developing this condition.

Physical Examination

Cherry red or pale, swelling, and edema of epiglottis are usually seen (**Fig. 3**); however, routine direct visualization is not advised as it may further cause airway compromise and completely obstruct the airway.

Investigations

Complete blood count should be sent, lateral view X-ray of neck—swelling of the epiglottitis is seen referred to as *"thumb print sign"*. Gold standard is laryngoscopy, flexible laryngoscope should be preferred.



(GABHS: Group A beta-hemolytic streptococci)

FLOWCHART 2: Management steps of pharyngitis.

FIG. 2: Leaning forward on hands, in the "tripod" position; mouth open, tongue out, head forward, and tilted up in a sniffing position in an effort to relieve the acute airway obstruction secondary to swollen epiglottis.

FIG. 3: Redness and edema of epiglottis. ***(For color version, see plate 16)***

Treatment

Airway patency should be addressed at the earliest, if airway is found to be compromised or obstructed patient must be intubated or taken for tracheostomy. Humidified oxygen should be inhaled if oxygen saturation is <94%. Empirical antibiotics should be administered, first-line drugs are cefotaxime and ceftriaxone along with vancomycin, alternatively levofloxacin with clindamycin may be used. Role of steroids is not clear; acetaminophen may be used for pain and fever. In case oral hydration is not maintained, intravenous (IV) hydration should be started. Otolaryngologist consultation should be given at the earliest.

Disposition

Uncomplicated cases with no airway compromise can be treated as outpatient. Hospitalize patients with poor general condition and hydration status, patients with compromised airway may require advanced airway adjuncts thus require critical care.

PERITONSILLAR ABSCESS

Also known as *quincy*, it is the collection of pus in peritonsillar space. It is a complication of tonsillitis which leads to spread of infection to tonsillar crypts further invading peritonsillar tissues causing cellulitis and abscess formation (**Figs. 4** and **5**).

Etiology

It occurs due to complication of tonsillitis. Various bacterial species are responsible for this condition: *Aerobic bacteria—GABHS, Corynebacterium diphtheriae, Staphylococcus aureus,* and *Streptococcus milleri* group and anaerobic bacteria—*Fusobacterium necrophorum, Bacteroides, Peptostreptococcus, and Prevotella.*

Clinical Presentation

Patients usually have prior symptoms of sore throat and fever. The symptoms progress once there is spread of pus through the neck structures. There is worsening of sore throat, dysphagia, odynophagia, otalgia (ipsilateral), high-grade fever, drooling,

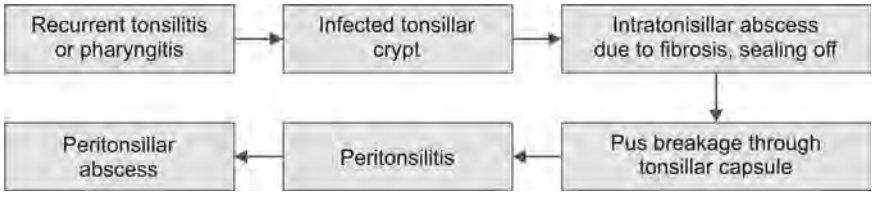


FIG. 4: Pathophysiology of peritonsillar abscess.

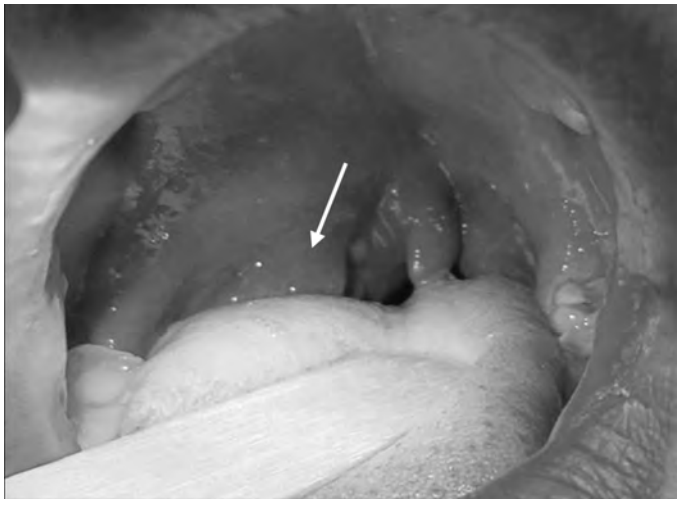


FIG. 5: A right-sided peritonsillar abscess with deviation of uvula to left side. ***(For color version, see plate 16)***

and trismus. Most patients have a characteristic muffled, "hot potato voice" with halitosis. Red flags (serious clinical features) are *toxic general appearance, altered mental status, airway obstruction, poor hydration status, and poor oral acceptance.*

Evaluation

History

Incidence peaks between 20- and 40-year age groups, patients with chronic tonsillitis, and smoking.

Physical Examination

Drooling, restricted jaw opening (trismus), and cervical lymphadenitis are usually seen. Upon direct visualization erythematous swollen soft palate, displacement, and inflammation of tonsillar pillar leading to deviation of uvula to contra lateral side.

Investigations

Aspiration of pus from the affected site establishes the diagnosis of PTA. Complete blood count, renal profile, and electrolytes are important investigations if patient has a toxic look with poor hydration status. Routine radiographs are not recommended if a clinical diagnosis has been established.

Treatment

The main surgical intervention includes needle aspiration, incision and drainage, and tonsillectomy. Needle aspiration of abscess acts a diagnostic aid, is easy to perform, and provides immediate symptom relief. Antibiotic treatment should not be delayed, oral antibiotics may not be suitable due to poor oral compliance thus IV antibiotics are preferred. IV penicillin G along with metronidazole or third-generation cephalosporins with metronidazole are drugs of choice. In case one is allergic to penicillin group IV piperacillin/tazobactam may be used. If the patient is stable with no complications they may be started on oral antibiotics, amoxicillin/clavulanate is the preferred oral drug.

Disposition

Patients with signs of toxemia, poor hydration status, and airway compromise should be hospitalized and surgical intervention should be performed without delay.

LUDWIG'S ANGINA

It is described first in 1836 by a German physician *Wilhelm Frederick von Ludwig*, it is a potentially life-threatening condition with rapid progression within hours, the cellulitis starts from the submandibular space and spreads to the connective tissues of floor of mouth and neck.

Etiology

Odontogenic polymicrobial cellulitis mostly caused by *viridans group streptococci (VGS), staphylococcus aureus,* and anaerobes. *Dental pathologies:* Dental caries, recent dental procedures, and poor oral hygiene. *Trauma*: Mandibular fractures, facial fractures, and piercings of tongue. *Other causes*: Submandibular sialadenitis, oral malignancy, and systemic illness with immunocompromised status [acquired immunodeficiency syndrome (AIDS), diabetes mellitus, and post-transplant patients).

Clinical Presentation

Patients mostly present with neck pain and swelling, along with dysphagia. Other symptoms include dysphonia "hot potato" muffled voice, drooling of saliva, pain over floor of mouth, tongue swelling, restricted neck movement, and fever. Red flags (serious clinical features) are *toxic general appearance, altered mental status, airway obstruction, poor hydration status, and poor oral acceptance*.

Evaluation

History

Dental caries and poor oral hygiene usually precipitates the risks. Any recent dental extraction should raise the suspicion for Ludwig's angina.

Physical Examination

Swelling over submandibular glands (**Fig. 6**), swelling, and protrusion of tongue are most commonly seen. Patients may also have elevation of floor of mouth with displacement of tongue posteriorly. There is marked tenderness of floor of mouth, neck, and surrounding tissue with crepitus on palpation. This tense swelling leads to restricted neck movement often termed as "bull neck".

Investigations

Clinical presentation forms the base of diagnosis, though no specific laboratorial tests are indicated, CT scan of neck with IV contrast enhancement is the study of choice, as it gives a details of airway compromise, soft tissue swelling, and involvement of mediastinum.

Treatment

Comforting the patient's posture, maintaining airway patency, and oxygenation should be the priority. Wide bore IV access should be immediately secured and crystalloid fluid should be administered. Advanced airway should be placed without any delay in case of compromised airway.

Antibiotic Therapy

Broad-spectrum empirical antibiotics should be administered with priority. Both aerobic and anaerobic coverage should be given. Patients with less severe symptoms and patent airway may be treated with oral antibiotics. Oral penicillin VK and amoxicillin are first-line choices while levofloxacin, cefuroxime, and amoxicillin-clavulanate are the second-line choices. Patients with suspicion of deep neck infections should be treated with IV piperacillin/tazobactam, imipenem-cilastatin, and ertapenem. Surgical drainage should be done if CT suggests abscess.

FIG. 6: Swelling of submandibular glands along with swelling of neck and surrounding tissue. ***(For color version, see plate 16)***

RETROPHARYNGEAL ABSCESS

Retropharyngeal abscess (RPA) is a polymicrobial abscess of posterior pharyngeal wall involving the deep tissues of neck mostly seen in children with peak incidence between 3 years and 5 years of age.

Etiopathogenesis

It is a multifactorial (**Fig. 7**) and polymicrobial infection caused by GABHS, *Staphylococcus aureus* [including methicillin-resistant *S. aureus* (MRSA), *H. influenzae, Bacteroides*, *Peptostreptococcus*, and *Fusobacterium* species.

Clinical Presentation

This condition is difficult to diagnose as the symptoms mimic other infective conditions of throat. Fever, neck swelling, throat pain, and dysphagia are most common symptoms. Chest pain is an indication for involvement of mediastinum as well. Increased irritability and poor oral intake in children is a marker of disease progression. Neck stiffness and breathing difficulty can be late presentation and may further lead to airway compromise.

Evaluation

History

It includes poor oral hygiene and lack of regular brushing and cleaning of oral cavity in children. Any penetrating neck injuries in adults along with the above-mentioned complaints should lead to suspicion of RPA.

Physical Examination

Though physical examination alone is not sufficient to make the diagnosis, one should look for cervical lymphadenopathy and restricted neck movement or torticollis. Also look for trismus, stridor, and drooling as these may indicate further worsening of the condition. There may be tenderness on moving larynx and trachea side to side referred to as tracheal "rock" sign. Red

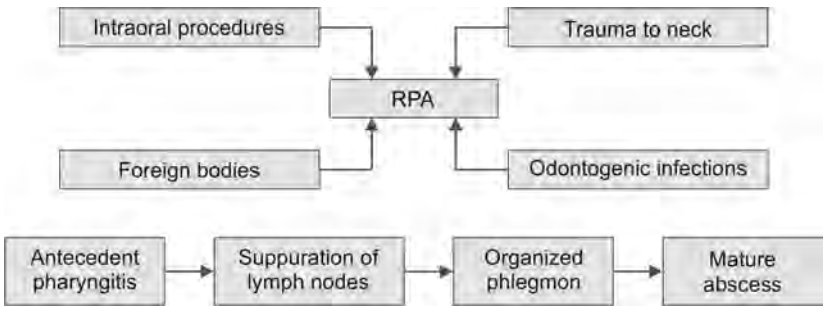


FIG. 7: Multifactorial cause of retropharyngeal abscess (RPA).

flags (serious clinical presentation) are airway compromise, drooling, neck tenderness and rigidity, stridor, respiratory distress, and trismus.

Investigations

There are no specific laboratorial tests for confirmation; however, contrast-enhanced CT scan of neck is the preferred modality of choice for diagnosis of this condition (**Fig. 8**). The abscess appears as a hypodense lesion with peripheral ring enhancement in retropharyngeal space.

Treatment

Assessing and securing the airway, breathing, and circulation is the key to save patients life. Early endotracheal intubation or tracheostomy should be performed on patient with impending obstruction and respiratory distress. Empirical IV antibiotic therapy should be started early; penicillin G with metronidazole or piperacillin/tazobactam is the first-line antibiotics to be given. In case patient does not respond well or there is risk for MRSA, patients should be given vancomycin or linezolid.

Intravenous fluids should be started if patient have dehydration or signs of inadequate perfusion. Supportive care including painkillers should be administered as per symptoms of patients. Urgent otolaryngologic consultation should be taken for any surgical intervention.

Disposition

This is a potentially life-threatening condition. There should not be any delay in hospitalizing these patients. Surgical intervention is required for patients not responding to antibiotics, with impending airway obstruction and if CT scan shows a hypodense lesion >2 cm in size, these cases need to be treated in the critical care units.

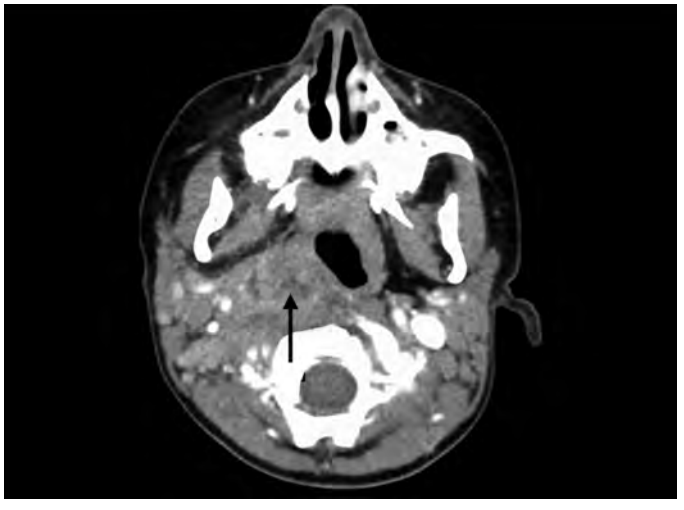


FIG. 8: Large retropharyngeal abscess with surrounding swelling.

INFECTIOUS MONONUCLEOSIS

It is often called as kissing disease or glandular fever that spreads through saliva. Most organisms causing this condition are from *Herpesviridae* family *[Epstein–Barr virus (EBV)]*. Most common causes of infection over 90% of the cases are caused by EBV and their pathogenesis is given in **Figure 9**. *Non-EBV causes* are *Cytomegalovirus* (CMV), adenovirus, hepatitis A, *Toxoplasma gondii*, and GABHS.

Clinical Presentation

The incubation period is between 4 and 6 weeks; the clinical course may vary from person to person. Patient complain that the sore throat is "worst ever" and is often associated with fever, malaise, fatigue, and body ache. Some may complain of breathing difficulty as the enlarged tonsils cause significant narrowing of airway and may cause an impending airway compromise. One should suspect splenic enlargement or splenic rupture if patient present with severe abdomen pain.

Evaluation

History

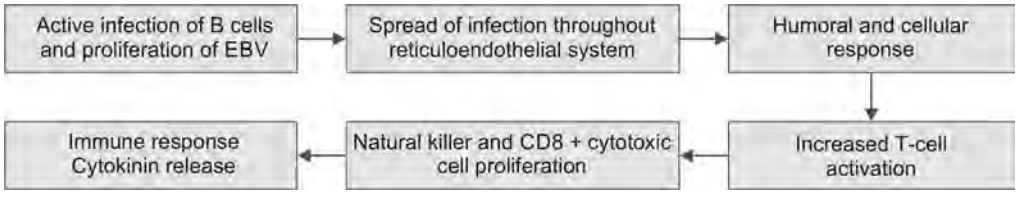
The symptoms usually increase in the initial days followed by a dip in their course often referred to as "waxing and waning". Sore throat along with rashes in young adolescents one should suspect infectious mononucleosis (IM).

Physical Examination

Since it spreads throughout reticuloendothelial system, one should thoroughly examine the lymph nodes. It shows symmetrical lymphadenopathy with tenderness. Exudative pharyngitis may be seen (**Fig. 10**), which may cause airway compromise. Splenomegaly is also common with splenic rupture being a rare but potentially life-threatening complication. Nonspecific rashes or petechiae may also be present. *Red flags* (serious clinical features) are airway compromise—tonsillar enlargement, abdominal tenderness—splenic rupture, anemia and jaundice—hepatic failure, neurological involvement, signs of shock, and secondary bacterial infections—PTA or RPA.

Investigations

Complete blood count is a must; it usually reveals leukocytosis with over 50% lymphocytes. Liver function tests may show elevated transaminases up to three times normal value along


Active infection of B cells and proliferation of EBV
Spread of infection throughout reticuloendothelial system
Humoral and cellular response
Increased T-cell activation
Natural killer and CD8 + cytotoxic cell proliferation
Immune response Cytokinin release

(EBV: Epstein–Barr virus)

FIG. 9: Etiopathogenesis of infectious mononucleosis.

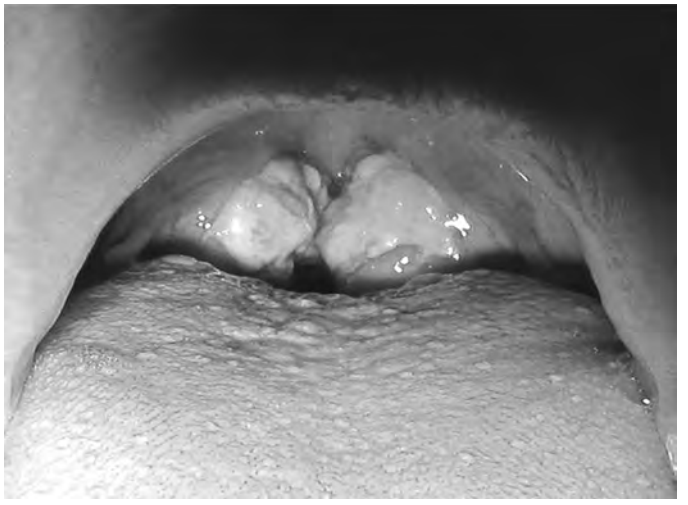


FIG. 10: Exudative pharyngitis in the throat with mononucleosis. ***(For color version, see plate 16)***

with hyperbilirubinemia causing clinical jaundice. Monospot tests detect the presence of heterophile antibodies which has high specificity and sensitivity. Ultrasound of abdomen, if there is splenic enlargement in examination, also helps to differentiate for appendicitis.

Treatment

Always secure airway, breathing, and circulation (ABCs) and access for airway patency. Start patient on crystalloid fluids if dehydration is present, antipyretics and analgesics should be given according to patient's symptoms. Steroids should be given if one has chances for impending airway compromise, methylprednisolone should be administered intravenously for rapid relief. Prednisolone and dexamethasone may also be considered. Patients should be advised to avoid contact sport activities and other strenuous activities. Surgical consultation should be given if one suspects complications including splenic rupture or secondary bacterial infections including PTA or RPA.

Disposition

Patients with significant airway edema causing airway compromise should be hospitalized and treated with utmost swiftness. They may require critical care support as well. Patient may be given symptomatic aid and treated as outpatient. If airway patency is well maintained, other complications are not evident.

ORAL CANDIDIASIS

Candida is among the normal flora present in human body. When there is disturbance of this normal flora it leads to overgrowth leading to candidiasis or thrush. The species most commonly causing infection in humans is *Candida albicans*. Oral thrush in one of the most common fungal infections and can be found in all age groups though mostly found in the early and late stages of life. It is more of a clinical diagnosis; proper history and physical examination are enough to establish a diagnosis but confirmatory laboratory studies must be sent for confirmation. Prophylactic doses should not be given to all affected individuals, but to reduce the severity and incidence for patients falling in high risk groups. The disease has a favorable prognosis in most of the cases. Predisposing conditions leading to infections are mentioned in **Box 1**.

BOX 1: Risk factors for oral candidiasis.

Local factors

- Altered or immature oral flora
- Atrophic oral mucosa
- Dental prosthesis
- Decreased saliva production
- Impaired defense mechanism
- Oral lichen planus
- Poor oral hygiene
- Steroid
- Tobacco

Systemic factors

- Acquired immunodeficiency syndrome
- Broad spectrum antibiotics (long-term use)
- Congenital conditions
- Diabetes mellitus
- Endocrine disorders
- Immunosuppressant medications
- Malignancy
- Malnourishment
- Systemic immune suppression

Etiopathogenesis

These harmless commensals are found in various parts of body as normal flora but opportunistic overgrowth may lead into disease (**Fig. 11**). Other than *Candida albicans* other species of oral *Candida* are: *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. pseudotropicalis*, *C. stellatoidea*, and *C. tropicalis*. Usually it is a self-limiting disease; however, certain local and systemic factors may favor overgrowth and lead to invasive candidiasis. *Candida albicans* is one of the most common inhabitants of oral and gut flora, found in about 50% of individuals.

Clinical Presentation

Oral candidiasis is commonly called as oral thrush. Usually patients do not exhibit any symptoms. Most types of oral candidiasis are painless, but a burning sensation may occur in some cases. It appears as patches of gray or white friable material covering an erythematous base on buccal mucosa, tongue, gingiva, palate, and tonsils. Oral thrush is much more common in infants and usually occurs within the first week of life. *Red flags (severe clinical features)* are lesions >3 weeks, ulcerous/vesicular lesions, fresh lesion over other body area, and inflamed and striated oral patches (**Fig. 12**).

Evaluation

History

Infant—white coating present over tongue and difficulty in lactation. Pediatric—whitish/gray coat over tongue usually asymptomatic. Adults—intake of antibiotics or steroids.

FIG. 11: Etiopathogenesis of oral candidiasis.

FIG. 12: Hyperplastic candidiasis. ***(For color version, see plate 16)***
Courtesy: Devinder Singh, DNB gastroenterology

Physical Examination

Physical examination reveals classical whitish lesions in oral cavity which are usually not easily removable and may cause pain and bleeding, if scraped.

Investigations

Though diagnosing oral thrush is mostly clinical, but samples should be obtained for identification of species causing the disease and its quantification. The following laboratory investigation techniques can be used—whole saliva culture, imprint culture, or swab.

Treatment

The treatment plan consists of conservative measures and pharmacological treatment—topical and systemic. Keeping good oral hygiene, removal of dentures during night hours, and oral rinse with chlorhexidine help in treating the condition. Oral fluconazole and clotrimazole form the first line of treatment. Alternatively, caspofungin or amphotericin B may be used in case patient develops complications or does not respond to the initial pharmacological therapy.

Disposition

The condition usually does not require hospitalization unless one develops any complications or systemic features. Routine follow-up should be advised to elderly and the ones on immunosuppressant medications.

ORAL HERPES SIMPLEX

Oral herpes simplex, commonly known as herpes labialis, is an infection commonly caused by herpes simplex virus (HSV). It is common in the young, very contagious causing blisters over lips, mouth, tongue, or gums.

Etiology

Herpes simplex labialis is most commonly caused by herpes simplex virus type 1 (HSV-1). The infection is typically spread between people by sharing the household objects of infected person, direct nonsexual contact can also leads to spreading of disease, direct exposure of infected fluid from blisters, kissing the infected person, sexual contact, sharing objects of infected person—clothes, linen, and towels, stress, and hormonal imbalances in body.

Pathophysiology

Once a person is infected with HSV, the virus becomes dormant after the primary infection and lays itself in facial nerve cells (trigeminal nerve ganglion). It reinfects when the person is exposed to triggering factors and leads to recurrent infection (**Fig. 13**).

Clinical Presentation

The primary infection may be asymptomatic. One may notice small fluid-filled vesicles/blisters around the lips (**Fig. 14**) or other parts of face within 1–3 weeks of initial contact. The blisters may burst and transform to scab in few cases. During recurrence of infection the severity is usually less than the primary infective state. The common symptoms seen are burning sensation and pain over the affected areas (lips, buccal mucosa, gingival, and other parts of face), itching over the blisters, fever, headache, malaise, and running nose. *Red flags* are central nervous system (CNS) involvement—encephalitis, ocular infections—conjunctivitis, disease in pregnant women and neonates, and bacterial and fungal super infections.

Evaluation

History

Contact with infected person, young individuals, history of cold, cough, or fever. It is usually a self-limiting condition and rarely requires hospitalization. It affects in early stages of life so one must not miss such earlier events during history taking and also the recurrence is associated with any stress.

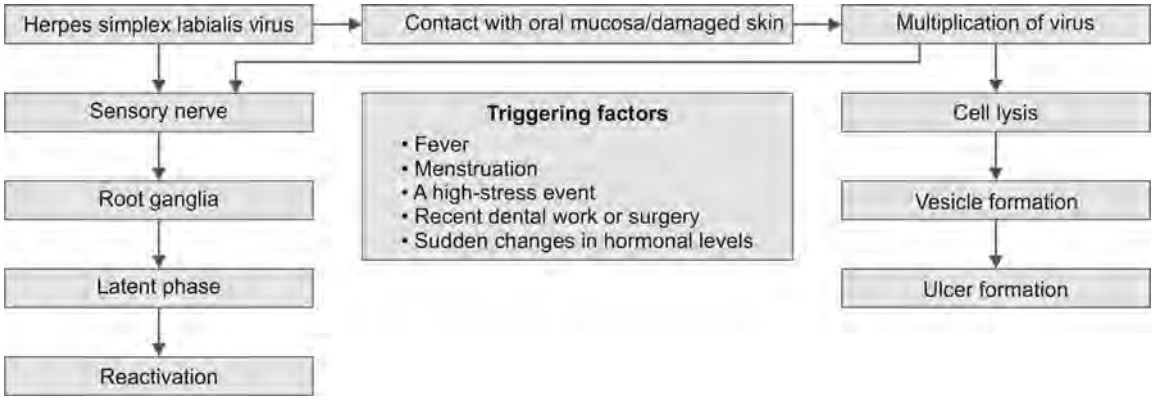


FIG. 13: Pathophysiology of herpes simplex infection.

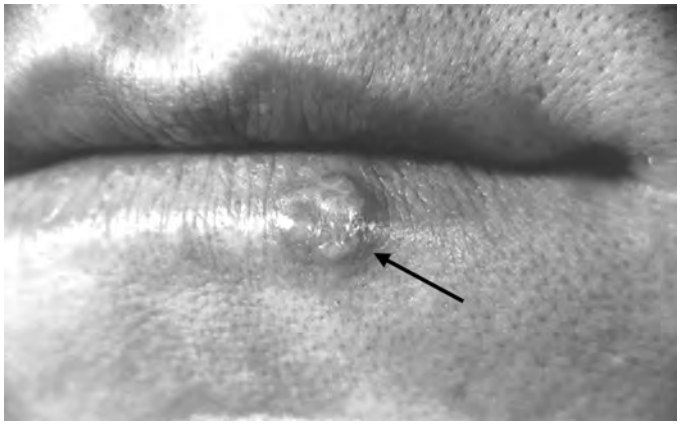


FIG. 14: Vesicles/blisters around the lips. ***(For color version, see plate 16)***

Physical Examination

The physical examination of herpes infection reveals fluid-filled vesicles/blisters.

- *Site*: Lips, oral cavity, tongue, gingival, hard, and soft palate
- *Size*: Small (2–5 mm) usually in groups
- *Shape*: Round/circular

Investigations

Various investigations can be utilized to identify the presence of HSV.

- *Cell culture*: It is the standard test for diagnosis, isolating HSV in the culture is the standard test for confirmation.
- *Polymerase chain reaction (PCR)*: It is more sensitive than cell culture, usually used in CNS involvement and eye infections.
- *Direct fluorescein antibody (DFA) methods*: Differentiates between HSV-1 and HSV-2 infections.
- *Tzanck smear*: Also known as herpes skin test, presence of Tzanck cells confirm infection by HSV.

In case of super infection with bacteria and fungi, punch biopsy may be taken for histological evaluation.

Treatment

It involves preventive measures and pharmacological therapy. Preventive measures—avoid contact with the infected person—touching, kissing, and sexual contact. Do not use linens and clothes of infected person. Pharmacological therapy—topical—*acyclovir*—5% cream, five times a day for 4 days, or *penciclovir*—1% cream, every 2nd hourly (when awake) for 4 days. Oral—*acyclovir:* 400 mg—five times a day for 5 days (adults); 15 mg/kg (maximum of 200 mg per dose) five times a day for 5 days, or *valacyclovir:* 2,000 mg twice daily for two doses, *famciclovir*: 750 mg twice daily for two doses or single dose of 1,500 mg stat.

Disposition

Most of the patients do not require hospitalization and can be treated as outpatient.

DENTAL PAIN

The most common dental problem and symptom is toothache for which a patient can visit an ED. Be it children or adult toothache may occur at any age and due to varying reasons. Most common finding associated with pain is dental caries, leading to inflammation of pulp causing pain. On the basis of its intensity, the time of occurrence and duration of pain, toothache may lead to diagnosis of its origin. It is necessary to know the site of pain and the etiology associated with pain. Pain due to pulpitis and abscess are usually same. Abscess pain is mostly associated with swelling. Teething pain occurs at age of 3–6 months. Pain due to wisdom tooth eruption occurs at 20–30 years age. Pain from teeth are referred to temporal and infraorbital region. Neuralgias are paroxysmal of pain. Here are some most common causes of dental pain for which a patient visits ED—teething pain (**Table 1**), pain due to caries (**Table 2**), pain due to trauma (**Table 3**), pain due to abscess (**Table 4**), pain due to wisdom tooth eruption (**Table 5**), referred pain (**Table 6**), periodontal pain (**Table 7**), pain in temporomandibular joint TMJ (**Table 8**), and neuralgic pain (**Table 9**).

GINGIVITIS

Gum is part of the oral mucosa, partly is fixated in the alveolar bone, cement of the root of the tooth, and partly free. Gingivitis means disease that is manifested in the gum. Gingivitis is a mild form of gum disease, but without proper treatment it can lead to the more serious periodontitis, according people having it to different strengths and due to loss, the teeth. Gingivitis is the first state of gum disorders.

TABLE 1: Teething pain.	
Pathophysiology	As the tooth erupts inflammatory mediators are released at the eruption site, causing pain
Clinical presentation	• There is hyperemia or swelling of the mucosa overlying the erupting teeth • Redness is visible at the mucosa • Increased salivation and drooling
Red flags	• General irritability • Loss of appetite and sleep
History	It is a physiologic phenomenon so teething pain occurs almost in every child. Seen most commonly at the age of 4–6 months
Physical examination	Patches of erythema on the cheeks
Investigations	Radiographic investigations are done
Treatment	• Topical application of lignocaine hydrochloride over the area • Topical application of glycerin • Mild purgatives such as castor oil and milk of magnesia are also used in treating teething

TABLE 2: Dental caries.	
Caries in children as well as in adults leads to pulpitis. According to duration and severity of caries the pulpitis is of two basic types; reversible and irreversible	
Reversible pulpitis	
Pathophysiology	The pain is mainly due to rise in intrapulpal pressure due to exudative force
Clinical presentation	Any external stimuli like temperature change or biting force cause quick sharp pain. The response is hypersensitive or else asymptomatic
Red flags	• There is no spontaneous pain • The pain subsides as the stimuli are removed
History	There is occurrence of prolonged food lodgment because of caries exposing the pulp
Physical examination	• Black lesion over tooth surface • Long-term food lodgment • No pain on percussion
Investigations	Intraoral periapical radiographs are preferred
Treatment	• Treatment of choice is root canal treatment • Nonsteroidal anti-inflammatory drugs (NSAIDs) can be given to relieve pain
Irreversible pulpitis	
Pathophysiology	With pulpal inflammation there is exudates, if the exudates come out of pulpal chamber it relieves pain, but it may cause edema. If exudates remain in pulpal chamber it causes pain
Clinical presentation	It may be of two types: 1. Symptomatic: It is associated with spontaneous pain. Pain occurs even after stimuli are removed 2. Asymptomatic: No pain is felt
Red flags	Prolonged pain to temperature
History	Long-term exposed pulp due to wide caries
Physical examination	• Caries involving very large area of tooth surface • Tenderness on percussion is positive
Investigations	Intraoral periapical radiographs are preferred
Treatment	• Treatment of choice is root canal treatment • NSAIDs can be given to relieve pain

Plaque is the primary cause of gum disease. However, other factors can contribute to periodontal disease. These include hormonal changes, chronic illnesses, medications, smoking, tobacco chewing, poor oral hygiene, and family history of gum disease.

When gingivitis left untreated, it can advance to periodontitis. In a person with periodontitis, the inner layer of the gum pulled away from the teeth and form pocket. These small spaces between teeth and gums collect debris and can become infected. The body's immune system fights the bacteria as the plaque spreads and grows below the gum line.

Toxins produced by the bacteria in plaque as well as the body's "good" enzymes involved in fighting infections—start to break down the bone and connective tissue that hold teeth in the place. As the disease progresses, the pockets deepen and more gum tissue and bone is destroyed. When bacteria build up in the mouth, it forms plaque; a condition characterized by red and inflamed sensitive gums. When this happens, teeth are no longer anchored in place, they become loose, and tooth loss occurs. Gum disease is the leading cause of tooth loss in adults.

Clinical Features Red flags

Bleeding gums (major red flag), canker sours, receding gums, chronic bad breath, and itchy feeling around the gum line. Gingivitis based on the location in the gum are classified with these reaction: exudative, proliferative, and necrobiosis.

Gingivitis Catarrhalis

Gingivitis catarrhalis, also termed as gingivitis superficialis, is inflamed gum with exudative reaction. Gingivitis catarrhalis is a disease that happens often. It is considered that 95% of the population, who has their own teeth, has these diseases. Iatrogenic factors such as dental caries, bad habits, and nutritive factors give rise to this situation. Physiologic state (puberty, menstrual cycle, and pregnanacy) or common disease (diabetes) can also give rise to this condition but only in the presence of local factors. but only in the presents of local factors. Bleeding and being sensitive to food material are the usual symptoms things. Therapeutic measures include removal of dental plaque and dental tartar. To use antiseptic preparation like hydrogen peroxide 3%. Besides that, oral hygiene should be improved.

TABLE 3: Pain due to trauma.

Traumatic injuries to teeth are very common and usually associated with road traffic accidents, contact sports such as boxing, taekwondo, karate, etc., or fights. This is very common with children than adults while playing or falling	
Pathophysiology	Pain due to trauma can be caused by exposure of pulp, avulsion, or luxation
Clinical presentation	Pain is severe like pulpitis but associated with bleeding
Red flags	Fractured crown of tooth
History	It is very important for clinician to know cause of injury, angle of impact, and objet of impact to know the extent of injury
Physical examination	Mobility of tooth is very common, sometimes fracture can occur at the root which is very painful but show no sign clinically. Radiographs are helpful in such cases
Investigations	Radiographs OPG or IOPA are most commonly done
Treatment	• If the fracture is at crown of the tooth exposing the pulp of tooth then root canal treatment is done followed by restoration of the tooth • If there is luxation, splinting is done • In case of avulsion, teeth can be replanted under half an hour of injury • If the tooth is preserved in saliva or milk and periodontal ligament fibers are intact

(IOPA: intraoral periapical radiograph; OPG: orthopantomogram)

TABLE 4: Pain due to abscess.

When a prolonged infection in tooth or in gingival tissue persists for a long time asymptomatically or there is sudden trauma to the tissue there is formation of abscess	
Pathophysiology	Usually of sudden onset on marginal or interdental gingiva. Purulent exudates may be expressed
Clinical presentation	Localized, painful, and rapidly expands
Red flags	Gingiva is fluctuant
History	Long-standing infection of tooth or gingival, forceful embedding of apple core, and tooth brush into gingiva
Physical examination	Purulent exudate in 24–48 h
Investigations	Radiographs OPG or IOPA are most commonly done and FNAC
Treatment	Removal of exudate under LA with an incision or opening the canal

(FNAC: fine needle aspiration cytology; IOPA: intraoral periapical radiograph; LA: local anesthesia; OPG: orthopantomogram)

TABLE 5: Pain due to wisdom tooth eruption.

This pain usually occurs in the early 20s. The pain aggravates and subsides by its own periodically, but sometimes persists for a longer duration	
Pathophysiology	Infection of soft tissue surrounding the crown of partially erupted tooth
Clinical presentation	Spontaneous pain, operculum may get traumatized by opposing teeth
Red flags	Pericoronitis is seen
History	Occurrence at the age of 21 years and onwards, erupting wisdom tooth is visible
Physical examination	It is seen usually around mandibular third molar. Edema in submandibular region and peritonsillar area
Investigations	Circumferential bone resorption around tooth seen in radiograph
Treatment	• Antibiotics—metronidazole 200 mg three times for 7 days • Drainage of abscess • Extraction of concerned tooth • Operculectomy can also be done

TABLE 6: Referred pain.

Pain may be referred to teeth from inflamed nasal mucosa, nonspastic myofascial pain from temporalis and masseter muscle or the pain arriving from the tooth may be referred to temporal and frontal region	
Pathophysiology	Pain occurring in the mandibular posterior tooth is referred to the area where the mandibular nerve arises
Clinical presentation	Pain referred to tooth is intense or sometimes mild. Pain referred from tooth is intense and involves almost half of the face including temporal and frontal bone
Red flags	Referring area is tender to touch
History	Long-term inflammation of the referring area
Physical examination	Trismus and sinusitis
Investigations	OPG
Treatment	Analgesics to relieve pain

(OPG: orthopantomogram)

Hyperplastic Gingivitis

Hyperplastic gingivitis is manifested with exudative inflammation of gingiva. It is a rare disease and appears in children and adolescent. Etiology factors are of the local nature such as dental plaque, poor dental hygiene, and teeth tartar. In this disease medicine has an impact on the epilepsy disease. It is said that the hyperplastic gingivitis is a hereditary disease.

TABLE 7: Periodontal pain.	
Pathophysiology	It may occur due to inflammation of periodontium directly such as trauma, adjacent impacted tooth, or indirectly through pulpal infection
Clinical presentation	Intense pain which can be easily localized, sometimes mobility in teeth
Red flags	Tooth is tender to lateral percussion
History	Inflammation of periodontium occurs due to trauma or long-term caries
Physical examination	Inflammation over periodontium and bleeding on probing from gingiva
Interpretation of findings	Acute or chronic periodontitis
Investigations	OPG or IOPA
Treatment	Complete oral prophylaxis has to be done

(IOPA: intraoral periapical radiograph; OPG: orthopantomogram)

TABLE 8: Pain in TMJ.	
Pain in TMJ occurs due to trauma, infection, dislocation, or disk displacement. The pain is mild or may be sometimes severe	
Pathophysiology	Pain usually emanates from capsular ligament
Clinical presentation	Pain in disk occurs usually during function such as opening, closing, or mastication
Red flags	Pain in response to pressure
History	The pain in TMJ is usually associated with displacement of disk due to trauma, or infection in the TMJ. Patient usually gives history of sudden jerk in the associated area
Physical examination	Pressure bearing surface of the joint are usually painless
Interpretation of findings	The findings are suggestive of TMJ arthralgia
Investigations	OPG, CBCT, or CT scan
Treatment	Occlusal disengagement of TMJ with occlusal splints. Analgesics are prescribed to relieve pain. Injecting local anesthesia into the joint also helps

(CBCT: cone-beam computed tomography; CT: computed tomography; OPG: orthopantomogram; TMJ: temporomandibular joint)

Swelling of gingiva is more common in the upper jaw and in the labial part. Gums are soft and red. There is pain while chewing and bad breath. Removal of local precipitating factors and use of antiseptic preparations are the common modalities of managing this situation.

Fibromatous Gingivitis

Fibromatous gingivitis, also termed as gingivitis neoplastic, is rare gum disease, cause is not known, and these factors have an impact on the formation of connective tissue. It affects mostly kids from 8 to 12 years old. It is believed that this disease is hereditary, but dental plaque does not have an impact in the forming of this gingivitis.

Disease is characterized by hyperplasia of gum, without exudative inflammation, that's why it becomes very hard and pale. Hyperplasia is localized in the region of lateral teeth in the upper jaw; it can cover the teeth entirely. The patient can have problems during chewing and talking. Healing process is mostly done by surgery but recurrence is common.

TABLE 9: Neuralgia.	
These are unilateral or sometimes bilateral paroxysmal pain occurring along the course of the nerve trunk	
Pathophysiology	These pains occur due to neuropathic changes occurring in the sensory fibers of the ganglion and dorsal root sometimes due to unknown causes or due to some conditions such as neoplasm, trauma, and aneurysm
Clinical presentation	Paroxysmal pain lasting for few seconds or minutes but of extreme intensity
Red flags	Usually unilateral pain which is aggravated by triggering factors like touch and movement of face such as yawning, chewing, drinking, and shaving
History	The patient gives history of sharp shooting episodes of pain occurring in response to some triggers and the pain is unresponsive to pain killers
Physical examination	There is no sensory loss along the nerve
Treatment	• Drugs such as phenytoin, carbamazepine, baclofen, and clonazepam can be given • Injection of nerve with anesthetic solution or alcohol • Nerve sectioning or nerve avulsion • Electrocoagulation of ganglion

Ulcerative Gingivitis

It is a gum disease which appears with alterative inflammation type, it appears in form of ulceronecrotic changes in the gum. It is common disease; it affects young people from the ages 20–30 years old, after the age of 45 the disease is rare. The illness has sessional characters; it appears during fall and winter.

Two microorganisms, i.e., *Bacillus fusiformis* and *Borrelia Vincentii* are common infective causative agents of ulcerative gingivitis. Some toxic materials like heavy metals (antimony, mercury, and lead) can toxically damage the parazonium and favor infection. Other precipitating factors are smoking, diabetes, malnutrition, leukemia, agranulocytosis. Gum becomes swollen and red, ulceronecrotic changes are localized in the top of interdental gum, covered with yellow or green membrane. Antiseptics and antibiotics are used for managing this condition. Consequences of the illness are curable with chirurgical intervention, gum massage, and electrophoresis with vasodilatation preparations.

Desquamative Gingivitis

It is a rare disease. Because of the desquamation of gum mucosae, the gum becomes really thin. It appears more on females; it affects at the ages 20–40 years old. It is believed that it is due to imbalance of hormones. Maintaining good oral hygiene, steroid vitamin and hormonal therapy are helpful in managing this situation.

DENTAL ABSCESS

It is a soft fluctuation swelling on tooth and associated tissues which can rapidly expands in facial spaces. Staphylococci-associated infection causes abscess. Incision and drainage is the treatment of choice with antibiotics and analgesics. It can be due to acute as well as chronic reasons.

Etiology/Causes

- Dental infections involving staphylococci are frequently associated with abscess
- Trauma to tooth may lead to abscess formation
- Chemical or mechanical irritation to gingival tissue

Pathophysiology

Staphylococci produce coagulase enzyme which causes fibrin deposition and helps in walling off lesion. Small pockets of necrotic tissues are formed inside cellulitis. Then pockets join together and enlarge to form abscess.

Clinical Presentation

Severe throbbing pain, affected area is sensitive to pressure, and swelling is seen in adjacent tissues. Teeth are nonsensitive to hot, cold, sweet, or sour.

Red Flags

Fluctuant swelling is seen in the associated tissue of teeth. Swelling may extend to facial spaces.

Evaluation

History

A long-standing infection in the periodontium or trauma or wedging of food in gingiva leads to abscess formation.

Physical Examination

Soft and fluctuant swelling in associated tooth. The tissue of swelled surface appears taut and inflamed and becomes distended. Patient may appear irritable, weak from pain, loss of sleep, and may have slight fever.

Interpretation of Findings

Depending upon location of abscess and the duration, it can be classified into acute periapical (PA) abscess, periodontal abscess, acute exacerbation of chronic lesion, and pericoronal abscess.

Investigations

Image quality of intraoral periapical (IOPA) radiograph and orthopantomogram (OPG) are done.

Treatment

Treatment include drainage of the abscess either via root canal or incision.

BLEEDING AFTER DENTAL SURGERY

Bleeding after extractions is not a major complication unless it is associated with any systemic cause or drug side effects. Mild bleeding can be managed by patient. Systemic diseases are associated with severe blood loss. Apply digital pressure over the bleeding area, if it does not work, then control the bleeding by ligating the major vessels.

Etiology/Causes

It includes single/multiple tooth extraction, implant placement, and traumatic injury.

Clinical Presentation

Bleeding after extraction can be of three types; primary—continuously after surgery, reactionary—after few hours of surgery, and secondary—after few days. Bleeding during surgery like implant placement is expected and usually easily controlled. However, if a large vessel is cut, then hemorrhage is uncontrolled, and it requires suturing the vessel.

Pathophysiology

After extraction of tooth, the bleeding usually occurs from small blood vessels which stops by its own by applying pressure for few minutes. However, sometimes if there is any bleeding disorder or if a venous plexus is present at apex of root of tooth the hemorrhage can be difficult to control.

Evaluation

History

If the bleeding is persistent after surgery then past medical history is very important. Systemic bleeding disorders such as hemophilia, thalassemia, or von Willebrand disease are commonly associated with uncontrolled bleeding. Other causes may include drugs like aspirin which usually taken by hypertensive patients.

Physical Examination

Hemophilia

The most common manifestation is hemorrhage in joints, which is spontaneous and associated with warmth and muscle spasm. Superficial trauma causes uncontrolled bleeding. Processes such as tooth eruption and exfoliation cause prolonged and severe bleeding.

Thalassemia

Patient appears pale and weak, with prominent cheek and other bones. Mongoloid appearance—frontal head bossing with overdeveloped malar bone and short nose. Oral mucosa is usually pale due to chronic jaundice.

von Willebrand Disease

It includes excessive bleeding even after minor trauma. Most common intraoral sites of bleeding are gingiva and nose. Menorrhagia is also very common. Bleeding tendencies decrease with age.

Investigations

Investigations for bleeding disorders are done before surgery based on past medical history of the patient. Thalassemia—typical safety pin cells and nucleated RBCs in circulation. Hemophilia—clotting time is prolonged but bleeding time, platelet count, and prothrombin time are all normal. von Willebrand disease—prolonged bleeding time, normal platelet count, decreased factor VIII, or factor IX.

Treatment

Management of Postsurgical Bleeding

As soon as continuous bleeding is detected, apply digital pressure for 2–3 minutes. If bleeding stops, close the wound by sutures to stabilize the clot. If bleeding still persists, it can be due to bony vessels, apply gel foam, fibrin foam, or bone wax over the area and close with suture. If bleeding still persists, then it is very important to identify the bleeding area and cauterize it with diathermy or if there is larger vessel, that can be ligated. The blood sample can be sent for testing for any systemic disorder and appropriate measures should be taken like blood transfusion.

Managing Bleeding after Implants

Bleeding during surgery is expected and usually easily controlled by cauterization or by ligation. Postoperatively patients are given instructions about normal expectation of bleeding and how to prevent and manage it. However, submucosal or subdermal hemorrhage into soft tissue spaces can lead to hematoma formation. Larger hematoma or those occur in systemically compromised individual can cause infections. It is advisable to prescribe antibiotics in such cases.

Bleeding in Systemic Disorder Patients

- *Hemophilia*: Raise factor VIII (in hemophilia A) and factor IX (in hemophilia B) levels. Various replacement therapies are available such as plasma, cryoprecipitate, and factor VIII concentrates.
- *Thalassemia*: Blood transfusion is required in severe blood loss. Folic acid maybe required due to erythropoiesis. Chelating agents like deferoxamine can be given.

DENTAL TRAUMA

Traumatic injuries to teeth are very common and usually associated with any injury occurring in the face. Usually any person having a road traffic accident is prone to dental trauma, also fights and contact sports such as boxing and karate cause trauma over teeth. To know the extent of injury to teeth it is very important to know the object, the angle, and the force of impact on the teeth. If there is only fracture of tooth (without bone) then it is not associated with swelling. Splinting is done in luxated tooth. Avulsed tooth can be replanted.

Types of Dental Traumas

- Fracture of crown of tooth involving only enamel
- Fracture of crown of tooth involving enamel and dentin
- Fracture of crown of tooth involving pulp causing pulpal exposure
- Concussion
- Subluxation and luxation—intrusive, extrusive, and lateral luxation
- Avulsion
- Fracture of alveolar socket wall
- Injuries to gingival and oral mucosa
- Injury to facial bones

Pathophysiology of the Condition

Trauma to tooth, if associated with the alveolar socket wall fracture, causes swelling due to release of mediators of inflammation. These mediators cause swelling and pain in the associated gingival and the face tissues.

Clinical Presentation

Fracture of tooth leading to exposed enamel does not cause any pain unless it is associated with any internal bone fracture. Pain occurs only if pulp is exposed in a fractured crown or if there is concussion or luxation or avulsion of tooth. If the tooth fracture is associated with bone fracture like alveolar bone or maxilla or mandible then it leads to facial edema and mobility in bone fragment.

Red Flags

If traumatized tooth is sore to percussion—concussion. If percussion pain is associated with bleeding—luxation.

Evaluation

History

It is very important to note the: (1) Object of impact, (2) Angle of impact, and (3) Force of impact to decide the amount of harm caused to the orofacial structures. If a soft object hits the face like tennis or rubber ball, then there are less chances of tooth fracture. If a hard object hits and the angle of impact is perpendicular to tooth, then the fracture of tooth can be at the apical, middle, or incisal third, if the impact is from above or the angle is from incisal to root of tooth, then it causes intrusive luxation of tooth, if impact is parallel to long axis of tooth, then there are chances of longitudinal fracture of tooth.

Physical Examination

Pain in percussion—concussion, luxation, and pulp exposed due to fracture. Mobility of segment—fracture of bone.

Investigations

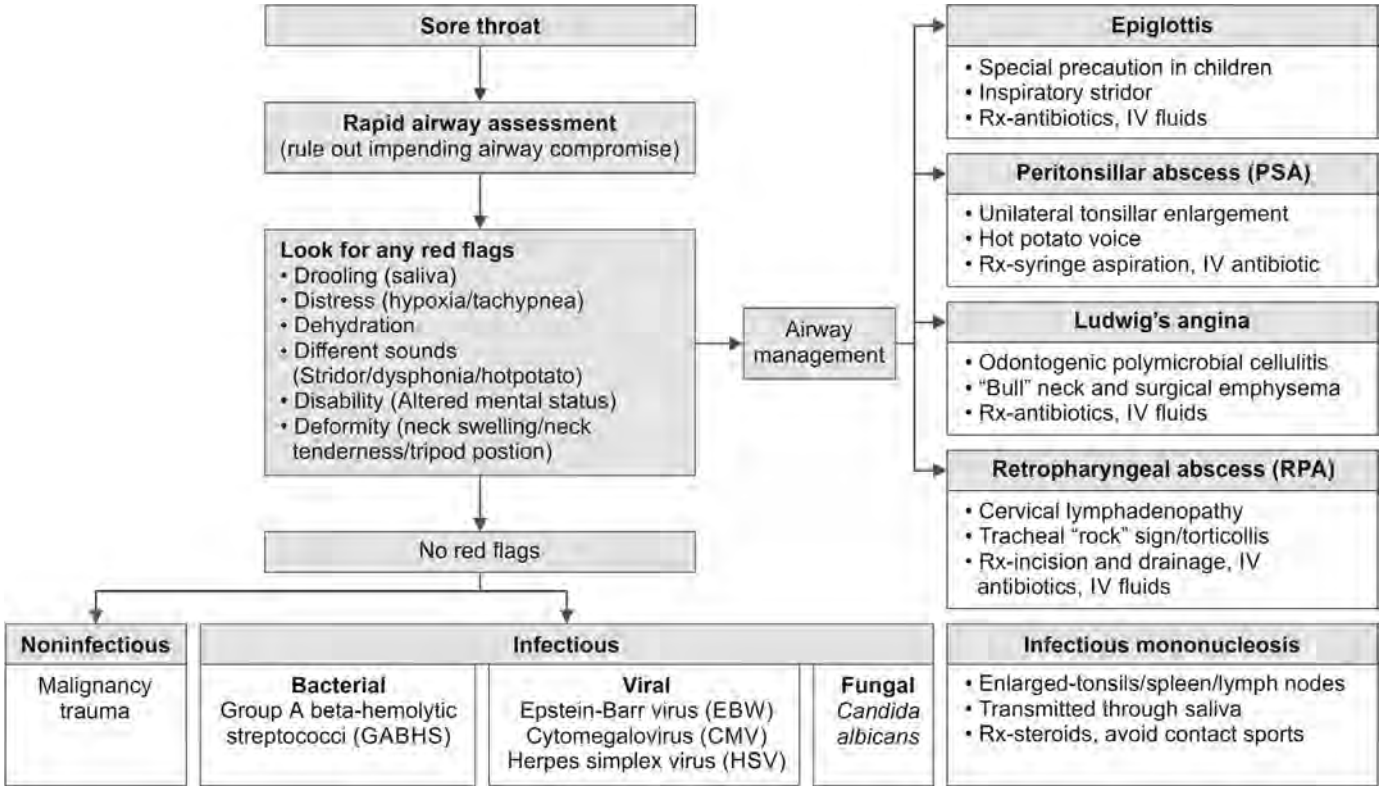
It includes IOPA, OPG, and PA radiographs.

Treatment

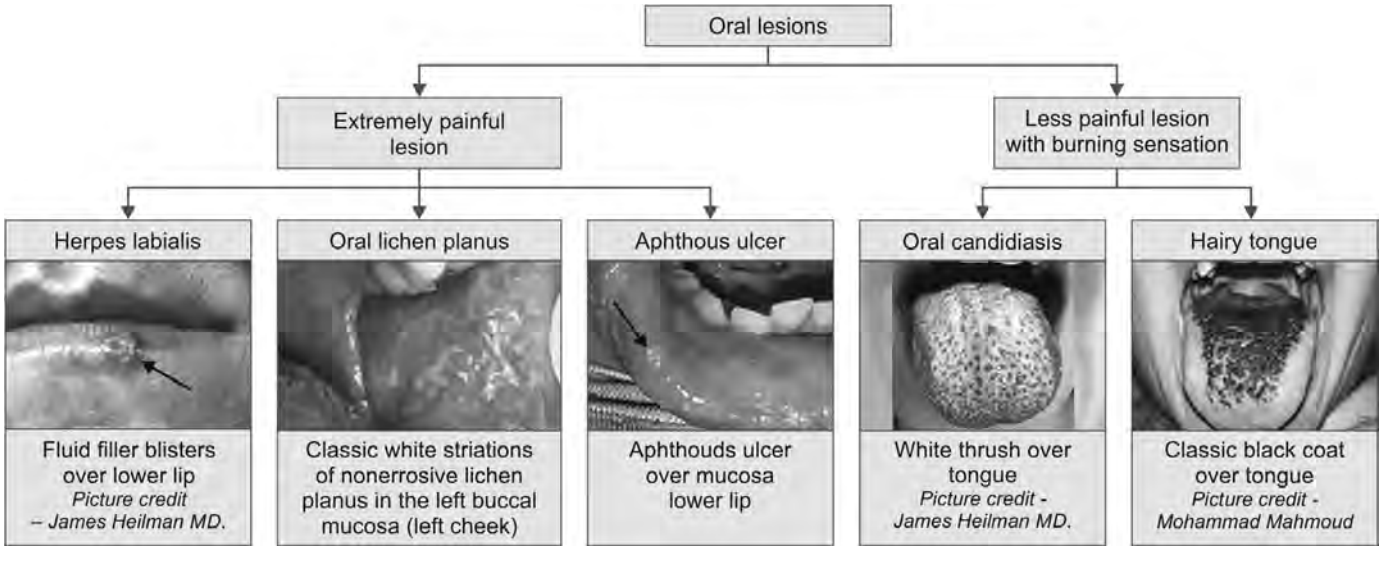
- *Concussion and luxation*: Splinting of the mobile segment is done.
- *Avulsion*: Replantation of teeth, if it is preserved in saliva or cold milk within half an hour of trauma.
- *Bone fracture*: Joining of bony segment with implants or mini plates.

SUMMARY

Oral, neck and throat emergencies are multiple and they may present as various form, most commonly they presents sore throat and oral lesion. Their evaluation is important to figure out life-threatening emergencies. Evaluation of common symptomatology like sore throat is summarized in **Flowchart 3** and oral lesion evaluation is summarized in **Flowchart 4**.



FLOWCHART 3: Evaluation of sore throat.



FLOWCHART 4: Evaluation of oral lesions. ***(For color version, see plate 17)***

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Management of Foreign Bodies of Ear, Nose and Throat

Mohammad Anzal Rehman, Neha Hudlikar, El Rasheed Salih

INTRODUCTION

Foreign bodies in the ear, nose, and throat (ENT) are frequently encountered problems in patients presenting to the emergency department (ED), constituting up to 30% of ENT-related emergencies in some centers. The majority of patients are children, with the highest prevalence found in children under the age of 5 years. Although uncommon, adverse events such as tympanic perforation and bronchoaspiration can occur as a consequence of foreign bodies, especially when care is delayed in younger patients, making improved public awareness and access to healthcare vital components in preventing complications.

Most foreign bodies are easily removed within the ED. However, multiple failed attempts can lead to highly preventable complications in patients. Therefore, the ED physician should aim to develop skills and awareness on the various approaches and removal techniques for these cases. Where there is doubt regarding type of foreign body or anticipated difficulty during removal, it is best to either consult ENT specialists or involve them in the removal procedure rather than risk further injury.

HISTORY TAKING AND PRESENTATION

The location of foreign body impaction is variable between different countries and may even differ based on changes in season, cultures, and customs. One study in Japan revealed that foreign bodies in the throat were more commonly encountered during times of the year associated with increased consumption of fish, whereas foreign bodies in the ear and nose were more frequent during rainy days, where children were more likely spend time indoors and insert small objects into the ear and nose. Foreign bodies of the ENT are usually a consequence of explorative curiosity, accidental entry of body or secondary to regular insertion due to irritation or habitual cleaning. Although most commonly seen in children, adults with psychiatric illness may also represent a subset of patients presenting with this complaint, with intentional insertions by nonpsychiatric adults also contributing to the patient population, albeit in smaller frequencies. Most patients are either brought or present themselves to the ED in the first few hours, usually with no obvious symptoms but a history suggestive of witnessed or suspected foreign body insertion into either ear, nose, or throat. Delay in seeking care often leads to a higher chance of symptoms developing, such as pain or discharge from the affected area and even difficulty breathing or swallowing with throat foreign bodies. Often, the risk of complications also goes up with prolonged time before presentation to the ED. Foreign bodies of the ear and nose are more frequently encountered on the right side, likely owing to right hand predominance in the patient population. The foreign substance itself is usually inorganic, such as beads, paper, coins, batteries, toy parts, and rubber. However, organic substances can also be involved and include nuts, seeds, bone, and meat. Animate (living) foreign bodies can also present, usually as insects who become lodged inside the ear canal.

APPROACH AND MANAGEMENT

The primary goals in management of foreign bodies in the ED are centered around removal of the foreign body where possible and feasible. Ideal removal should be immediate, painless, and usually "backtracked" along the same path traversed by the foreign object. Successful removal will invariably depend on several factors, including material composition and dimensions, anatomical location of the impacted foreign body, physician experience, equipment setup, and patient cooperation. As with any patient, it is essential to conduct a primary survey and evaluation of the airway, breathing, and circulation for all patients, with vital signs including blood pressure, temperature, heart rate, respiratory rate, with pulse oximetry to assess for any acute decompensation, and look for and address any other acute pathology that may be present. Once the suspicion of foreign body impaction or insertion is established, the physician should prepare for early removal of the foreign body, except in cases where removal is not appropriate to the patient situation. Specific circumstances and red flags are discussed later in this chapter.

One of the most essential components of successful foreign body removal is good preparation prior to attempting the procedure. Before commencing any maneuver, ensure that all equipment is functional, instruments are available and accessible, the environment is clear of distractions and hazards, and precautions are in place to address any patient destabilization or deterioration during the procedure. The

first attempt is commonly the best opportunity for removal, as subsequent attempts may be significantly hindered by patient apprehension and pain, especially in young children. While adequate instruction may be sufficient to immobilize an adult or older child for foreign body removal, it may be judicious to preemptively stabilize younger children by having a parent or relative hold the child in their lap with limbs wrapped by a sheet or anchored by holding hands and legs in crossed position, leaving the head relatively free. The head can then be held gently by an assistant during the procedure to anticipate any sudden head movements and stabilize accordingly without distraction from limb and body movements. Younger patients can also be offered distractions in the form of colorful objects, music, images, and videos on mobile phones or tablet devices that may reduce the perception of pain and mitigate distress and movement during the procedure.

Use of devices such as the headlamp (**Figs. 1A** and **B**) can enable the physician to free both hands, with one hand used to hold instruments designed to optimize visualization (e.g., speculum, depressor, laryngoscope, and tongue depressor), while the other is used to hold the tool or equipment chosen for removal of foreign body.

FOREIGN BODIES OF THE EAR

While any age group may present with aural (ear) foreign bodies, it is perhaps more prevalent in children younger than 6 years of age, with a higher overall frequency of occurrence in males compared to females. The types of foreign body found in this area range from pieces of cotton, erasers, small stones, popcorn kernels and paper to beans, beads, and even live insects. One US study found that, while the majority of aural foreign bodies were successfully removed by ED physicians, the removal technique depended heavily on the dimensions, consistency, and location of the substance involved in the external auditory canal, where the nonlinear and constrictive pathway lends itself to difficulty during instrumentation.

Anatomy

The ear is divided into three major sections. The inner ear is the most internal portion, existing as a labyrinthine cavity of semicircular canals, the vestibule and cochlea that together function to deliver information on sound to the central nervous system and regulate balance and coordination. The middle ear is primarily involved in bony conduction of sound and consists of the malleus, incus, and stapes between the oval window internally and tympanic membrane externally. The external ear is comprised of the auricle and the external acoustic meatus (external auditory canal). The external auditory canal through the opening at the auricle is understandably where most foreign bodies become lodged. The canal is lined with a thin layer of skin and periosteum and narrows at the bony cartilaginous junction (separating the lateral cartilaginous third of the canal from the bony medial two-thirds), increasing the susceptibility of impaction for inserted objects.

Clinical Features

The majority of patients presenting with foreign bodies in the ear are asymptomatic, with the finding being incidental or guided by a history of witnessed or suspected insertion. However, a number of symptoms may manifest, especially as time progresses since impaction. These include pain in the ear (otalgia), bleeding, otorrhea, hearing loss, and fullness in the ear. Pain with fever and discharge may indicate developed infection, while hearing loss and presence of button batteries are red flags that require judicious evaluation for any secondary insults or disease processes with the aural foreign body. The ED physician should consider differential diagnoses such as otitis media or externa, cerumen impactions, and even tumors.

Evaluation and Management

Attempts to remove the foreign body from the ear are often painful and carry the risk of advancing the object even further down the canal. The first attempt is usually the one with the highest success rate and the least number of complications, which is why care must be taken to adequately prepare both the patient and equipment prior to attempting removal. After counseling the patient or guardian on the need for extraction and obtaining appropriate consent as needed, the physician should ideally assign tasks to any assistants that are available in the room that can facilitate immobilization of the patient as required. This is particularly useful in pediatric and psychiatric patients where compliance cannot be assured during the removal procedure. Identify the affected ear and position the patient to allow for maximal comfort whilst the ear faces

FIGS. 1A AND B: Use of a headlamp can allow for optimized visualization without occupying the hands.

the physician's side, providing them with a clear view of the auricle and external auditory canal. Use of a headlamp can allow for the physician to use both hands during the removal procedure. Some of the techniques that can be used to remove ear foreign bodies are outlined below.

Irrigation

An irrigation syringe or similar syringe filled with saline at body temperature, attached to a plastic cannula can be advanced beyond the foreign object inside the ear and used to instill water at pressure inside the ear canal in an attempt to "flush" the impacted substance outward for removal. This is useful in cases of inorganic objects such as beads or popcorn kernels as well as insects in many cases. It should, however, not be used to remove batteries, organic material such as food, vegetable matter or other substances that may expand with absorption of water (e.g., polystyrene balls and expandable water toys). In addition, irrigation should only be done after ensuring the tympanic membrane is intact.

Grasp and Remove

Various instruments are designed to acquire a direct hold on the foreign object, following which they can be moved toward the exterior of the ear canal and removed. The Hartmann alligator forceps and Bayonet forceps (**Figs. 2** and **3**) are both excellent tools for this purpose and are especially useful when dealing with soft, easily graspable objects or insects within the ear canal. They should be avoided when dealing with spherical objects, as these are inherently difficult to grasp and may even be pushed further into the canal.

Anchor and Drag

The right angle hook (**Fig. 4**) is especially useful for rounded objects. If advanced beyond the midpoint of the object and behind it in the ear canal, the distal end of this instrument anchors the foreign body, allowing it to be dragged outward as the equipment is pulled under direct visualization. The wax loop/curette (**Fig. 5**) uses the same concept with a loop instead of a hook, whereas the Katz extractor (**Figs. 6A** and **B**) uses an inflatable balloon to secure the object as it is pulled out of the ear. All these techniques should avoid being used where proper visualization of the distal ends of foreign bodies is adequately maintained during the procedure (**Figs. 7A** and **B**).

Bonding to Object

Limited evidence exists surrounding use of a bonding agent such as glue (cyanoacrylate) at the end of a cotton-tipped applicator to attach to the foreign body for removal under direct visualization. A similar mechanism is employed when using a magnet to attach to a metallic foreign body within the ear canal. These techniques have been used with variable efficacy and care must be taken not to utilize these methods where the patient is uncooperative or where visualization is suboptimal to avoid complications. Live insects within the ear canal are a cause of significant distress and irritation for patients presenting to the ED. Prior to removal, live insects may be killed by instilling alcohol, mineral oil, or lidocaine (also available as a spray). Removal then proceeds using any of the methods described above. Suction devices have also been successfully used to facilitate extraction.

FIG. 2: Hartmann alligator forceps.

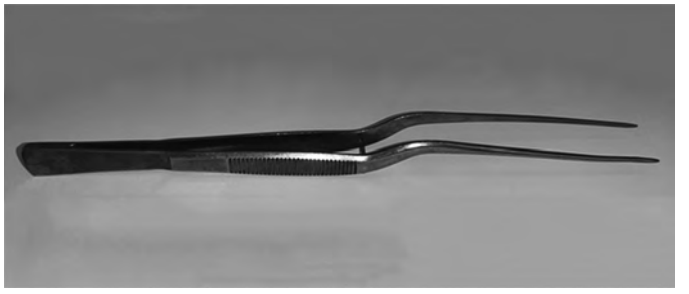


FIG. 3: Bayonet forceps.

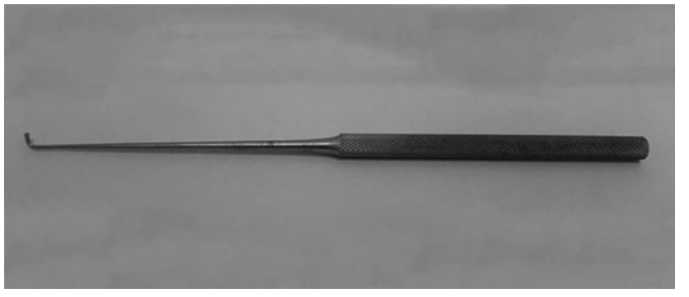


FIG. 4: Right angle hook.

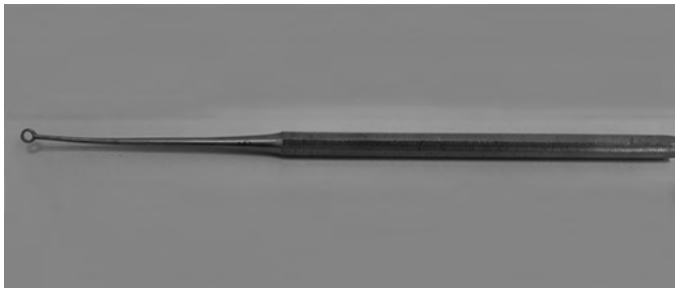
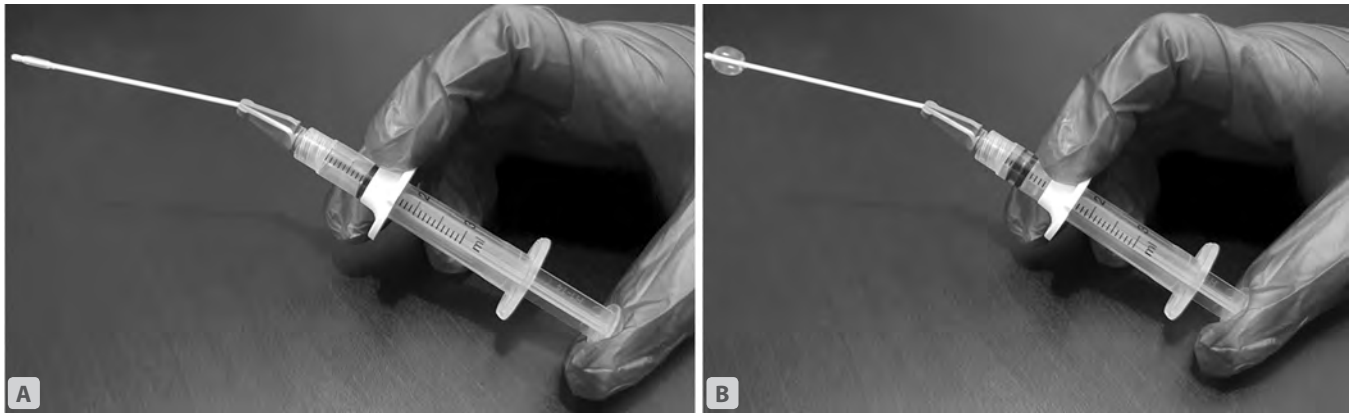


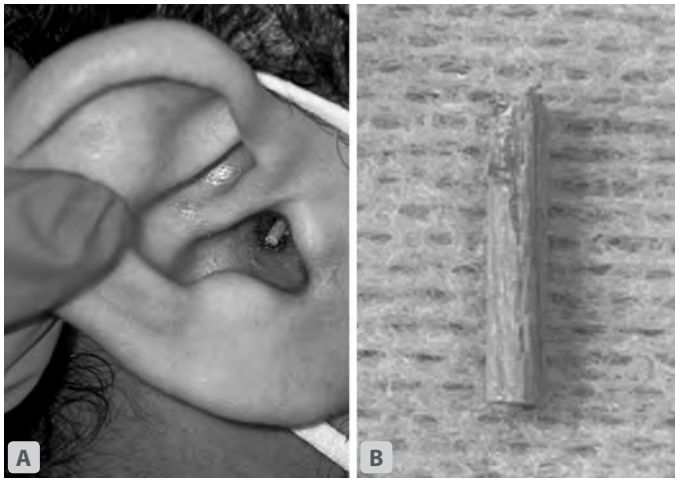
FIG. 5: Wax loop/curette.

Complications

Repeated attempts at removal of an ear foreign body are associated with an increase in complications, usually encountered with objects that are difficult to grasp, spherical, close to the tympanic membrane, or with prolonged impaction. Button batteries always require urgent removal, as they may corrode into and damage surrounding tissues, especially when left for long periods of time within the ear canal.



FIGS. 6A AND B: Katz extractor.



FIGS. 7A AND B: (A) Foreign body impacted in the external auditory canal, visible on direct visual examination of the ear. (B) Removed foreign body object revealed to be a small piece of wood.

Disposition

The majority of patients with successful foreign body removals, in the absence of significant associated injury, may be safely discharged with no further management needed. Otolaryngologists should be consulted by the ED physician for any foreign body that is considered to be difficult to remove by the responsible physician and where repeated attempts at removal have been unsuccessful. Objects deep within the canal, in contact with or damaging the tympanic membrane and those with significant associated injury, hearing loss, or nerve damage should be managed emergently by or in conjunction with the otolaryngologist.

FOREIGN BODIES OF THE NOSE

Patients presenting with a foreign body in the nose are not an uncommon occurrence in the ED. This population of patients comprises mainly of children <4 years of age, but it may also present in patients with psychiatric disease or intellectual disabilities. Culprit objects found in the nasal cavities are often divided into organic (e.g., seeds, peanuts, insects, and worms) and inorganic (e.g., jewelry, toys, pens/pencils, button batteries, coins, and paper) substances, with inorganic items being more commonly encountered.

Anatomy

The nose can be imagined as an internal cavity that connects the nostrils externally to the nasopharynx internally. Its roof is comprised mainly of the cribriform plate (ethmoid bone) in addition to nasal, frontal, and sphenoid bones. Inferiorly, the floor is formed by the maxilla and palatine bones (hard palate). Medially, the nasal cavity is divided into left and right compartments by the nasal septum (ethmoid bone, the vomer bone, and the septal cartilage). As the cavity extends inward, the lateral walls of the cavity are lined by three (superior, middle, and inferior) bony projections, termed as conchae or turbinates that function to increase mucosal surface area and humidify the air flowing in. The spaces between conchae, called meatuses, function as channels through which various ducts and sinuses communicate with the nasal cavity. Most foreign bodies in the nose are often visible and anterior, found near or below the middle and inferior turbinates.

Clinical Features

Nasal foreign bodies are more likely to be found in the right side of the nose. Children who insert these objects into their nose are often brought by caregivers or parents who witnessed the insertion. Therefore, a significant number of nasal foreign bodies are brought due to an observed or suspected history of insertion, within 24 hours of the incident, and with no clinical symptoms secondary to the foreign body. However, as time passes, patients are more likely to manifest with nasal pain, unilateral nasal discharge, epistaxis, and, less frequently, with features of surrounding cellulitis or even meningitis.

Evaluation and Management

Radiography is seldom useful in the evaluation of nasal foreign bodies since substances such as wood or plastic are unlikely to be easily visualized. While button batteries and magnets can be visualized on plain X-rays, these foreign bodies carry a risk of corrosion and necrosis to the surrounding tissue and, as such, expeditious removal takes priority over pursuing identification through radiography, especially if the object is visible on direct examination. If, however, only suspicion of a nasal foreign body is maintained, a plain radiograph may be useful to rule

out the presence of a foreign body that may otherwise result in significant morbidity if missed.

As with any foreign body removal, the first attempt is most likely to be successful, with subsequent attempts associated with increased complications. Therefore, preparation is key and centers around optimizing visualization and examination of each nostril and nasal cavity, especially when mechanical removal is planned. A head lamp or stand lamp, with or without adjuncts such as nasal speculums (**Fig. 8**) can be used to enhance the visual field. Any object not adequately visualized may lie in the posterior aspects of the nasal cavity and, therefore, may be prone to deeper impaction or risk of aspiration if blind instrumentation is attempted. Therefore, for suspected foreign bodies where visualization is inadequate or perceived to be posterior, it is advisable to involve the otolaryngologist for removal. Since impacted nasal foreign bodies have a tendency to trigger inflammatory reactions in surrounding tissue or mucosa, it is often advisable to apply topical analgesia (e.g., lidocaine nasal drops) or topical decongestant (e.g., phenylephrine or oxymetazoline) prior to initiation of removal techniques. This, in conjunction with adequate restraint or instructions to facilitate patient immobilization, can significantly improve the likelihood of an uncomplicated foreign body extraction.

Techniques for nasal foreign body removal can grossly be divided into two categories.

Positive Pressure Methods

This method generally employs the concept of introduction of positive pressure through an alternate orifice such as the mouth or nostril opposite to the affected side in order to push the foreign body outward from its impacted region. In older children who can follow instructions, you may ask them to blow their nose whilst keeping the unaffected nostril occluded, making sure to have them inhale through the mouth only to decrease risk of aspiration. The "mother's kiss" or "parent's kiss" is another method that originated in the 1960s and requires the parent to form a seal over a child's mouth with their own and, while keeping the unaffected nostril occluded, blow with force into the mouth in an attempt to introduce positive pressure behind the foreign body inside the nostril and push it outward. A systematic review in 2012 discovered this technique to be generally safe with success rates approximating 60%. A bag-valve mask may be incorporated in a similar fashion to form a seal over the patient's mouth and deliver positive pressure.

Mechanical Extraction

Similar to aural foreign bodies, various instruments can be used to grasp or anchor behind the nasal foreign body under direct visualization, including Alligator forceps, Katz extractors, wax curettes, and right angle hooks, with care taken not to push the foreign object further into the nasal cavity during manipulation. Bonding to the object using glue at the end of a cotton tip, similar to the technique described for ear foreign bodies, is also sometimes used. Visualization prior to instrumentation is often augmented with use of a nasal speculum. A nasal washout technique is also found to be effective in many cases, where a bulb syringe with normal saline is advanced into the contralateral nostril until an adequate seal is obtained, following which the syringe is rapidly and forcibly squeezed, causing the saline to push the foreign body outward from the affected nostril. This technique is not recommended for use with button batteries where the saline fluid may exacerbate battery corrosion.

FIG. 8: Nasal speculum.

Complications and Disposition

After a foreign body is successfully removed from the nose, it is important to reexamine both sides of the nasal cavity for retained secondary foreign bodies, injuries from mucosal trauma, persistent epistaxis, or signs of infection within the nasal cavity. Ongoing bleeding should be evaluated and observed and signs of infection or cellulitis may require consideration of antibiotics at discharge. Significant damage to the mucosa or septum warrants urgent ENT consult to aid in repair and prevents further complications, especially in the setting of button batteries and magnets.

FOREIGN BODIES OF THE THROAT

Foreign bodies in the upper aerodigestive tract are a common and important clinical problem seen in the EDs. Other than the pediatric population, those with learning difficulties, psychiatric patients, and prisoners can also present with ingested foreign bodies. Children usually present with foreign bodies such as toy parts and coins while adults commonly present with fish/meat bone, artificial dentures, etc. Foreign bodies in the aerodigestive tract can present with irritation at the back of the throat, drooling, or signs of respiratory distress (such as cough, shortness of breath, and stridor).

Anatomy

The pharynx is a muscular structure comprised of three sections: (1) Nasopharynx, (2) Oropharynx, and (3) Laryngopharynx. It begins at the base of the skull and ends at the inferior border of the cricoid cartilage (C6). The oropharynx is located between the soft palate and the superior border of the epiglottis and is involved in the voluntary and involuntary phases of swallowing. The laryngopharynx is located between the superior border of the epiglottis and the inferior border of the cricoid cartilage (C6) and continues inferiorly with the esophagus. There are two main groups of pharyngeal muscles; circular and longitudinal. The vagus nerve innervates all the muscles of the pharynx except the stylopharyngeus which is innervated by the glossopharyngeal nerve. The pharyngeal plexus provides sensory and motor innervation to the majority of the pharynx. Arterial supply is via the branches of the external carotid artery and venous drainage is by the pharyngeal plexus. The esophagus begins at the inferior border of the cricoid cartilage and has four areas of anatomical narrowing which are the most common sites of foreign body entrapment—

upper esophageal sphincter (UES), aortic arch, left mainstem bronchus, and lower esophageal sphincter (LES) at the diaphragmatic hiatus. The UES or cricopharyngeus muscle is the most common site of impaction.

Clinical Features

Adult patients can often describe the precipitating event and commonly report symptoms such as throat pain, dysphagia, odynophagia, choking, or retrosternal chest pain. Foreign body ingestions in the pediatric population can be challenging, as approximately 40% of the cases are unwitnessed and many children remain asymptomatic. Pediatric patients brought to the ED after witnessed ingestion or lodged foreign body may present with a refusal to eat choking, drooling, new cough, voice change, or stridor. Red flags for ingested foreign bodies include stridor, drooling, dysphonia, surgical emphysema, or signs of esophageal perforation including chest pain or signs of sepsis. The ingestion of a button battery is also considered a red flag as it causes caustic injury.

Differential Diagnosis

In most cases, the history will be enough to confirm the diagnosis. It is important to distinguish the location of the foreign body; airway versus the digestive tract. One of the top differentials to consider is a food bolus. Other differentials based on the symptoms could include ischemic acute coronary syndrome (ACS) for retrosternal chest pain.

Evaluation

The evaluation of ingested foreign bodies begins with looking for airway compromise. Any patient with airway compromise or impending compromise will need emergent management of their airway. A visual inspection of the oropharynx can be done using Lack's tongue depressor and light source. The neck can be palpated for points of tenderness as well as surgical emphysema. Direct visualization with flexible nasal endoscopy can be attempted if the patient is stable.

Investigations

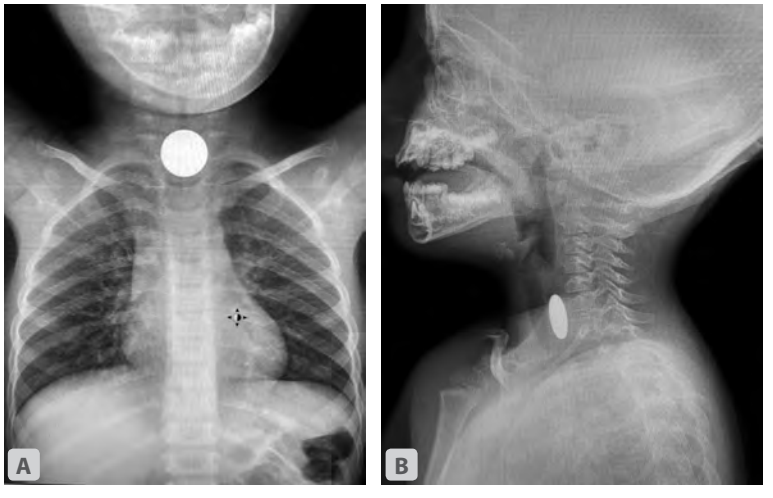
Imaging studies are required in cases where the clinical presentation is unclear or equivocal. Plain radiographs of the neck, chest, and abdomen can be done if a radio-opaque foreign body is suspected (**Fig. 9**). Loss of cervical lordosis or widening of retropharyngeal space in the lateral neck X-ray (>7 mm at C2 and >22 mm at C7 approximately) can be suggestive of an impacted foreign body. Other signs include surgical emphysema and widening of the mediastinum. It is important to note that a negative plain radiograph does not rule out the presence of a foreign body, as false-negative rates can be as high as 47%. Fishbone, which is one of the most common foreign body found in the upper aerodigestive tract is rarely seen in a radiograph. If clinical suspicion remains high, computed tomography (CT) has a sensitivity close to 100% in detecting foreign bodies. Contrast studies (barium or Gastrografin) are not preferred due to the risk of aspiration. Direct visualization by laryngoscopy or endoscopy is other options if clinical suspicion remains high and imaging is equivocal.

Management

Initial management depends on the clinical status of the patient as well as the risk of airway compromise. The other factors include the type of foreign body, location, and time since ingestion of the foreign body. Ingestion of button batteries, coins impacted in the upper esophagus, sharp objects, and objects causing complete obstruction need urgent intervention.

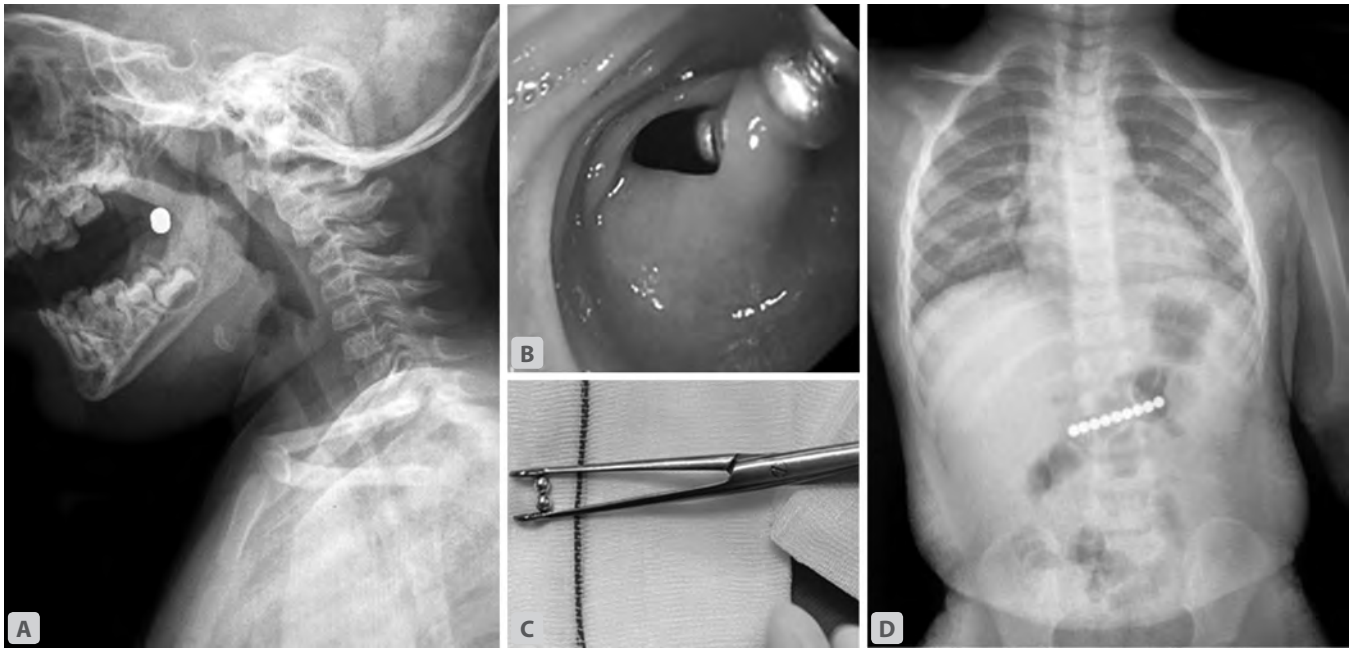
Foreign Body in the Throat

Foreign bodies directly visualized in the oropharynx can be removed using Magill forceps or a Kelly clamp (**Fig. 10**). If removal is not tolerated, one may have to use procedural sedation or attempt removal under general anesthesia (GA) via endoscopy. Blind finger sweeps should never be performed to remove the foreign body.



FIGS. 9A AND B: (A) Anteroposterior (AP) plain X-ray view of a child with coin ingestion, displaying a well circumscribed, radio-opaque density in the upper esophagus. (B) Lateral view revealed coin position to be posterior to the air-filled, radiolucent tracheal pathway, confirming its position in the esophagus.

FIGS. 10A AND B: Adult male who presented to the emergency department with complaints of dysphagia and throat pain after a recent meal. (A) Lateral X-ray of the neck reveals a thin and curved density impacted in the pharynx. (B) Under visualization using a laryngoscope, Magill forceps removed the foreign body, revealed to be a fishbone.



FIGS. 11A TO D: Child who presented after pain and dysarthria after being found playing with magnets. (A) Lateral X-ray revealed two circular and superimposed densities within the oral cavity. (B): Bronchoscopy revealed the patient's uvula to be entrapped between two magnets. (C) Removed spherical magnets. (D) X-ray of the chest and abdomen revealed multiple secondary ingested foreign bodies within the abdomen forming a sequential chain within the intestine. ***(For color version, see plate 17)***

Foreign Body in the Upper Esophagus

A Foley catheter is an inexpensive technique to remove smooth foreign bodies in the upper esophagus. To use this technique, place the patient in a prone position and pass the catheter past the impacted foreign body and inflate the balloon. The catheter is then withdrawn pulling the foreign body with it. This technique is avoided in patients with esophageal perforation/structural abnormalities, sharp objects, and objects that have been impacted for more than a week. Specifically, for impacted coins, an esophageal dilator can be used to advance the coin into the stomach. All button batteries regardless of the location [respiratory or gastrointestinal (GI) tract] are a medical emergency and should be removed endoscopically within 6 hours of ingestion/aspiration to prevent necrosis or perforation (**Fig. 11**).

Food boluses causing incomplete obstruction have traditionally been treated with glucagon [1–2 mg intravenous/intramuscular (IV/IM)], which causes smooth muscle to relax and allows the passage of the food bolus. However, glucagon causes vomiting which increases the risk of aspiration and esophageal perforation. Recent studies concerning its efficacy are mixed and, based on the lack of evidence, glucagon is better avoided in treating impacted food boluses. Other treatments include carbonated drinks and medications such as benzodiazepines, papain, nitroglycerin, and nifedipine. They have been shown to have variable efficacy and are generally

not recommended. While endoscopy is indicated emergently in complete obstruction, it is recommended that food boluses causing incomplete obstruction are removed endoscopically within 24 hours to avoid complications. Gastroenterology consultation for emergent endoscopy is indicated in airway obstruction, complete esophageal obstruction (drooling), button battery in the esophagus, sharp objects (>6 cm long and >2 cm wide), coin at the level of UES, multiple foreign bodies, or if there is any concern for esophageal perforation.

Complications

Complications can range from mild irritation of the pharynx to abscess, esophageal perforation, and mediastinitis. Adverse outcomes of ingested foreign bodies include airway compromise, pneumonia, esophageal stricture/perforation, fistula formation (aortoenteric or tracheoesophageal), and abscess.

Disposition

All patients with red flags or concerns for continued obstruction should have a gastroenterology consult. Patients who undergo endoscopy for removal of the foreign body are typically admitted and observed for a period of time after the procedure. Patients with no red flags and successful removal of the foreign body may be discharged with follow-up. Patients with food bolus impaction will usually require a follow-up endoscopic evaluation for structural abnormalities of the esophagus.

SUMMARY

Foreign bodies in the ENT are frequently encountered problems in patients presenting to the ED, and majority of patients are children, under the age of 5 years. When care is delayed in younger patients, adverse events such as tympanic perforation and bronchoaspiration can occur as a consequence of foreign bodies. Most foreign bodies are easily removed within the ED. However, multiple failed attempts can lead to complications in patients. Therefore, the ED physician should aim to develop skills and awareness on the various approaches and removal techniques for these cases. Where there is doubt, it is best to either consult ENT specialists or involve them in the removal procedure rather than risk further injury.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Anemia

Akanksha Rastogi, Amit Mittal

INTRODUCTION

Anemia shall be noted as decrease in hemoglobin (Hb), red blood cell (RBC) count, or hematocrit for the patient's age, sex, and altitude of residence. The average Hb values are different in different laboratories. According to the World Health Organization, criteria for anemia are: In men: Hb <14 g/dL and in women: Hb <12 g/dL. This may not apply to certain group of population such as smokers (high Hb level than normal), athletes [low Hb level since dilutional anemia/gastrointestinal (GI) bleed], living at high altitude (high Hb), African-Americans (low Hb), and presence of chronic disease (less Hb). Anemia is one of the most common problems seen in clinical practice, but the cause of anemia can be single to multifactorial. Grossly anemia can be classified as emergent (life-threatening) and nonemergency (no immediate threat to life).

PATHOPHYSIOLOGY

Red blood cells main functions are transport of oxygen from lungs to tissue and carbon dioxide from tissue to lung. This process is affected by hemoglobin level, oxygen affinity of Hb, and blood flow. During severe disease and pathological conditions compensatory mechanism may fail to respond and result in hypoxia and cell death. Anemia stimulates compensatory mechanism of erythropoiesis by erythropoietin hormone (produced in kidney 90% and liver 10%). In bone marrow, RBC production (erythropoiesis) needs following four things:

1. *Stimulus, trophic hormones: Erythropoietin* (secreted from kidney peritubular cells), e.g., reduced in kidney failure, *thyroid hormone,* e.g., reduced in hypothyroidism.
2. *Bone marrow precursor cells* response to that stimulus, e.g., reduced in aplasia and bone marrow infiltration
3. *Nutrients (vitamin B12 and iron),* e.g., less in dietary lack and celiac sprue
4. *RBC life span* (life span ~4 months), e.g., less in hemolytic anemia (<100 days)

In approximately 5 days in circulation (transit time), 1 *proerythroblast* divides to form eight *reticulocyte* (1% of total RBC), which form mature erythrocyte in ~1 day. In *acute anemia*, transit time decrease to 2 days (due to skipped divisions and accumulation of debris), so RBC become macrocytic.

TYPES OF ANEMIA

- *Red cell morphology disorder*:
  - Hypoproliferative anemia (three-fourths cases)
  - Red cell maturation disorder (ineffective erythropoiesis)
  - Hemolysis/blood loss
- *Iron deficiency*:
  - *Increase demand:* Rapid growth and pregnancy
  - *Decreased intake:* Inadequate diet, celiac sprue, and gastrectomy
  - *Increased iron loss:* Menstrual, blood donation, and acute or chronic blood loss
- *Vitamin B12 deficiency*: Vegans, pernicious anemia, gastrectomy, intestinal stricture, tropical sprue, fish tapeworm, and Crohn's disease.

CLASSIFICATIONS

Anemia can be classified by many ways such as (1) *Blood loss*: *Acute blood loss emergent anemia*—(life-threatening)*/ chronic blood loss—nonemergent anemia;* (2) *Morphological classifications,* e.g., microcytic hypochromic, macrocytic hypochromic, normocytic normochromic, and dimorphic anemia; (3) Anemia due to decreased red cell production or due to increased red cell destruction (**Box 1**).

CLINICAL PRESENTATION

Clinical features of anemia depend on how rapidly hematocrit falls and ability to compensate by the patient. Children and young adult tolerate blood loss well without alteration in vital signs. Symptoms are because of:

- *Hypoxia (decreased oxygen delivery to tissues)*: Tiredness, fatigue, breathlessness, palpitations, and confusion.
- *Hypovolemia (acute and marked bleeding)*: Easy fatigability, lassitude, muscle cramps, dizziness, lethargy, syncope, drop in blood pressure (BP). The bleeding can be *obvious, occult, and induced*, i.e., hemodialysis, excess blood donation, or *underappreciated menstrual loss*.
- *Hemolysis*: Dark urine (gold to red to black) and acrocyanosis on exposure to cold

BOX 1: Classification of anemia.

I. **Anemia caused by decreased RBC production/RBC maturation disorder**
   - A. **Nuclear maturation defect** *(macrocytosis—elevated MCV)*
     1. Vitamin B12 or folate deficiency
     2. Drugs: Methotrexate
     3. Alcohol
     4. Myelodysplasia
   - B. **Cytoplasmic maturation defect** *(microcytosis and hypochromia-decreased MCV)*
     1. Iron deficiency
     2. Thalassemia
     3. Sideroblastic anemia
     4. Anemia of chronic disease
   - C. **Hypoproliferative disorder** *(normocytic normochromic-normal MCV)*
     1. *Marrow damage (infiltration/fibrosis and aplastic anemia)*
     2. *Less stimulation (kidney disease, hypothyroidism, and inflammation)*

II. **Anemia caused by increased RBC destruction: Hemolysis/blood loss**
   - A. **Extravascular RBC destruction in liver, spleen, bone marrow, and lymph nodes**
     1. *Intrinsic RBC defects*
        Thalassemia, sickle cell disease, spherocytosis, elliptocytosis, G6PD, or pyruvate kinase deficiency
     2. *Extrinsic RBC defects*
        Hypersplenism, autoimmune hemolytic anemia (AIHA), intravenous immunoglobulin infusion, snake bite, liver disease, dapsone, aniline dyes, and malaria
   - B. **Intravascular RBC destruction**
     1. *Hereditary*
        Hemolytic uremic syndrome (HUS), Wilson's disease, and TTP
     2. *Acquired*
        Mechanical valves, paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria (PCH), ABO incompatibility, copper poisoning, clostridial sepsis, severe malaria, and TTP

(G6PD: glucose-6-phosphate dehydrogenase; MCV: mean corpuscular volume; RBC: red blood cell; TTP: thrombotic thrombocytopenic purpura)

RED FLAGS

Clinical approach is important. Blood loss can occur in few scenarios which can be missed (repeated blood drawing, surgery, and bleed in upper thigh or retroperitoneal space).

In acute blood loss, Hb and hematocrit values do not tell the volume of blood loss as hypovolemia predominates. Pale skin and mucous membranes indicate Hb <8 g%.

Use two approaches: *Kinetic* (decrease in Hb) and *morphological* [altered mean corpuscular volume (MCV) and reticulocyte count). This can lead to death in few settings such as malignancy, heart failure, and hospitalized elderly.

EVALUATION OF ANEMIA

History

- Onset, duration awareness, severity (more symptomatic in severe anemia), and progression.
- *Past history*: Recurrent blood transfusion, drugs, fever, and surgery (pigment gallstone removal and splenectomy)
- *Personal and family history* (alcohol, smoking, anemia in family members, consanguinity, and low socioeconomic status) *How are the symptoms now?*—progression or improvement

Symptoms

- *Nonspecific:* Weakness, headache, and blurred vision
- *Neurological:* Limb weakness, tingling, numbness, and swaying while walking in dark
- *Cardiovascular:* Chest pain, palpitations, swelling of feet, and breathlessness
- *Gastrointestinal*: Loss of appetite, pica, pain abdomen, altered bowel habits, dysphagia, and jaundice
- *Miscellaneous:* Fever, bony pain, bleeding tendencies, leg ulcers, gallstones, and stunted growth
- *Cause related:* Blood loss (hematemesis, melena, hemoptysis, menstrual blood loss, repeated childbirth, occult peptic ulcer disease, constipation and diarrhea, bleeding spots in skin, mucosa, or joints); nutritional intake (vegetarian, nonvegetarian, and milk ingestion); worm infestation (pain abdomen, worm in stools, and poor hygiene); and malabsorption

Physical Examination

Look for built, nourishment, edema, chipmunk facies, puffiness of face, neck veins, oral cavity, pigmentation over skin, nails, bony tenderness, bleeding spots, retina, leg ulcers, joint status, and systemic examination.

Interpretation of Finding

- *Age and sex*: Vitamin B12 and folate deficiency predominantly noted in elderly population and iron deficiency more in children and pregnant females.
- *Nutrition and socioeconomic status*: Vitamin B12 deficiency in true vegetarian, inadequate intake because of poverty (iron deficiency), poor toilet facility (worm infestation), alcoholics (erosive gastritis, peptic ulcer, and esophageal varices-related bleed), smoker (peptic ulcer, Hb is more normally), consanguinity (hemolytic anemia), and residence in high altitude (high normal Hb)
- *Nonspecific symptoms*: Due to tissue hypoxia
- *Breathlessness*: Exertional (Hb <7 g%) and at rest (Hb <3 g%) indicates cardiac failure
- *Pica, worm, and dysphagia due to postcricoid webs*: Iron deficiency anemia
- *Jaundice*: Hemolytic anemia
- *Pain abdomen*: Peptic ulcer, GI malignancy, and worm
- *Neurological symptoms*: Vitamin B12 deficiency
- *Fever*: Infection, e.g., malaria, lymphoma, leukemia, endocarditis, and collagen vascular disease

- *Bleeding tendencies and bony pain*: Blood cancer, myeloma, and lymphoma
- *Drugs*: Phenytoin, primidone, sulfasalazine (folate deficiency), primaquine, and dapsone [hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency]
- *General physical examination*: Stunted growth (hemolytic anemia), lymphadenopathy [supraclavicular in gastrointestinal tract (GIT) cancer, generalized in lymphoma, and leukemia), edema (cardiac failure, kidney or liver disease, and hypoalbuminemia), chipmunk facies with frontal bossing and protuberant teeth (thalassemia major), bald tongue (iron deficiency), beefy red tongue (niacin deficiency), flat and spoon-shaped nails (iron deficiency), leg ulcers (sickle cell anemia and hereditary spherocytosis), Roth spots in eyes (endocarditis), and venous thromboembolism in autoimmune hemolytic anemia and hereditary spherocytosis
- *Abdominal examination*: Abdominal tenderness (peptic ulcer, stomach cancer, and lymphoma), hepatomegaly (liver cirrhosis and lymphoma), splenomegaly (hemolytic anemia), and ascites (cardiac failure)
- *Hemolysis*: Consider when no bleed, rapid onset of anemia, jaundice, dark urine, recent blood transfusion, new drug, history of hemolytic anemia, unexplained anemia in family, pigmented gallstones, and splenomegaly.

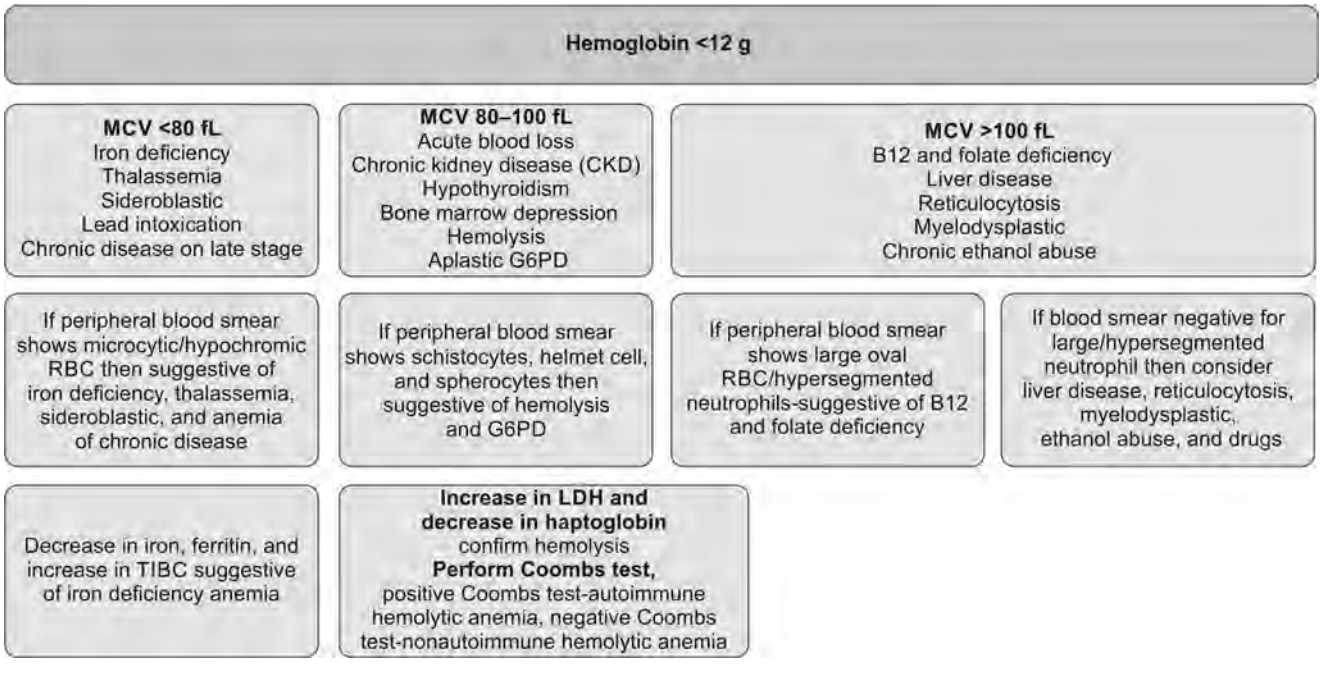
DIFFERENTIAL DIAGNOSIS

Classification of anemia is helpful in differentiating the various types of anemia. Classification which involves decreased RBC production, increased RBC destruction, and blood loss (**Box 1**) with morphological classification (**Fig. 1**) collectively used to narrow down the specific type of anemia.

INVESTIGATIONS

Evaluation of anemia needs series of test as described below while Hb and hematocrit should be measured in emergency department itself. On the basis of this further investigations are planned (**Table 1**).

- *Complete blood count (CBC)*:
  - *Red blood cell count:* (affected by age, sex, pregnancy, smoking, and altitude)
    - Hemoglobin
    - Hematocrit
    - Reticulocyte production index (RPI) (reticulocytes are immature RBC)
      <2 ~inappropriate marrow response: Red cell morphology disorder (i.e., type I and II)
      >2 ~accelerated RBC production: Hemolysis/blood loss (i.e., type III)
      (*Refer **Table 1** as described below*)
  - *Red blood cell indices:*
    - Mean cell volume (MCV in femtoliters, normal ~90) (<80 ~microcytosis and >100 ~macrocytosis)
    - Mean cell hemoglobin (MCH in picograms per cell)
    - Mean cell hemoglobin concentration (MCHC in gram per liter)
      MCH and MCHC denote hypochromia
    - *Red cell distribution width (RDW)*: If RPI <2—*Type I* has normal indices and *Type II* has abnormal indices *(Refer **Table 1** as described above)*
  - *White blood cell count*
- Cell differential
- Nuclear segmentation of neutrophils in vitamin B12 deficiency


Hemoglobin <12 g
MCV <80 fL
Iron deficiency
Thalassemia
Sideroblastic
Lead intoxication
Chronic disease on late stage
MCV 80–100 fL
Acute blood loss
Chronic kidney disease (CKD)
Hypothyroidism
Bone marrow depression
Hemolysis
Aplastic G6PD
MCV >100 fL
B12 and folate deficiency
Liver disease
Reticulocytosis
Myelodysplastic
Chronic ethanol abuse
If peripheral blood smear shows microcytic/hypochromic RBC then suggestive of iron deficiency, thalassemia, sideroblastic, and anemia of chronic disease
If peripheral blood smear shows schistocytes, helmet cell, and spherocytes then suggestive of hemolysis and G6PD
If peripheral blood smear shows large oval RBC/hypersegmented neutrophils-suggestive of B12 and folate deficiency
If blood smear negative for large/hypersegmented neutrophil then consider liver disease, reticulocytosis, myelodysplastic, ethanol abuse, and drugs
Decrease in iron, ferritin, and increase in TIBC suggestive of iron deficiency anemia
Increase in LDH and decrease in haptoglobin
confirm hemolysis
Perform Coombs test,
positive Coombs test-autoimmune hemolytic anemia, negative Coombs test-nonautoimmune hemolytic anemia

(G6PD: glucose-6-phosphate dehydrogenase; LDH: lactate dehydrogenase MCV: mean corpuscular volume; RBC: red blood cell; TIBC: total iron-binding capacity)

FIG. 1: Differentiating various types of anemia.

TABLE 1: Investigations for approach to anemia.

Complete blood count	*Iron and vitamin B12 studies*	*Biochemistry*	*Test for hemolysis*	*Bone marrow studies*	*Others*
Red blood cell (RBC) count: (Affected by age, sex, pregnancy, smoking, and altitude) hemoglobin, hematocrit, and reticulocyte production index (RPI) (reticulocytes are immature RBC) <2—*inappropriate marrow response*: Red cell morphology disorder (i.e., Type I and II] and >2—accelerated RBC production: Hemolysis/blood loss (i.e., Type III) *Red blood cell indices*: Mean cell volume (MCV in femtoliters, normal ~90) (<80—microcytosis, >100—macrocytosis), mean cell hemoglobin (MCH in picograms per cell), mean cell hemoglobin concentration (MCHC in gram per liter). MCH and MCHC denotes hypochromia *Red cell distribution width (RDW)*: If RPI <2—Type I has normal indices and Type II has abnormal indices *White blood cell count*: Cell differential, nuclear segmentation of neutrophils in vitamin B12 deficiency *Platelet count*: Low in hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) *Peripheral blood smear (P/S)/cell morphology*: Abnormal cells, e.g., schistocytes, sickle cells, spherocytes, and burr cells seen in hemolytic anemia *Cell size*: Microcytes in iron deficiency, macrocytes in vitamin B12 and folate deficiency Hemoglobin content Anisocytosis—variation in cell size Poikilocytosis—variation in cell shape Polychromasia—larger greyish blue RBC (in fibrosis and malignancy)	*Serum iron*: <60 µg/dL in iron deficiency anemia *Total iron binding capacity (TIBC)*: >400 µg/dL in iron deficiency anemia *Serum ferritin level*: <10 mg/mL in iron deficiency anemia *Vitamin B12 level*: <200 µg/L suggestive of megaloblastic anemia *Folate level*: <3 µg/L suggestive of megaloblastic anemia	*Blood urea nitrogen (BUN)*: High [in slow gastrointestinal (GI) bleed hemoglobin is being absorbed from gut] *Creatinine*: High (chronic kidney disease) *Bilirubin*: Indirect (raised in hemolytic anemia)	*Haptoglobin*: Low in hemolysis *Lactate dehydrogenase (LDH)*: Raised (intravascular hemolysis) *Coombs test (direct and indirect)*: Positive in autoimmune hemolytic anemia *Urine*: Look for hemoglobinuria and hemosiderin (intravascular hemolysis)	*Bone marrow aspirate to look for*: Myeloid/erythroid ratio Cell morphology Iron stain *Bone marrow biopsy to look for*: Cellularity and morphology	*Ultrasound and CT scan abdomen*: To look for hepatosplenomegaly and ascites *Stool test*: Positive occult blood indicates loss of blood, routine microscopy to look for worm infestation GI endoscopies to look for bleed

    - *Platelet count*: Low in hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP)
    - *Peripheral blood smear (P/S)/cell morphology* (Abnormal cells, e.g., schistocytes, sickle cells, spherocytes, and burr cells seen in hemolytic anemia)
        - Cell size (microcytes in iron deficiency and macrocytes in vitamin B12 and folate deficiency)
        - Hemoglobin content
        - Anisocytosis—variation in cell size
        - Poikilocytosis—variation in cell shape
        - Polychromasia—larger greyish blue RBC (in fibrosis and malignancy)
- *Iron and vitamin B12 deficiency studies*:
    - Serum iron
    - Total iron binding capacity (TIBC)
    - Serum ferritin
    - Vitamin B12
    - Folate
- *Bone marrow studies*:
    - *Aspirate to look for*
        - Myeloid/erythroid ratio
        - Cell morphology
        - Iron stain
    - *Biopsy to look for*
        - Cellularity
        - Morphology
- *Biochemical tests*:
    - *Blood urea nitrogen (BUN):* High (in slow GI bleed Hb is being absorbed from gut)

- *Creatinine:* High (chronic kidney disease)
- *Bilirubin:* Indirect raised in hemolytic anemia

- Test that depicts hemolysis:
  - *Haptoglobin:* Low in hemolysis
  - *Lactate dehydrogenase (LDH):* Raised (intravascular hemolysis)
  - *Coombs test (direct and indirect):* Positive in autoimmune hemolytic anemia
  - *Urine*: Look for hemoglobinuria and hemosiderin (intravascular hemolysis)
- *Others*:
  - *Ultrasound and CT scan abdomen:* To look for hepatosplenomegaly and ascites
  - *Stool test*: Positive occult blood indicates loss of blood and routine microscopy to look for worm infestation
  - *GI endoscopies to look for bleed*

HEMOLYTIC ANEMIA

Whenever suspicion of hemolytic anemia: Low Hb (with no another obvious cause) and high reticulocyte count (with no recent bleed, no repletion of iron, vitamin B12, folate, or erythropoietin) (**Table 2**)

Features of *RBC destruction*: High LDH and indirect bilirubin, low haptoglobin, and it is important to localize site of hemolysis, It tells the:

- By-products of hemolysis will route through reticuloendothelial system (RES) *(extravascular)* or directly into blood circulation *(intravascular)*
- Cause
- Need for more aggressive treatment

TREATMENT

Treatment depends on individual clinical status. Emergent anemia due to acute blood loss due to trauma should be stabilized in emergency department. Nonemergent anemia needs admission if they develop chest pain, breathlessness, or unexplained drop in Hb or hematocrit. Nutritional improvement is important aspect of management.

Blood transfusion (uncrossmatched blood only if life-threatening condition), if acute blood loss results in severe hypovolemia, autoimmune hemolytic anemia (AIHA), ongoing hemorrhage, tissue hypoxemia, or cardiovascular instability.

Iron Deficiency Anemia

- *Oral iron* (elemental ~200 mg/day, in empty stomach) (ferrous sulfate, gluconate, and fumarate) in individual with iron deficiency without any symptom
  Side effect: Nausea, vomiting, and constipation
  Target: Till 6–12 months after normalization of Hb
- *Intravenous iron (*ferric carboxymaltose, sodium ferric gluconate, and sucrose dextran) if oral iron is not tolerated, requirement of iron on ongoing basis
  Dose calculated by *2.3 × body weight (kg) × (15 – Hb of patient) and add 500/1,000 mg for stores*

Side effect: Anaphylaxis more with dextran

TABLE 2: Suspicion of hemolytic anemia and indicators for hemolysis.

Subtle indicators of extravascular hemolysis	*Subtle indicators of intravascular hemolysis*
• History of jaundice • P/S: Spherocytes and sickle cells • High indirect bilirubin	• History of pink (oxyhemoglobin) or brown (methemoglobin) serum • Dark urine • Free serum hemoglobin (it binds to haptoglobin and this complex is removed by liver) • Reduced haptoglobin • High LDH • Urine hemoglobin/heme • Urine hemosiderin (after few days as kidney degrades heme to hemosiderin) • Kidney damage, thrombosis, and disseminated intravascular coagulation

(LDH: lactate dehydrogenase; P/S: peripheral blood smear)

Vitamin B12 Deficiency

- Six 1,000 µg intramuscular injections (hydroxocobalamin) after every 3–7 days, then once in 3 months
- Sublingual or oral treatment if bleeding tendencies (intramuscular not allowed)

Folate Deficiency

About 5–15 mg oral folic acid daily for minimum 4 months.

Hemolytic Anemia

- Treat the cause.
- AIHA is a medical emergency. Consider blood transfusion only if life-threatening, otherwise immediately start prednisolone 1 mg/kg/day and consider rituximab (second-line treatment). If relapse occurs, plan splenectomy. Hematopoietic stem cell transplantation in refractory in very severe cases.
- *Paroxysmal nocturnal hemoglobinuria (PNH)*: Supportive and blood transfusion
- *Cold agglutinin disease*: Avoid cold exposure (mild case) and azathioprine (severe case)

SUMMARY

- Is there any history of bleeding?
- Young age and slower development of anemia are better tolerated.
- Iron deficiency can be detected several weeks after bleeding.
- Always order for CBC, reticulocyte count, and peripheral blood smear tests before hematinics or blood transfusion.
- Low serum ferritin confirms iron deficiency anemia.

- If bone marrow does not respond appropriately to anemia (e.g., iron/vitamin B12/folate/copper deficiency, chronic inflammation, alcohol, and transient RBC aplasia); hemolytic anemia can be seen without reticulocytosis.
- If bone marrow has sufficient capacity to overcome the anemia caused by hemolysis, hemolysis can be seen without anemia.
- Prognosis depends on underlying cause.
- Mortality is low in hemolytic anemia, though risk is more in elderly and cardiac patients.
- In elderly people, anemia is linked with prolonged hospitalization
- Do follow-up of patient at regular interval.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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140 CHAPTER

Approach to Pancytopenia

Benita Florence, Dodiy Herman

INTRODUCTION

Pancytopenia is not an illness or disease in itself; it is the laboratory manifestation of underlying bone marrow dysfunction or failure in the production or reduction in the levels of all the three types of blood cells—erythrocytes, leukocytes, and platelets, manifested with symptoms resulting from anemia, leukopenia, or thrombocytopenia.

Emergency physicians are expected to acquire a high index of suspicion to the subtle signs and symptoms of pancytopenia, which may present as a benign or some of which are life-threatening condition. In most cases of pancytopenia, management of these patients will require multidisciplinary approach and timely referral to a hematologist.

DEFINITION

The presence of anemia with a hemoglobin (Hb) < 13.5 g/dL in males or 11.5 g/dL in females, leukopenia where leukocyte count < 4×10^3/L and thrombocytopenia with platelet count < 150×10^3/L is termed as pancytopenia.

Neutropenia is defined as mild (1,000–1,500/mm^3), moderate (500–1,000/mm^3), and severe (<500/mm^3) based on the absolute neutrophil count (ANC). This number is directly proportional to the prognosis of the patient. Agranulocytosis describes a virtual absence of neutrophils in peripheral blood which the ANC is <100/mm^3.

Thrombocytopenia is classified as platelet count of mild (100,000–150,000/mm^3) moderate (50,000–100,000/mm^3), and severe (<50.000/mm^3). Risk of bleeding increases significantly with platelet count < 20,000/mm.[3]

More often, diagnostic confirmation of pancytopenia is an incidental laboratory report. However, thorough history taking and clinical examination will aid with the diagnosis and the subsequent management of these patients. Further probing into the etiology leads to a range—transient suppression or dysfunction of the bone marrow due to infections, nutritional deficiencies, and may extend to malignancy.

ETIOLOGY

Major causes of pancytopenia are geographically and socioculturally determined, as hematological malignancies are more common in industrialized and developed nations, whereas vitamin deficiencies, hypersplenism, and infections are seen in developing countries.

Causes of Pancytopenia

- Idiopathic
- Bone marrow failure:
  - Aplastic anemia
  - Acute leukemia
  - Bone marrow fibrosis
  - Myelodysplastic syndrome and infiltrative diseases
- Hypersplenic state
- Autoimmune disorders—systemic lupus erythematosus (SLE)
- Infections [tuberculosis, human immunodeficiency virus (HIV), leishmaniasis, and brucellosis]
- Iatrogenic/drug-induced, e.g., drugs used in the treatment of rheumatoid arthritis
- Chronic liver disease
- Nutritional deficiencies (folate and B12)
- Macrophage activation syndrome (MAS) or hemophagocytic syndrome (rare)
- Paroxysmal nocturnal hemoglobinuria
- Miscellaneous

Eating disorders (anorexia nervosa), bariatric surgery, malabsorption syndromes, inadequate consumption of food, and alcoholism also lead to nutritional deficiencies. Inadequate dietary intake and alcoholism lead to folate deficiency, however, vitamin B12 deficiency occurs due to ineffective absorption. Megaloblastic anemia is commonly caused by folate and B12 deficiency and these usually present with anemia and thrombocytopenia; however, may present solely as thrombocytopenia. Pancytopenia may also be noted in pregnancy. Patients on long-term total parenteral nutrition, gastrointestinal surgery, weight reduction surgery, excessive zinc intake, and renal failure may develop pancytopenia due to copper deficiency.

Infections are known to lead to bone marrow failure. These are mostly reversible causes. Hence patients who are unwell with indwelling catheters, these should be considered as a primary source of infection and treated accordingly with a background picture of sepsis.

Infections can also cause acquired hemophagocytic lymphohistiocytosis (HLH). The clinical diagnosis of this syndrome requires the presence of five or more of the following:

- Fever
- Splenomegaly
- Cytopenia involving two or more cell lines
- Hypertriglyceridemia or hypofibrinogenemia
- Hepatitis
- Low or absent natural killer cell activity
- Serum ferritin level > 500 mg/L
- Soluble CD25 > 2,400 U/mL
- Hemophagocytosis as demonstrated in bone marrow, spleen, or lymph node

CLINICAL FEATURES

Patients may present to the emergency department (ED) acutely unwell as in fulminant sepsis, disseminated intravascular coagulation or rapid hemolysis or with chronic manifestations progressing over weeks or months. There are no specific signs and symptoms directly correlating to the presentation of the disease condition. Mild pancytopenia may be asymptomatic and may be an incidental finding. Presentation may be as follows:

- Nonspecific fever, fatigue, dizziness, weight loss, anorexia, and night sweats
- Anemia causing pallor, shortness of breath, and pedal edema
- Neutropenia causing features of sepsis, skin lesions, and oral ulceration
- Thrombocytopenia causing prolonged bleeding, easy bruising, petechial rashes, menorrhagia, epistaxis, and melena may be seen

Hepatomegaly, splenomegaly, and lymphadenopathy may be seen on clinical examination.

History of splenectomy, any other conditions treated, medications prescribed, nonprescribed, recreational drugs, smoking and alcohol, occupation, hobbies, etc., should be noted along with travel history, family history, any previous history of blood transfusion, or if the patient has been a donor also should be recorded.

DIAGNOSTIC WORKUP

Pancytopenia patients pose a diagnostic challenge, due to variable etiology which may be influenced by demography—country and other living conditions. It is essential to reach a definitive diagnosis as treatment and disease progression depend on the etiology of the pancytopenia. Therefore, clinical evaluation should include:

- Medication history
- Family history
- Recreational drug history
- Environmental exposure history
- Comorbid illnesses

Initial laboratory workup includes full blood count with peripheral smear, erythrocyte sedimentation rate, C-reactive protein, renal and liver function tests, lactate dehydrogenase levels, iron studies, clotting studies, reticulocyte count, and blood type and screen. A chest X-ray at presentation will help to exclude infection and as a comparison for subsequent films.

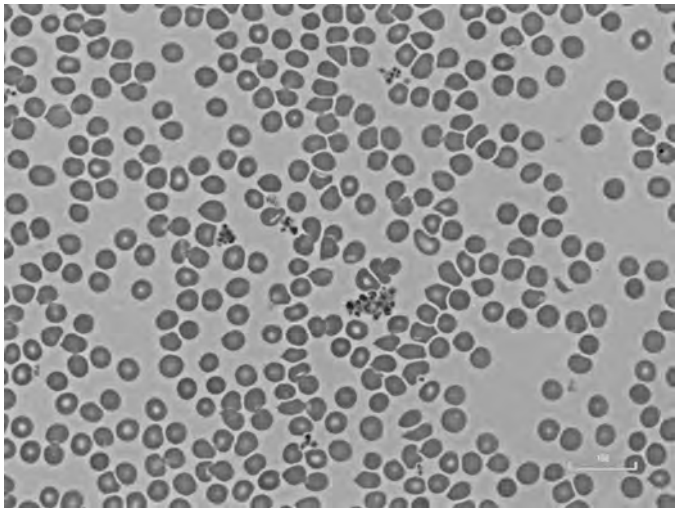


FIG. 1: Platelet clumping. Not an emergency but can give an erroneously low platelet count. ***(For color version, see plate 18)***

Bone marrow examination may reveal the underlying condition causing pancytopenia, but is not always conclusive. Hypoplastic bone marrow, megaloblastic anemia, and hematological malignancies, i.e., acute myeloid leukemia and erythroid hyperplasia are the common causes of pancytopenia seen on bone marrow examination. Unexplained pancytopenia, macrocytosis, hypersegmented neutrophils, and unexplained neurological signs and symptoms can be caused by folate and vitamin B12 deficiencies.

A caveat to remember that rarely, pseudothrombocytopenia may be a laboratory finding discovered incidentally, in an asymptomatic individual. Additionally, patient should be tested for copper, zinc, Coombs test, vitamin B12, folate level, HIV, hepatitis, and ultrasound of abdomen to look for hepatosplenomegaly. Ultrasonography with abnormal or anatomically displaced kidneys is a feature of Fanconi anemia.

Platelet clumping may be due to the calcium chelator in the ethylenediaminetetraacetic anticoagulant contained in the sample collection tube (**Fig. 1**). A repeat sample for confirmation should be sent in a citrated or heparinized tube.

APLASTIC ANEMIA

Aplastic anemia is a rare disorder which, if untreated, is associated with very high mortality. The incidence of aplastic anemia is approximately two to three per million per year in Western countries with the incidence is estimated to be two- to three-fold higher in East Asia. There is a biphasic distribution with peaks at 10–25 years and >60 years and a sex ratio of 1:1. The exact mechanism by which aplastic anemia occurs is still unknown in most of the cases. Important causes of aplastic anemia are shown in **Table 1**. It is defined as pancytopenia (reduction in the number of red cells, neutrophils, and platelets in the peripheral blood) with hypocellular marrow in absence of abnormal infiltrate or increased fibrosis. In order to diagnose aplastic anemia, there must be at least two of the following criteria:

- Hemoglobin concentration < 100 g/L
- Platelet count < 50×10^9/L
- Neutrophil count < 1.5×10^9/L

TABLE 1: Causes of aplastic anemia.

Drugs, radiation, and toxins	• Cytotoxic chemotherapy • Azathioprine • Gold • Chloramphenicol • Sulphonamides • Nifedipine • Carbamazepine • Valproic acid • Phenytoin • Ionizing radiation • Industrial chemicals • Insecticides • Benzene
Viral infection	• Hepatitis virus • Human immunodeficiency virus
Miscellaneous	• Systemic lupus erythematosus • Graft-versus-host disease • Paroxysmal nocturnal hemoglobinuria • Pregnancy • Anorexia nervosa

For purposes of risk stratification and severity, aplastic anemia further classified according to the following criteria:

- *Nonsevere aplastic anemia*:
  - Hypocellular bone marrow as per severe aplastic anemia
  - Peripheral blood cytopenia not fulfilling the criteria for severe aplastic anemia or very severe aplastic anemia
- *Severe aplastic anemia*:
  - Bone marrow cellularity <25% (or 25–50% with <30% of residual cells are hematopoietic)
  - At least two of the following:
    - Neutrophils $<0.5 \times 10^9$/L
    - Platelets $<20 \times 10^9$/L
    - Reticulocyte count $<20 \times 10^9$/L
- *Very severe aplastic anemia*: As for severe aplastic anemia but neutrophils $<0.2 \times 10^9$/L

INHERITED APLASTIC ANEMIA

Fanconi Anemia

Fanconi anemia is the most common form of inherited aplastic anemia, characterized by pancytopenia, predisposition to malignancy, and any of the physical abnormalities such as short stature, limb abnormalities, café-au-lait lesions on the skin, microcephaly, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, structural malformations of the urogenital tract, or developmental delay. Though diagnosis is made in children there may be late presentation in adulthood. Fanconi anemia was first described in 1927 by a Swiss pediatrician Guido Fanconi. It is a rare, genetic heterogeneous multisystem disease transmitted as autosomal recessive with the exception of *FANCB*, which is X-linked transmitted.

Shwachman–Diamond Syndrome

Shwachman–Diamond syndrome also known as Shwachman–Bodian–Diamond syndrome, Shwachman–Diamond–Oski syndrome, or Shwachman syndrome is a rare inherited autosomal recessive disorder characterized by hematological abnormalities with pancytopenia, aplastic anemia, vulnerability to acquire myelodysplastic syndrome, and/or acute myeloid leukemia; exocrine pancreatic dysfunction with malabsorption, malnutrition, short stature, skeletal anomalies, cardiac defects, ear malformations/hearing loss, or skin rashes.

Approach to Clinical Treatment for Aplastic Anemia

- Eliminate exposure to causative agents
- Supportive therapy
- Immunosuppressive treatment, e.g., antithymocyte globulin
- Hemopoietic stem cell transplantation
- Screening for paroxysmal nocturnal hemoglobinuria

In the ED, supportive therapy and symptomatic care play a major role (**Flowchart 1**). In patients with aplastic anemia who have severe anemia/thrombocytopenia requiring transfusion; it is advisable that the red blood cell (RBC) units given are leukoreduced to minimize the risk of febrile nonhemolytic transfusion reactions and reduce transmission of cytomegalovirus (CMV) to CMV-negative patients. This is also important for those patients who may undergo allogeneic hematopoietic cell transplantation (HCT) in the future. Irradiation depletes lymphocytes and reduces the risk of transfusion-associated graft-versus-host-disease (ta-GVHD), during the initial phase of intensive immunosuppressive therapy (IST). Irradiation may not be required for all patients with supportive care as those who are not severely T cell immunodeficient are unlikely to develop ta-GVHD.

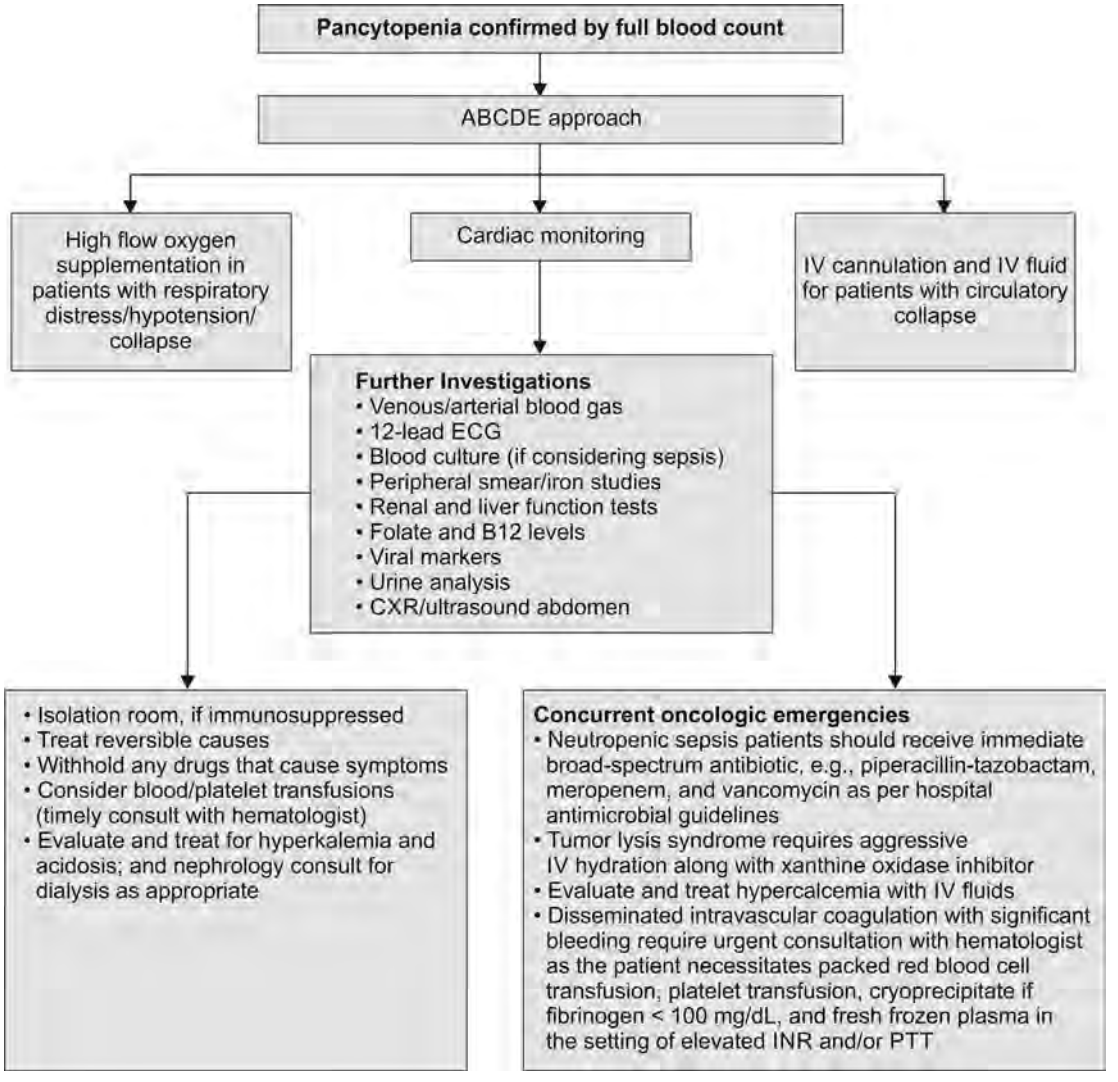
SUMMARY

Identification of potential causes of pancytopenia present a diagnostic challenge for emergency physicians. It is important to identify the etiology of the pancytopenia rather than the primary disease itself. Furthermore, multitude of diseases presenting with pancytopenia are potentially life-threatening if not treated with caution. Detailed history taking, systematic examination in conjunction with initial screening and laboratory evaluation, an early consultation with multidisciplinary team, and hematologist will assist emergency physicians to optimize clinical treatment and guiding further workup.

- Aplastic anemia is the most common cause of pancytopenia worldwide.
- Review various etiological factors that lead to pancytopenia.
- Vitamin B12 deficiency should be considered as the cause for pancytopenia in low-income countries.
- Pseudothrombocytopenia may be a laboratory finding discovered incidentally, in an asymptomatic individual.

ACKNOWLEDGMENT

We are grateful for the help of Dr Dewi Eden, Consultant Hematologist, Shrewsbury and Telford Hospital, who was instrumental in providing us with the histopathological images.


Pancytopenia confirmed by full blood count
ABCDE approach
High flow oxygen supplementation in patients with respiratory distress/hypotension/ collapse
Cardiac monitoring
IV cannulation and IV fluid for patients with circulatory collapse
Further Investigations
• Venous/arterial blood gas
• 12-lead ECG
• Blood culture (if considering sepsis)
• Peripheral smear/iron studies
• Renal and liver function tests
• Folate and B12 levels
• Viral markers
• Urine analysis
• CXR/ultrasound abdomen
• Isolation room, if immunosuppressed
• Treat reversible causes
• Withhold any drugs that cause symptoms
• Consider blood/platelet transfusions (timely consult with hematologist)
• Evaluate and treat for hyperkalemia and acidosis; and nephrology consult for dialysis as appropriate
Concurrent oncologic emergencies
• Neutropenic sepsis patients should receive immediate broad-spectrum antibiotic, e.g., piperacillin-tazobactam, meropenem, and vancomycin as per hospital antimicrobial guidelines
• Tumor lysis syndrome requires aggressive IV hydration along with xanthine oxidase inhibitor
• Evaluate and treat hypercalcemia with IV fluids
• Disseminated intravascular coagulation with significant bleeding require urgent consultation with hematologist as the patient necessitates packed red blood cell transfusion, platelet transfusion, cryoprecipitate if fibrinogen < 100 mg/dL, and fresh frozen plasma in the setting of elevated INR and/or PTT

(ABCDE: airway, breathing, circulation, disability, and exposure; CXR: chest X-ray; ECG: electrocardiogram; INR: International Normalized Ratio; IV: intravenous; PTT: partial thromboplastin time)

FLOWCHART 1: Approach to clinical management of patient with pancytopenia.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Approach to Leukemia

Dodiy Herman, Benita Florence

INTRODUCTION

Leukemia in the emergency department (ED) often presents as persistence of vague symptoms. However, the role of the emergency physician (EP) is to ensure early recognition of life-threatening complications, management of reversible causes, and initial therapeutic stabilization of this patient. Delay in prompt management increases the risk of morbidity and mortality.

Acute leukemia is characterized by rapid proliferation of abnormal white cells, due to bone marrow dysfunction. Transformation occurs due to abnormal proliferation, clonal expansion, aberrant differentiation, and diminished apoptosis leading to replacement of normal blood elements with malignant cells. It also suppresses production of normal blood cells and suppression of the immune system. Any organ system may become affected, although lymph nodes, liver, spleen, central nervous system (CNS), and skin are the most common sites for clinical detection.

EPIDEMIOLOGY

Globally around 300,000 new cases of leukemia (2.8% of all new cancer cases) are diagnosed annually. Chronic lymphocytic leukemia (CLL) constitutes the most frequent type of leukemia with 25% of cases, chronic myeloid leukemia (CML) represents 20% of cases, and acute myeloid leukemia (AML) represents 20% of cases in the Western countries. About 30% of the patients presenting with CML may be asymptomatic and may present as an incidental finding on complete blood count (CBC).

The global 5-year survival is 20% with all leukemias put together. In developing countries, 15% survive for 5 or more years compared to developed countries which is 30%.

RISK FACTORS

- Genetic predisposition—Down's syndrome and neurofibromatosis
- Exposure to radiation—atomic bomb survivors, radiographers before 1950, patients with cancer receiving cancer therapy, exposed to multiple computed tomography scans
- Exposure to benzene
- Exposure to household pesticide
- Obesity
- History of hematological malignancy
- Familial
- Smoking

CLINICAL PRESENTATION

Undiagnosed cases may present to the ED with a broad spectrum of nonspecific signs and symptoms:

- Fatigue
- Anemia
- Loss of appetite
- Weight loss
- Easy bruising and bleeding
- Persistent fever/recurrent infections
- Generally feeling unwell
- Night sweats
- Poorly healing skin wounds
- Sepsis

In the extremes of age groups, difficulty or refusing to walk should raise a suspicion, although bone and joint pain are less common presenting symptoms of leukemia. Hypoxia, retinal hemorrhage, altered sensorium, and diffuse pulmonary shadowing are all features of leukostasis. Splenomegaly causes satiety, left hypochondriac pain, and sensation of fullness. Patients diagnosed with leukemia and those on treatment may present to the ED with:

- *Fever/neutropenia*: In patients undergoing chemotherapy, severe underlying infection may present as a single fever spike as other inflammatory response of the body system is weakened. A single documented temperature of >38.3°C (101°F) or a sustained temperature >38°C (100.4°F) for >1 hour is significant. Absolute neutrophil count (ANC) of 500 cells/mm^3 or that which decreases to <500 cells/mm^3 during the next 48 hours is defined as neutropenia.
- Bleeding due to thrombocytopenia
- Bleeding may be the presentation to ED in 60% of patients with leukemias
- Thrombosis
- Gastrointestinal symptoms—nausea/vomiting/diarrhea causing dehydration

CLASSIFICATION

Classification of leukemia is derived from two main systems.

1. The French–American–British (FAB) classification
2. The World Health Organization (WHO) classification

The FAB classification is based on the morphology of the abnormal leukocytes, providing a diagnostic type and does not provide any prognostic value. The WHO classification is a combination of clinical, morphologic, immunophenotypic, and genetic features. They are broadly classified as acute or chronic, based on the number of blasts in the bone marrow or blood and as myeloid or lymphoid which is determined by the lineage of the malignant cells.

The American Cancer Society, in 2020, estimated the distribution of new US cases of leukemia as:

- Acute myeloid leukemia: 33%
- Acute lymphoblastic leukemia: 10%
- Chronic myeloid leukemia: 14%
- Chronic lymphocytic leukemia: 35%
- Other leukemias: 8%

CLINICAL MANIFESTATION AND ASSESSMENT

The initial presentation to the ED may be with vague symptomatology and repeated hospital visits. Patient may be febrile with tachycardia, hypotension, and tachypnea or in respiratory distress. Anemia may cause shortness of breath and heart failure. Ecchymosis and excessive bleeding from intravenous sites may be seen.

Examination may also reveal splenomegaly, hepatomegaly, or lymphadenopathy. Further clinical assessment includes dentition which shows dental abscesses and/or gum hypertrophy.

Fundoscopy

Eyes and the CNS are the common sites where vascular obstruction secondary to leukostasis and thrombosis is noted.

In the early 1,800 patients with splenomegaly and abnormal blood viscosity were found to have more number of white blood cells (WBCs) on blood smear. However, leukocytosis is present in only about one-third of patients with leukemia.

INVESTIGATIONS

In the acute emergency setting, a CBC and peripheral smear will aid as screening tools in diagnosing leukemia. Bone marrow aspirate and biopsy is essential for definitive diagnosis (**Fig. 1**). Hyperleukocytosis (white cell count >100 × 10^9/L) (**Figs. 2A** and **B**) should be considered in newly diagnosed AML patients with either dyspnea or altered mental status. These manifestations are due to by impairment of microvascular perfusion.

Clotting studies, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) form part of the routine investigations. Venous blood gas analysis facilitates identification of patients presenting with life-threatening emergencies. Serum electrolytes, renal function tests, liver function tests, lactate dehydrogenase, calcium, phosphate, and random blood sugar are necessary to risk stratify the disease and treat reversible causes. Potassium may be falsely elevated due to release of intracellular cations from blasts in sample collection tube, hence to correlate with echocardiogram (ECG) and clinical

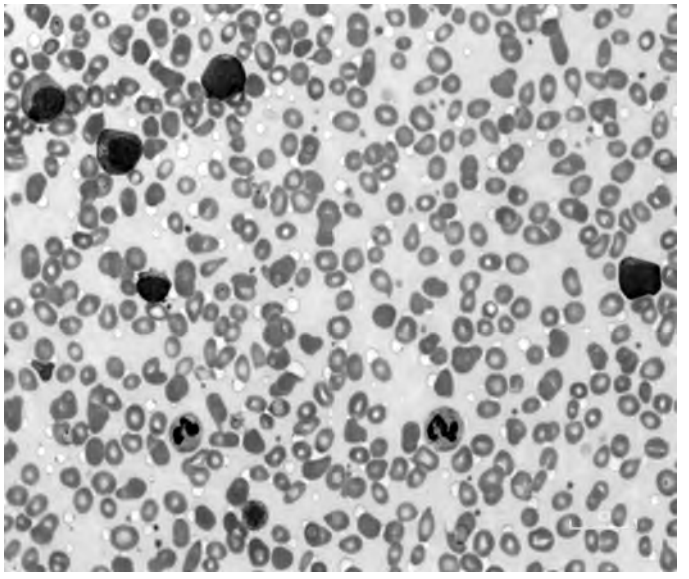


FIG. 1: Slide of acute myeloid leukemia, myelocytes, myeloid blast, dysplastic giant platelets, and polychromasia. ***(For color version, see plate 18)***

presentation. Procalcitonin levels have shown good specificity and sensitivity in helping differentiate bacterial infections from tumor fevers in febrile neutropenic patients.

Viral serology, Epstein–Barr virus, and cytomegalovirus are to be included in patients who are newly diagnosed or in those with no clear etiology of infection. Blood grouping and screening may be requiring for transfusion of blood and blood products.

Blood Cultures

If a central venous catheter is present, a set from each lumen is to be collected from a peripheral vein site. In the absence of a central venous catheter, two blood culture sets from separate venipuncture sites should be collected and sent for analysis.

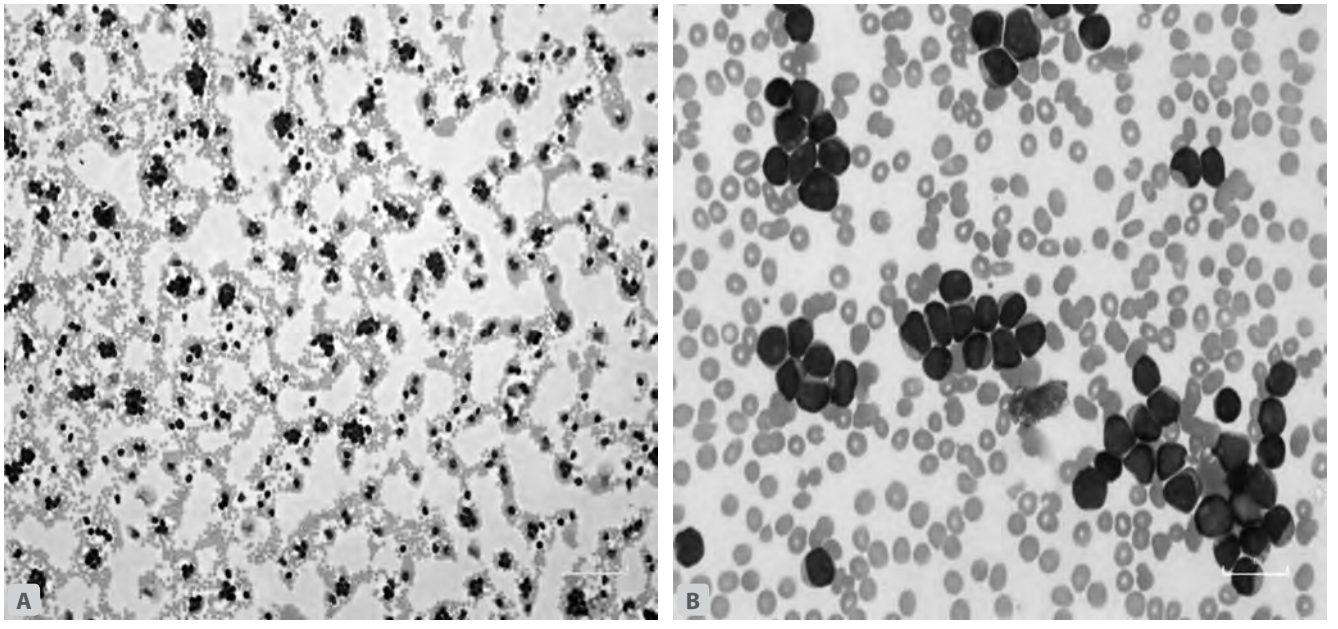
Culture of certain other sites should be done guided by clinical signs and symptoms and not be performed routinely.

- *Stool*: In a patient with diarrhea for *Clostridium difficile* toxin assay and if there is any history of recent travel to or residence in areas of endemicity.
- *Urine*: If signs or symptoms of urinary tract infection exist, a urinary catheter is in place, or urine microscopy is abnormal.
- *Cerebrospinal fluid*: If meningitis is suspected. Platelet transfusion should be given prior to lumbar puncture in patients whom thrombocytopenia is a concern.
- *Skin*: Cytological testing, Gram staining, and culture should be done if skin lesions are suspected of being infected.
- *Respiratory specimens*: In patients with a productive cough sputum samples should be sent for bacterial culture.

The majority of patients who develop fever with neutropenia have no clear identifiable site of infection and negative culture results. However, every patient with fever and neutropenia should receive empirical antibiotic therapy urgently, because of rapid progression of infection.

Chest X-ray

A chest radiograph is indicated for patients with respiratory signs or symptoms. ECG, if cardiac dysfunction is noted.



FIGS. 2A AND B: (A) Slide shows hyperleukocytosis in a patient with acute myeloid leukemia (AML). (B) Slide shows myeloid blasts seen in the AML with hyperleukocytosis. Myeloid blasts contain granules, best seen in the highlighted cells. ***(For color version, see plate 18)***

TREATMENT IN THE EMERGENCY DEPARTMENT

Management primarily starts with an ABC approach of airway, breathing, and circulation. Intravenous access and hydration where appropriate and should be established. These patients may also present with bone pain, neuropathic pain, or other discomfort. Analgesics need to be prescribed according to the WHO pain ladder scale consisting of opioids, nonopioids, and adjuvant therapy. Ibuprofen is not recommended in children as it may affect platelet function. Antipyretics, if patient has fever and also to prevent hypothermia. Antiemetic may be added based on the clinical presentation.

Risk stratification helps in determining the route of empirical antibiotic therapy, inpatient or outpatient care, and the duration of antibiotic therapy. This helps to avoid unnecessary hospital admissions as this group of patients are more prone to iatrogenic infections. **Table 1** shows risk stratification of patients.

Apart from bloodstream infection, other sites are the respiratory tract (pneumonia and sinusitis), skin and soft tissue infection (mucositis and cellulitis), gastrointestinal (diarrhea, typhlitis, perirectal abscess, and enterocolitis) with the oral cavity causing polymicrobial bloodstream infection and the genitourinary tract (urinary tract infection). Neutropenic enterocolitis has high morbidity and mortality rate.

Monotherapy is started with an antipseudomonal β-lactam agent, such as cefepime, a carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam. Other antimicrobials (aminoglycosides, fluoroquinolones, and/or vancomycin) may be added for the management of associated systemic illness (e.g., hypotension and pneumonia) or if antimicrobial resistance is suspected or proven. Vancomycin is not routinely used in the empiric treatment of neutropenic fever. As the emergence of resistance has increased, vancomycin is started if the patient meets any of the following criteria: positive blood cultures with smears showing gram-positive cocci, in critically ill patients, with the presence of skin or soft tissue infection, suspicion of catheter-related infection, or prior infection with methicillin-resistant *Staphylococcus aureus* (MRSA).

Afebrile neutropenic patients who have signs or symptoms suggestive of new infection should be evaluated and treated as high-risk patients. In low-risk patients, ciprofloxacin plus amoxicillin-clavulanate in combination is recommended for oral empirical treatment. Other treatment regimens with levofloxacin or ciprofloxacin monotherapy or ciprofloxacin plus clindamycin can be used. In patients with persistent or recurrent fever after 4–7 days of antibiotics empirical antifungal therapy and investigation for invasive fungal infections should be considered. This is for the treatment of any “occult" fungal infection presenting as persistent neutropenic fever despite empirical antibiotic therapy. In systemically unwell patients and in those patients with uncertainty of diagnosis, consider high-dose steroid, hydroxyurea, broad-spectrum antibiotics, and hydration with approach from an expert multidisciplinary team.

OTHER EMERGENCIES

Apart from febrile neutropenia, sepsis, and septic shock the other conditions that need to be dealt with immediately are hypercalcemia, acute transfusion reactions, hyperviscosity syndrome, disseminated intravascular coagulation, tumor lysis syndrome, hyperleukostasis, and paraparesis/spinal collapse.

Hyperleukocytosis

Total leukemia blood cell count > 50 × 10/L (50,000/μL) or 100 × 10/L (100,000/μL) is referred to as hyperleukocytosis (**Figs. 2A and B**). The diagnosis of hyperleukocytosis and leukostasis (also called symptomatic hyperleukocytosis) in patients with leukemia (common in those with AML or CML) is an oncological emergency. The presence of elevated blast cell count and symptoms of decreased tissue perfusion leads to high mortality rates.

TABLE 1: Risk stratification—leukemia.

	High risk	*Low risk*
Duration of symptoms	>7 days	<7 days
Absolute neutrophil count (ANC)	Profound neutropenia (ANC) ≤100 cells/mm^3	
Renal function	Creatinine clearance <30 mL/min	Normal renal function
Liver function	Aminotransferase levels more than five times normal value	Normal liver function
Associated symptoms: • Clinically unstable • Gastrointestinal symptoms • Not tolerating orally • Altered mental status intravascular catheter infection • Respiratory: New oxygen requirement, lung infiltrates on chest X-ray (CXR)	Many	None/few
Underlying comorbid conditions	Diabetes Chronic obstructive lung disease Recent surgical procedures	None
Multinational Association for Supportive Care in Cancer (MASCC) scoring system	Score of <21	Score ≥21
Disposition	Inhospital admission for antibiotics and further management	Consider oral empirical antibiotic therapy

Prophylaxis for tumor lysis syndrome should be started immediately to prevent its exacerbation. Hematology or expert advice should be obtained as early as possible.

- Administer oxygen
- Intravenous fluid hydration should be started promptly (with input/output charting). This helps in enhancing renal blood flow and promotes urinary excretion.
- Unless transfusion of packed red blood cell (PRBCs) is required as a life-threatening emergency, leukocyte reduction needs to be achieved as blood products (especially PRBCs) may increase serum viscosity exacerbate leukostasis.
- Consider allopurinol and/or rasburicase. This reduces the risk of uric acid crystallization in the kidneys.
- Monitor for disseminated intravascular coagulation.
- Keep platelet count above 20×10^9 per liter to minimize bleeding risk.

PRECAUTIONS

Hand hygiene and standard barrier precautions should be followed for all patients, and infection-specific isolation should be used. Patients with hematopoietic stem cell transplantation (HSCT) require strict isolation. Menstruating immunocompromised patients should not use tampons, which can cause abrasions leading to infection. In patients with neutropenia rectal thermometers, enemas, suppositories, and rectal examinations are contraindicated. For patients with mucositis, oral rinses four to six times/day with sterile water, normal saline, or sodium bicarbonate solutions are recommended.

SUMMARY

The ED should have treatment guidelines keeping the following factors in mind:

- The disease characteristics and patient's condition
- The type and stage of leukemia
- The clinical presentation and reason for admission
- Prognosis of the disease, if applicable
- Escalation of care when required

Multidisciplinary care involving the physicians, hematologists, and intensivists should be obtained whenever appropriate. Age, ethnicity, and presence of neutropenia should not influence the EP in making a decision on the prognosis of the disease. Population-based registries are required due to variations in genomics based on race and ethnicity.

In this era of rapid advances in diagnostic techniques and development of newer chemotherapeutic and antibiotic medications in the fight against leukemia, the spectrum of infections continues to change yet a patient-oriented approach to achieve the best outcome should be given priority.

ACKNOWLEDGMENT

We acknowledge the help of Dr Dewi Eden, Consultant Hematologist, Shrewsbury and Telford Hospital, who was instrumental in providing us with the histopathological images.

MULTIPLE CHOICE QUESTIONS

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ONLINE REFERENCES

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142 CHAPTER

Oncological Emergencies

Amit K Jain

INTRODUCTION

An oncologic emergency is any acute, potentially morbid, or life-threatening event, related directly or indirectly to a patient's tumor or its treatment. It needs to be managed urgently and appropriately to avoid its devastating consequences such as permanent damage and death. It is broadly classified into four types as given in **Table 1**.

ONCOLOGICAL EMERGENCIES RELATED TO LOCAL TUMOR EFFECTS

Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome is the clinical manifestation resulting from obstruction of blood flow to the right atrium due to compression, invasion, thrombosis, or fibrosis of the SVC. Important causes of SVC are malignant (60–85%): Lung cancer, lymphomas, and other malignancies (primary and metastatic) and benign (15–40%): Thrombosis due to central vein catheters and other causes.

TABLE 1: Classification of oncological emergencies.

Types	*Oncological emergencies*
Related to local tumor effects	• Superior vena cava syndrome • Increased intracranial pressure • Malignant spinal cord compression • Malignant pericardial effusion • Malignant central airway obstruction • Bone metastasis
Related to biochemical derangements	• Tumor lysis syndrome • Hyponatremia • Hypercalcemia • Lactic acidosis
Related to hematological derangements	• Febrile neutropenia • Hyperviscosity syndrome • Thromboembolic disease
Related to therapy	• Chemotherapy-induced nausea and vomiting • Chemotherapy-induced diarrhea • Extravasation of chemotherapy • Cytokine release syndrome

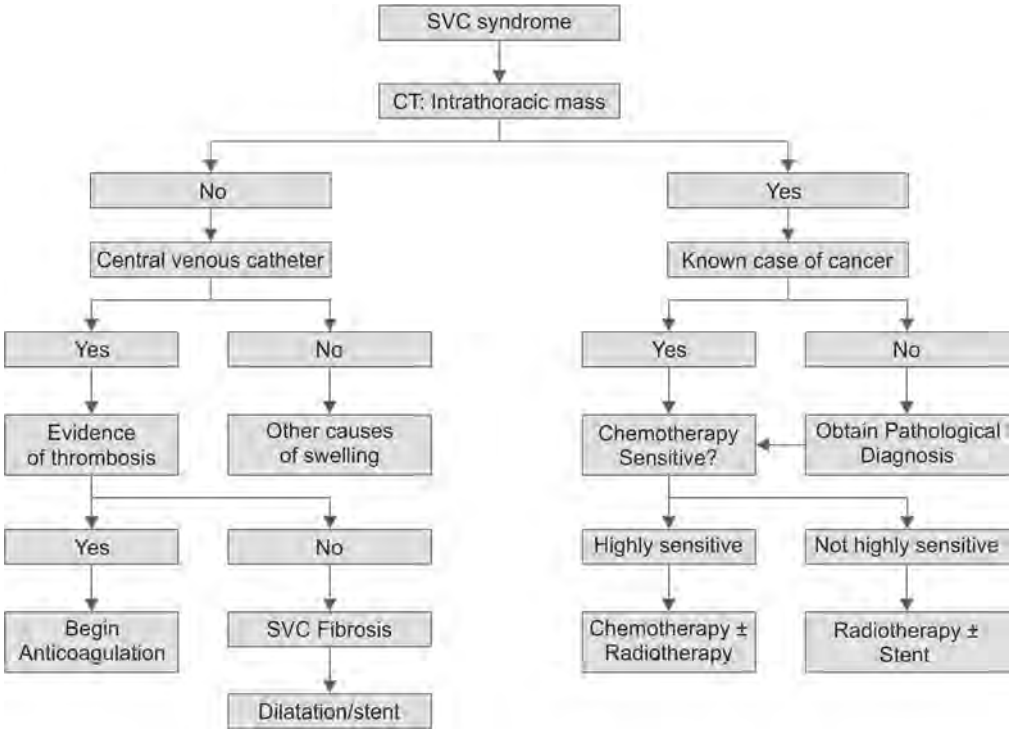
Superior vena cava syndrome develops when the flow of blood in SVC is obstructed; venous collaterals develop if it gradually develops allowing time for the collateral veins to form. Collateral pathway arises from the azygos (most important), internal mammary, lateral thoracic, paraspinal, and esophageal venous systems. Despite well-developed collateral pathway, the venous pressure of the upper compartment is elevated in SVC syndrome. *Common symptoms of SVC syndrome are*: Dyspnea, facial swelling and head fullness, cough, arm swelling, etc., which aggravates on lying down or bending. Common physical findings: Distention of neck and chest wall veins, plethora of face, facial edema, cyanosis, etc.

Diagnostic workup of SVC syndrome includes chest X-ray: Superior mediastinal widening and pleural effusion. Contrast-enhanced computed tomography (CECT) chest (magnetic resonance venography if iodinated contrast is contraindicated): Cause of obstruction, level and extent of blockage, and evaluation of collaterals. In a patient with suspicion of malignant etiology, if feasible pathological diagnosis should always be established prior to initiation of therapy via endobronchial fine-needle aspiration cytology (FNAC), mediastinoscopy, CT-guided biopsy, thoracentesis, supraclavicular lymph node biopsy, thoracoscopic biopsy or thoracotomy, and also staging workup, thus guiding into the intent of treatment.

Treatment of the SVC syndrome depends on cause and extent of the disease (**Flowchart 1**).

Supportive measures: Bed rest, oxygen, head end elevation (decrease the hydrostatic pressure), steroids (relieve inflammation and edema; avoid before pathological diagnosis), loop diuretics, and avoid placement of cannula in the arms.
Definitive therapy includes:

- Radiation treatment
- *Chemotherapy*: In chemosensitive tumor such as lymphoma, germ cell tumors, or small cell lung cancer
- *Endovascular therapy, i.e., thrombolysis, stenting, and angioplasty*: In patients with thrombosis and patients not responding to cancer treatment



FLOWCHART 1: Management of superior vena cava (SVC) syndrome.

- *Surgery*: Failure of radiotherapy, chemotherapy, and endovascular therapy, like in cases of retrosternal goiter and aortic aneurysm

Increased Intracranial Pressure

Increased intracranial pressure (ICP) refers to increase in ICP ≥ 20 mm Hg. Etiolgy of the raised ICP includes *increase in cerebral parenchymal pressure, e.g.,* brain tumor (primary or metastatic), intracranial hemorrhage, edema, and infection. *Disorders affecting cerebrospinal fluid (CSF) flow, production, and/or reabsorption*: Carcinomatosis, meningitis, subependymal, or intraventricular tumors. *Venous flow obstruction*: Cerebral venous thrombosis, dural sinus stenosis or occlusion by mass lesion, obstruction/compression of internal jugular vein or SVC by mass lesion. *Pathophysiological process for raised ICP*: Intracranial volume is fixed and increase in volume of one component occurs at the expense of the others. Increase in ICP leads to decrease in cerebral perfusion pressure which can lead to ischemia. Raised ICP can also lead to shift of brain structures, hydrocephalus, and brain herniation.

Clinical presentation of raised ICP includes headache (severe, maximum intensity in morning on awakening, resistant to common analgesics, and relieved by vomiting), nausea, vomiting, somnolence, and ultimately coma. Seizures and paresis/plegia may also occur. Chronic increased ICP: Sphincter incontinence. Increased ICP in infants: Increased head circumference. In patients with meningitis: Kernig's sign and Brudzinski's sign. Cushing reflex is present with raising ICP and may indicate impending herniation. It consists of systolic hypertension, bradycardia, and irregular and decreased respiration. Focal neurological deficits may be present and may help localize mass. Example: Tectal mass—upward gaze paresis. *Diagnostic workup for raised ICP includes*:

- *Fundus*: Absence of venous pulsations, papilledema, small hemorrhages, and optic nerve atrophy may be seen
- *CT brain*: Presence of mass lesion and CSF obstruction
- *Contrast-enhanced magnetic resonance imaging (CEMRI) brain*: More comprehensive neuroanatomic imaging distinguishing neoplastic, infectious, inflammatory, or ischemic process
- *Cine MRI scan*: CSF flow studies
- *MRI spine*: Unexplained cases of communicating hydrocephalus
- *MRI or CT venography*: Dural venous sinus obstruction or infiltration
- CSF pressure measurement by lumbar puncture in lateral decubitus position. It should not be done in cases with CSF obstruction resulting in compartmentalization.

Treatment

- Head end of bed to be elevated at approximately 30°.
- Avoid body temperature >100.5°F by use of antipyretics, if needed.
- Maintain serum osmolality towards upper limit of normal.
- Maintain blood pressure avoiding mean arterial pressure peaks.
- *Steroids*: Dexamethasone in moderate to high doses to reduce vasogenic edema. In cases of suspected lymphoma, before pathological diagnosis is established use of steroids should be avoided.
- Hyperosmolar agents like mannitol or glycerol to induce osmotic diuresis. Mannitol first dose of 0.75–1 g/kg, followed by 0.25–0.5 g/kg every 4–6 hours with serum osmolality monitoring to avoid hyper osmolality.
- *Intubation and mechanical ventilation*: Decreasing and maintaining partial pressure of carbon dioxide between 25 and 30 mm Hg (most rapid method, but the effect is only transient).
- In obstructive hydrocephalus with clinical features of cerebral herniation—urgent external ventriculostomy.

When CSF obstruction cannot be definitively cannot be treated ventriculoperitoneal (VP) shunt or endoscopic third ventriculostomy. VP shunt may be avoided in patients with leptomeningeal disease to prevent peritoneal seeding.

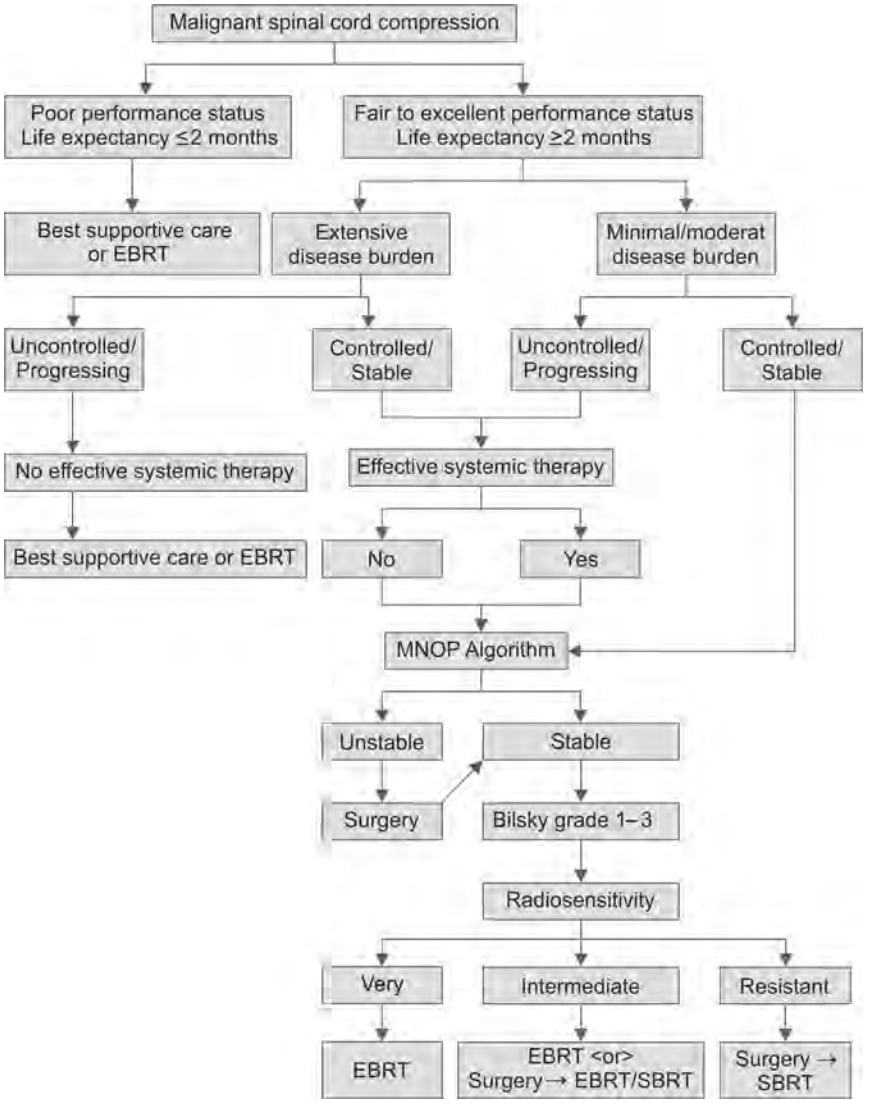
Malignant Spinal Cord Compression

Malignant spinal cord compression (MSCC) refers to compressive indentation, displacement, or encasement of the dural sac that surrounds the spinal cord and/or cauda equina by tumor, spinal fracture, or other conditions related to tumor. Spine is the most common (60%) site of bone metastases and among them ~10% of the cases develop MSCC. Thoracic spine (~60%) is the most common location. The most common cancers associated with MSCC in adults are lung, prostate, multiple myeloma, and breast. In children Ewing's sarcoma, primary vertebral osteosarcoma, neuroblastoma, germ cell tumors, and lymphomas are common cause of MSCC. Direct extension of tumor from osseous vertebral column (usually from hematogenous spread) is the most common mechanism and pathological fracture is the second most common method. Compression leads to obstruction of the epidural venous plexuses, thus development of vasogenic edema. If untreated, can lead to spinal cord infarction and permanent damage. In *MSCC,* pain, sensory deficit, weakness, and autonomic dysfunction are the most common clinical presentation. *Diagnostic workup includes* MRI (if MRI not possible then CT myelogram).

Histological diagnosis, i.e., biopsy (excision or CT-guided) in patient with no history of any malignancy (~20%) or history of very early stage tumor should be done on urgent basis as pathology would guide appropriate management of the tumor including use of steroids for therapy. (Bilsky grading system based on MRI: Grade 0—bone only disease. Grade 1—epidural extension and impingement of on the thecal sac without spinal cord compression. Grade 2—epidural extension without spinal cord compression or obliteration of CSF space. Grade 3—spinal cord compression, deformation of spinal cord, and obliteration of CSF space.)

Treatment options includes (**Flowchart 2**):

- *Steroid*: High dose, reduces cord edema
- Further treatment is guided by patient's life expectancy, performance status, disease burden, and systemic therapy



(EBRT: external beam radiation therapy; MNOP: mechanical, neurologic, oncologic, and preferred treatment; SBRT: stereotactic body radiation therapy)

FLOWCHART 2: Management of malignant spinal cord compression.

options available (patients with life expectancy >2 months, good performance status, minimal/moderate disease burden, and/or effective systemic therapy available will probably benefit from neurosurgery and/or radiation).
- International spine oncology consortium has developed mechanical, neurologic, oncologic, and preferred treatment (MNOP) algorithm for management of MSCC.
  - *Mechanical*: Neurosurgical intervention is required in an unstable spine.
  - *Neurologic*: MSCC with Bilsky grade 1–3 and neurological deficits of <72 hours may benefit from neurosurgical decompression based on tumor pathology and radiosensitivity.
  - *Oncologic*: Radiosensitivity of various tumor pathology is different with some (example lymphoma) being highly sensitive.
  - *Preferred treatment*: Final decision usually is based on multidisciplinary decision after discussion between doctors with patient.
- *Surgery*: Decompress spine, stabilize an unstable spine, establish pathological diagnosis, remove epidural tumor to allow delivery of stereotactic body radiation therapy (SBRT) in a radioresistant histology, and local disease control when radiation cannot be delivered safely.
- *External beam radiation therapy (EBRT)*: Lymphomas, multiple myeloma, and germ cell tumors are highly radiosensitive whereas melanoma, sarcoma, and renal cell carcinoma are radioresistant.
- *SBRT*: Solid tumor spinal metastasis.

Malignant Pericardial Effusion

Malignant pericardial effusion (MPCE) refers to accumulation of extra fluid in the pericardial space. Various etiological factors includes: Tumor: Primary (mesothelioma, lymphangioma, and others), metastasis to pericardium (lung cancer, breast cancer, leukemia, and others), and other causes: Treatment-related complication and others. MPCE is a condition in which extra fluid accumulates due to excess secretion or/and obstruction of lymphatic drainage. It leads to compression of the ventricle and collapse of the right atrium, thus reducing cardiac output and increasing the venous back pressure. Clinical features depend on the rate and amount of fluid accumulated. Dyspnea, chest discomfort, and fatigue are the most common symptoms. The classical presentation (Beck's triad) of hypotension, tachycardia, and muffled heart sounds may be present in cardiac tamponade. *Diagnostic workup should include*—CXR: Water bottle pericardial silhouette. Electrocardiogram (ECG): Low voltage, sinus tachycardia is the most common feature seen. Electrical alternans and atrial fibrillation may also be present. Echocardiography: Fluid and its distribution, tumor location and size, and hemodynamic consequences of MPCE. Pericardial fluid cytology and/or pericardial biopsies as effusion can also be secondary to other causes like treatment-related complications. Treatment option includes for MPCE are:
- The goals of treatment are relief of symptoms with minimum morbidity and prevent recurrence.
- Further treatment is guided by patient's life expectancy, performance status, and systemic therapy options available.
- Pericardiocentesis with or without percutaneous tube pericardiostomy
- Sclerotherapy
- Subxiphoid pericardiostomy
- Transthoracic partial pericardiectomy or pericardial window

Malignant Central Airway Obstruction

Central airway obstruction (CAO) refers to the obstruction of the airflow in the trachea and mainstem bronchi. Important causes are:
- *Malignant*: Primary endoluminal tumors—bronchogenic carcinoma, carcinoid tumor, etc. Metastatic—renal cell carcinoma, carcinoma breast, thyroid cancer, colon cancer, sarcoma, melanoma, etc. Others—laryngeal carcinoma, nasopharyngeal carcinoma, esophageal carcinoma, mediastinal tumors (thymic carcinoma and germ cell tumor), and lymphadenopathy (lymphoma)
- *Nonmalignant*: Benign tumors—squamous cell papilloma and hamartoma. Others—lymphadenopathy (sarcoidosis, tuberculosis), vascular (aneurysm, ring), granulation tissue (tracheal tubes, airway stents, and foreign bodies), tracheomalacia, bronchomalacia, goiter, mucus plug, etc.

Airway obstruction may be mechanical, dynamic, or combined. Clinically present as dyspnea, cough, hemoptysis, wheeze, and stridor. *Diagnostic workup should include* bronchoscopy ± endobronchial ultrasound ± bronchial wash ± biopsy (after airway stabilization), chest radiography, CT chest, and pulmonary function tests (in patients with subacute symptoms).

Treatment modalities include:
- *Airway management*: Securing airway is pivotal. In case of severe CAO (life-threatening) bag valve mask ventilation followed by endotracheal intubation. If intubation is not feasible or unsuccessful, options include an emergency cricothyrotomy or tracheostomy, or rigid bronchoscopic intubation.
- *Bronchoscopy*: Diagnostic and in some cases, it is both diagnostic and therapeutic.
- *Management of cause*: Etiology-specific intervention, which may include debulking, removal, and/or by stenting which is usually done via bronchoscopic intervention but occasionally surgery or external beam radiation is needed.
- Various bronchoscopy interventions used single or in combination are laser, electrocautery, cryotherapy, brachytherapy, argon plasma coagulator, photodynamic therapy, debridement, dilatation, and stent.

Bone Metastasis

Bone is third most common site of tumor metastasis. The most common causes of bone metastasis are breast cancer, prostate cancer, lung cancer, thyroid cancer, and renal cancer. *Pathophysiologic process involved is* tumor cell disengagement, invasion into vascular and/or lymphatic system, arrest in sinusoids of bone marrow, migrate to bone marrow stroma, response to microenvironment, tumor cell proliferation, and bone metastasis. Based on metastatic bone interference with bone remodeling it is classified in three types, namely: osteolytic, osteoblastic, and mixed. *Clinical presentation* includes pain, hypercalcemia, pathological fracture, and MSCC. Morbidity associated with bone metastasis is known as skeletal-related events (SRE). *Diagnostic workup* includes X-rays, bone scans, CT (size of osseous lesion with its cortical

involvement extent), MRI (epidural and marrow disease), and positron-emission tomography (PET). Treatment options are:

- Analgesics and systemic therapy against malignancy
- *Bone-specific agents*: Bisphosphonates and denosumab—decreases risk of SRE
- *Radiotherapy*: Relieves bone pain, prevents impending fractures, and promotes healing of pathological fractures
- *Systemic radionucleotides*: Strontium 89 and samarium 153
- *Pathological fracture*: Surgery (pain relief, stabilization, and restore function) ± radiotherapy (pain relief and tumor control)
- *Impending fracture*: Surgery (fixation) ± radiotherapy (pain relief and tumor control). In highly vascular bone metastasis example: renal cell carcinoma, pre- or perioperative embolization may be done to reduce intraoperative blood loss.

ONCOLOGICAL EMERGENCIES RELATED TO BIOCHEMICAL DERANGEMENTS

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) refers to metabolic consequences resulting from sudden release of intracellular metabolites, nucleic acids, and proteins from tumor cells undergoing death spontaneously or post-treatment. It is divided into two groups, i.e., laboratory and clinical based on Cairo-Bishop definitions.

Laboratory TLS is defined as presence of ≥2 of following laboratory abnormalities, i.e., uric acid ≥8 mg/dL, potassium ≥6 mEq/L, phosphorus >4.5 mg/dL in adults (≥6.5 mg/dL in children), and calcium ≤7 mg/dL or 25% change in these laboratory values from baseline, present within 3 days before or 7 days after initiation of therapy. Clinical TLS is defined as laboratory TLS accompanied with ≥1 of the following: Serum creatinine ≥1.5 times the upper limit of normal, seizure, cardiac dysrhythmia, or death.

Risk of TLS depends on tumor-related factors such as high proliferation rate, high chemosensitivity, and large tumor burden and clinical features such as pretreatment hyperuricemia, impaired renal functions, and inadequate hydration. It is most frequently associated with acute leukemias and high-grade non-Hodgkin's lymphomas.

Tumor lysis syndrome occurs when the changes in electrolytes resulting from lysis of tumor cell exceeds body's ability to regulate them. When the compensatory mechanism of hyperphosphatemia is saturated, phosphate binds with calcium and precipitates in tissues and kidney (renal failure) resulting in hypocalcemia. Hyperuricemia which results due to excess of purine metabolism can also contribute to renal failure due to intraluminal tubular obstruction by urate crystals. Symptoms are largely due to the associated metabolic derangement and may include anorexia, lethargy, nausea, vomiting, diarrhea, muscle cramps, tetany, syncope, hematuria, heart failure, cardiac arrhythmias, seizures, and sudden death.

Risk stratification—Cairo et al., in 2010, classified risk of various tumor types in three risk groups (**Box 1**).

BOX 1: Risk stratification of tumor, Cairo et al., 2010.

High risk:

- Acute lymphoblastic leukemia (ALL) with leukocytes count >100,000/μL or lactate dehydrogenase (LDH) >2 times the upper limit of normal (ULN)
- Acute myeloid leukemia (AML) with leukocytes count >100,000/μL
- Burkitt leukemia
- Burkitt lymphoma with LDH >2 times the ULN or stage III/IV
- Other high-grade lymphomas (diffuse large B-cell lymphoma, blastoid variant mantle cell lymphoma, adult T-cell lymphoma, peripheral T-cell lymphoma, and transformed lymphoma) with LDH > ULN and bulky disease (>10 cm)
- Any tumor of the intermediate risk group and baseline renal dysfunction, uric acid, phosphate or potassium > ULN, renal involvement, or contraindication to allopurinol

Intermediate risk:

- AML with leukocyte count 25,000–100,000/μL or LDH >2 times the ULN
- ALL with leukocytes count <100,000/μL and LDH <2 times the ULN
- Chronic myelomonocytic leukemia and plasma cell leukemia
- Chronic lymphocytic leukemia (CLL) on targeted and/or biological therapies or white blood cell (WBC) count >50,000/μL
- Burkitt lymphoma with LDH <2 times the ULN and stage I–II
- Other high-grade lymphomas with LDH > ULN and nonbulky disease
- Any leukemia or lymphoma with renal dysfunction or renal involvement
- Bulky solid tumor and sensitive to chemotherapy such as germ cell tumors, small cell lung cancers, etc.

Low risk:

- AML with leukocyte count <25,000/μL and LDH <2 times the ULN
- Chronic myeloid leukemia
- CLL on alkylating agents
- Hodgkin's lymphoma
- Indolent non-Hodgkin's lymphoma
- Anaplastic large cell lymphoma
- Other high-grade lymphomas without LDH elevation
- Multiple myeloma
- Other solid tumors (even in preexisting renal dysfunction or renal involvement)

Diagnostic Workup

Complete blood count (CBC), electrolytes, urea, creatinine, uric acid (sample must be sent on ice, if post rasburicase), phosphorus, calcium, albumin, and ECG.

Uric acid, potassium, phosphorus, and creatinine should be monitored at least twice daily until risk of TLS with monitoring of weight, blood pressure, and urine output.

Prevention

- *Low risk*: Adequate hydration
- *Intermediate risk*: Aggressive hydration and allopurinol prophylaxis up to 7 days
- *High risk*: Aggressive hydration and rasburicase prophylaxis
- Aggressive hydration (3,000 mL/m^2/day) with urine output ≥100 mL/m^2/h (may require diuretics to maintain urine output and prevent fluid overload). Urine alkalinization is not recommended as it increases the risk of calcium phosphate precipitation.
- Allopurinol—300 mg/m^2/day or 10 mg/kg/day (max: 800 mg/day) in three divided doses begin 1–2 days before therapy and continue up to 3–7 days after therapy.
- Rasburicase—0.05–0.2 mg/kg/day for 1–7 days.

Treatment

- Aggressive intravenous (IV) hydration
- Correction of electrolyte disturbances. Hypocalcemia to be treated only if symptomatic.
- *Hemodialysis*: If there is persistent hyperkalemia, intractable hyperphosphatemia and hypocalcemia (calcium phosphate product ≥70 mg^2/dL^2), intractable fluid overload and oliguria or anuria (in absence of hypovolemia).
- *Rasburicase*: 0.2 mg/kg/day. Allopurinol to be used only in case of rasburicase hypersensitivity or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Hyponatremia

Hyponatremia refers to serum sodium <135 mEq. Important causes are summarized in **Table 2**.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia in malignancy and is due to increased production of arginine vasopressin (AVP) (mainly ectopic, by the tumor cells). In SIADH, increased levels of AVP result in water resorption/retention and sodium loss. Clinical features depends on rate of development of hyponatremia, instead of actual sodium levels (unless severely low). It ranges from being completely asymptomatic to coma. It consists of nausea, vomiting, dysgeusia, headache, memory loss, confusion, lethargy, fatigue, loss of appetite, irritability, muscle weakness, spasms or cramps, seizures, and decreased consciousness. *Diagnostic workup includes* serum electrolytes, serum osmolality, urine sodium, and urine osmolality. Treatment is guided by serum sodium levels, symptomatic or asymptomatic, duration of hyponatremia, and volume status of the patient (**Flowchart 3**). *Rate of Correction* up to 8 mEq/L/day whereas only 4–6 mEq/L/day in patients with high risk for osmotic demyelination syndrome (ODS). High-risk patients for ODS are one who has one or more of the following: serum sodium <105 mEq/L, associated hypokalemia, history of heavy alcohol intake, advanced liver disease, and malnutrition. Various therapeutic options for hyponatremia are isotonic fluids (hypovolemic hyponatremia), fluid restriction, 3% hypertonic saline, loop diuretics, sodium supplementation, urea, demeclocycline, and vaptans.

TABLE 2: Causes of hyponatremia.

Euvolemic	SIADH • Cancer: Lung cancer and head and neck cancer • Drugs: Cyclophosphamide and vincristine • Infections: Central nervous system, pulmonary • Hypothyroidism • Head and Neck cancers (paraneoplastic)
Hypovolemic	• Gastrointestinal losses: Chemotherapy-induced nausea and vomiting and chemotherapy-induced diarrhea • Cerebral salt wasting: Intracranial tumor
Hypervolemic	• Heart failure: Drug-induced (anthracyclines) • Liver failure: Drug-induced (methotrexate) and metastatic liver disease • Kidney failure: Drug-induced (cisplatin) and malignancy-associated nephrotic syndrome

(SIADH: syndrome of inappropriate antidiuretic hormone secretion)

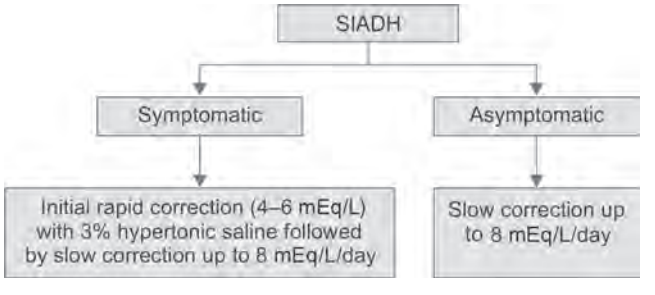
Hypercalcemia

Hypercalcemia of malignancy is rise in serum calcium levels above the upper limit of the normal laboratory reference range, related directly or indirectly to tumor. Causes are: Secretion of parathyroid hormone (PTH)-related peptide—any squamous cell carcinoma; osteolytic metastases—lung cancer, breast cancer, and prostate cancer; production of vitamin D analogs—lymphomas; and ectopic hyperparathyroidism.

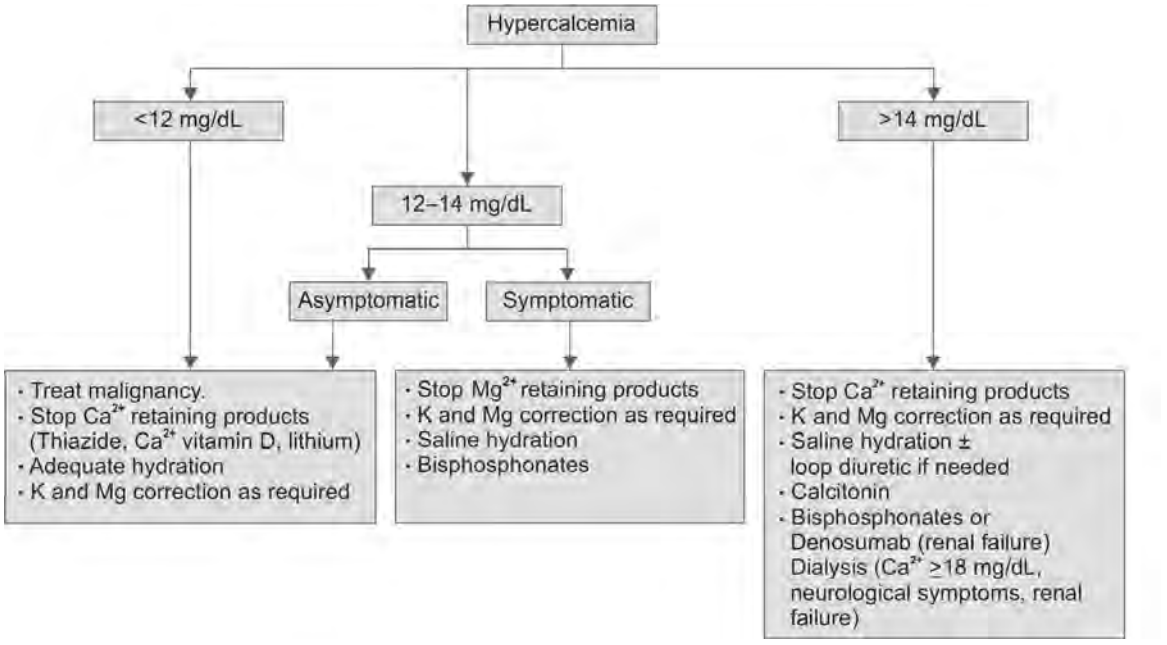
Clinical symptoms depend on rate of development of hypercalcemia, instead of actual calcium levels (unless very high levels). A well-known mnemonic describes it: Stones (kidney/biliary), bones (bone pain), groans (abdominal discomfort), moans (nonspecific symptoms), thrones (constipation and urinary frequency), muscle tone (muscle weakness and decreased reflexes), and psychiatric overtones (depression, anxiety, and cognitive dysfunction). Hypercalcemic crisis can also present with life-threatening complications such as acute pancreatitis, renal failure, and coma.

Diagnostic workup includes serum total and ionized calcium, serum albumin, PTH levels, urinary calcium, vitamin D levels, serum protein electrophoresis, and serum-free light chain assay. Treatment of hypercalcemia associate to malignancy includes the following and summarized in **Flowchart 4:**

- Treatment of underlying malignancy
- Stop any calcium retaining products (thiazides, calcium, vitamin D, and lithium)
- Correction of hydration (normal saline)
- Potassium and magnesium to be corrected as required. Hypophosphatemia should not be corrected unless


SIADH
Symptomatic
Asymptomatic
Initial rapid correction (4–6 mEq/L) with 3% hypertonic saline followed by slow correction up to 8 mEq/L/day
Slow correction up to 8 mEq/L/day

FLOWCHART 3: Management of syndrome of inappropriate antidiuretic hormone secretion (SIADH).


Hypercalcemia
<12 mg/dL
12–14 mg/dL
>14 mg/dL
Asymptomatic
Symptomatic
· Treat malignancy.
· Stop Ca2+ retaining products (Thiazide, Ca2+ vitamin D, lithium)
· Adequate hydration
· K and Mg correction as required
· Stop Mg2+ retaining products
· K and Mg correction as required
· Saline hydration
· Bisphosphonates
· Stop Ca2+ retaining products
· K and Mg correction as required
· Saline hydration ± loop diuretic if needed
· Calcitonin
· Bisphosphonates or Denosumab (renal failure)
Dialysis (Ca2+ ≥18 mg/dL, neurological symptoms, renal failure)

FLOWCHART 4: Management of hypercalcemia.

symptomatic, as it can lead to precipitation of salts of calcium.

- *Loop diuretics*: Enhance urinary excretion
- *Calcitonin [6–8 U/kg; subcutaneous (SC) or intramuscular (IM)]*: Rapidly acting (6–24 h)
- *Bisphosphonates-zoledronic acid (preferred):* Onset of action ~48 hours, nadir calcium levels in 5–7 days, duration of response ~32 days, and can be repeated weekly in persistent hypercalcemia
- *Rank ligand inhibitors (denosumab)*: Refractory to bisphosphonate and renal failure
- *Steroid*: In steroid-sensitive malignancy
- *Hemodialysis*: Renal failure, unable to tolerate the fluid load, and profound changes in mental status.

Lactic Acidosis

Lactic acidosis is defined as serum pH ≤7.35 and plasma lactate of ≥5 mEq/L. Causes includes hematological malignancies, solid tumors with liver metastasis, shock, heart failure, sepsis, hypoxia, hepatic insufficiency, and drugs (metformin and propofol). Pathophysiologic process includes—lactate is mainly metabolized in the liver. Unlike normal cells, tumor cell relies on anaerobic glycolysis disproportionately, even in presence of oxygen (Warburg effect). This leads to production of large quantities of lactate exceeding its ability to be metabolized leading to imbalance. It can lead to cardiac arrhythmias and hypotension with potential for cardiovascular collapse. *Diagnostic workup* includes lactate levels, arterial blood gas analysis, serum electrolytes, and serum albumin. Management strategy includes treatment of the underlying malignancy and other causes, if present, aggressive hemodynamic support (fluids and vasopressors), hemodialysis, and hemofiltration.

ONCOLOGICAL EMERGENCIES RELATED TO HEMATOLOGICAL DERANGEMENTS

Febrile Neutropenia

Febrile neutropenia (FN) is defined as "single oral temperature of >38.3°C (>101°F) or a temperature of >38.0°C (>100.4°F) sustained for >1 hour and an absolute neutrophil count (ANC) of <500 cells/mm^3 or expected to fall to <500 cells/mm^3 in next 48 hours". In FN, cultures are usually positive only in about 20% of the patients. Bacterial pathogens particularly gram-negative organisms are the most common followed by gram-positive organisms. Anaerobic organisms, polymicrobial infections, and fungal and viral organisms also occur, but are not so common. Neutropenia along with qualitative defects in neutrophil function, disruption of mucociliary barriers, invasive devices, and shifts in normal microbial flora predispose patients to infection. Risk assessment of FN patient can be done by Multinational Association for Supportive Care in Cancer (MASCC) risk index (**Table 3**).

It is critical to recognize FN early and initiate therapy promptly to avoid progression to sepsis.

Initial assessment includes targeted history, physical examination with emphasis on hydration, oral cavity, oropharynx, skin including any indwelling catheter, lungs, abdomen, perianal area, and mental status. CBC, creatinine, electrolytes, liver function test, blood culture (two sets), culture and stain samples from suspected site of infection, and imaging studies, if any site suspected.

Outpatient management may be considered in low-risk patient who resides close to the hospital, can come for frequent clinic visits and has a 24 hours care giver. Patient is advised to visit if any symptoms or signs of hemodynamic instability, persistent neutropenic fever, new symptoms or signs, oral

TABLE 3: Risk assessment of febrile neutropenia patient: MASCC risk Index.

Characteristics	*Weight*
Burden of FN with no or mild symptoms	5
No hypotension (systolic BP >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of FN with moderate symptoms	3
Outpatient status	3
Age <60 years	2

***High-risk patient*:** Patient with any one of the following criteria, i.e., Multinational Association for Supportive Care in Cancer (MASCC) score <21

- Neutropenia anticipated to be >7 days
- Hemodynamic instability
- Mucositis
- Abnormal mental status
- New pulmonary infiltrate or hypoxemia or underlying chronic lung disease
- Hepatic insufficiency and/or renal insufficiency

***Low-risk patient*:** Patient with all of the following criteria, i.e., MASCC score ≥21

- Neutropenia expected to resolve within 7 days
- No active medical comorbidity

(BP: blood pressure; FN: febrile neutropenia)

medication no longer possible or intolerable, and microbiologic tests identify species not susceptible to oral regimen.

Antibiotic: Fluroquinolone + amoxicillin-clavulanate (or clindamycin, if allergic to penicillin).

Inpatient management includes broad-spectrum antibiotics guided by patient's history and examination, allergies, and culture data of the institution should be started within 60 minutes of presentation.

Infectious Diseases Society of America (IDSA) recommends: Cefepime 2 g/8 hourly, ceftazidime 2 g/8 hourly, piperacillin tazobactam 4.5 g/6 hourly, meropenem 1 g/8 hourly, and imipenem cilastatin 500 mg/6 hourly. Aminoglycoside and fluoroquinolones may be added in patients with complicated presentation (example, hypotension and/or mental status changes) and focal findings (e.g., pneumonia and cellulitis). Anaerobic coverage should be included if there is evidence of necrotizing mucositis, sinusitis, periodontal cellulitis, perirectal cellulitis, intra-abdominal, or pelvic infection. Gram positive coverage should be included if patient has any of the following: hemodynamically instability or other evidence of severe sepsis, pneumonia, catheter-related infection, skin or soft tissue infection, severe mucositis, or positive culture for gram-positive organism awaiting susceptibility results. Empiric antifungal coverage should be considered in patients who have persistent fever even after 4–7 days of antibiotics or suspected to have fungal infection. In patients with diarrhea with abdominal signs, empiric *Clostridium difficile* therapy may be instituted. In case of catheter-related infection removal of catheter is recommended. IDSA does not recommend routine use of colony-stimulating factor in FN. American Society of Clinical Oncology state that colony-stimulating factor use can be considered in high-risk patients or who have prognostic factors that are predictive of poor outcome.

Hyperviscosity Syndrome

Hyperviscosity syndrome (HVS) refers to the clinically manifestation resulting due to increase in the viscosity of blood. *Causes include:* Increase in acellular component—Waldenström macroglobulinemia, multiple myeloma, systemic lupus erythematosus, etc. and increase in cellular component—leukemia, polycythemia, and myeloproliferative disorder. Disorders cause increase in blood viscosity, sluggish blood flow, relative decreased microvascular circulation, and hypoperfusion of tissues. Classical triad of HVS consists of mucosal bleeding (gum bleed, epistaxis, gastrointestinal (GI) bleed, menorrhagia, and prolonged bleeding after a procedure), visual changes (blurring of vision and loss of vision), and neurological symptoms (headache, giddiness, hearing defects, paresthesia, ataxia, seizures, stroke, stupor, and coma). Other feature may include chest pain, shortness of breath, heart failure, and myocardial infarction. *Diagnostic workup includes* serum viscosity, CBC with peripheral blood smear, total protein and albumin, and serum electrolytes. Other test: Coagulation profile, serum electrophoresis, urine routine, and bone marrow examination. Imaging: CT head (neurological symptoms) and chest radiograph (chest symptoms). Fundus: Retinal vein dilation or engorgement (sausage link or boxcar appearance), papilledema, and retinal hemorrhage. *Management strategy includes* IV fluids (hydration), plasmapheresis (increase in plasma component), or cytapheresis (increase in cellular component), when it is not immediately available phlebotomy may be done. Definitive therapy: Avoid blood transfusion unless emergency until plasmapheresis or cytapheresis as it can further increase the viscosity of blood.

Thromboembolic Disease

Cancer-associated thrombosis is a common complication of malignancy with venous thromboembolism (VTE) being the most common. VTE is one of the frequent causes of death in cancer patients and incudes deep vein thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis, and thrombosis of other veins. Various risk factors predispose a patient to develop thrombosis such as patient related (advanced age, obesity, etc.), treatment related (surgical interventions, etc.), and cancer related (advanced metastatic cancer, etc.).

Exact pathophysiology of cancer-associated thrombosis is not understood and mostly is due to multiple factors by various mechanisms such as production of procoagulants by the tumor cells (like tissue factor), suppression of fibrinolytic activity (like by plasminogen activator inhibitor-1), and platelet activation.

Clinical presentation includes DVT—pain, swelling, tenderness, discoloration/redness, and venous distension and PE—dyspnea, chest pain, cough, tachypnea, tachycardia, fever, crackles, and features of DVT. *Diagnostic workup includes* DVT—Doppler ultrasound and CT/MRI venography and PE—D-dimer, proBNP, troponin, CT pulmonary angiography, ventilation/perfusion scan, echocardiography in massive/submassive PE, right ventricular dysfunction, and ECG—sinus tachycardia and S1Q3T3.

Prophylaxis for VTE in cancer patients: Hospitalized patient, surgical patient with any of the high-risk feature like abdominal or pelvic surgery, history of VTE, anesthesia >2 hours, advanced cancer, perioperative bed rest of ≥4 days and age ≥60 years for up to 4 weeks postoperative, multiple myeloma patient receiving immunomodulator drugs with IMPEDE VTE score ≥3 (or SAVED score ≥2) and other cancer patients with Khorana score ≥2. Contraindication to anticoagulation prophylaxis: Active bleeding, platelet count <30,000–50,000/cu mm, hemorrhagic coagulopathy or bleeding disorder, and indwelling neuraxial catheter.

Contraindication to mechanical prophylaxis: Acute DVT and severe arterial insufficiency.

Agents: Low molecular weight heparin, apixaban, and rivaroxaban.

Treatment of DVT: DVT of femoral vein, popliteal vein, pelvic vein, iliac vein, and inferior vena cava (IVC): Anticoagulation, consider catheter-directed thrombolysis. If anticoagulation is contraindicated IVC filter.

Calf veins, peroneal veins, anterior and posterior tibial veins, soleal veins, and gastrocnemius vein: Anticoagulation. If anticoagulation is contraindicated IVC filter. *DVT of* upper limb veins, brachiocephalic vein, subclavian vein, axillary vein, internal jugular vein, brachial veins, and SVC: Anticoagulation, consider catheter-directed thrombolysis. *DVT of* catheter-related DVT: Anticoagulation for at least 3 months or as long as central venous catheter in place. Consider catheter removal if symptom persists, infected, dysfunctional, or no longer needed. Consider catheter-directed thrombolysis. If anticoagulation is contraindicated remove catheter.

Treatment of PE includes anticoagulation. Consider systemic or catheter-directed thrombolysis or embolectomy in hemodynamically unstable patients. Consider rescue thrombolysis or thrombectomy in hemodynamically stable patients who deteriorate on anticoagulation. If anticoagulation is contraindicated consider IVC filter ± embolectomy. Contraindication to anticoagulation: Active major bleeding and indwelling neuraxial catheter. Contraindication for thrombolysis: History of hemorrhagic stroke, history of ischemic stroke in last 3 months, brain tumor, history of major trauma, surgery or head injury in last 3 weeks, active bleeding, and bleeding diathesis. Agents: Unfractionated heparin, low molecular weight heparin, fondaparinux, warfarin, apixaban, rivaroxaban, dabigatran, and edoxaban.

ONCOLOGICAL EMERGENCIES RELATED TO THERAPY

Chemotherapy-induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) includes acute, delayed, and anticipatory nausea and vomiting. Acute CINV is nausea and vomiting which occurs within 24 hours of chemotherapy. Delayed CINV is nausea and vomiting which occurs after 24 hours of chemotherapy. Anticipatory nausea and vomiting is nausea and vomiting which occurs due to conditioned response, prior to chemotherapy.

Intravenous antineoplastic agents are divided based on percent risk of emesis into high emetogenic agents: >90%; moderate emetogenic agents: 30–90%; low emetogenic agents: 10–30%; and minimal emetogenic agents: <10%. Common agents in these groups are given in **Table 4**. Oral antineoplastic agents are also divided based on percent risk of emesis into moderate or high emetogenicity >30% and minimal or low emetogenicity <30%.

TABLE 4: Classification of chemotherapeutic agents based on percent risk of emesis.

	Intravenous antineoplastic agents	***Oral antineoplastic agents***
Highly/emetogenic agents	Anthracycline + cyclophosphamide, cisplatin, cyclophosphamide >1,500 mg/m^2, and dacarbazine	Abemaciclib, cabozantinib, ceritinib, crizotinib, cyclophosphamide, imatinib, lenvatinib, lomustine, niraparib, procarbazine, ribociclib, and temozolomide
Moderately emetogenic agents	Arsenic trioxide, azacitidine, bendamustine, carboplatin, cyclophosphamide <1,500 mg/m^2, doxorubicin, epirubicin, fam-trastuzumab deruxtecan, idarubicin, ifosfamide, irinotecan, oxaliplatin, and trabectedin	
Low emetogenic agents	Bortezomib, brentuximab, cabazitaxel, carfilzomib, cetuximab, cytarabine ≤1,000 mg/m^2, decitabine, docetaxel, eribulin, etoposide, fluorouracil, gemcitabine, methotrexate, paclitaxel, pemetrexed, topotecan, and trastuzumab-emtansine	Afatinib, alectinib, alpelisib, axitinib, brigatinib, capecitabine, chlorambucil, cobimetinib, dabrafenib, dacomitinib, dasatinib, encorafenib, entrectinib, erdafitinib, erlotinib, etoposide, everolimus, gefitinib, hydroxyurea, ibrutinib, lapatinib, lenalidomide, lenvatinib, lorlatinib, methotrexate, nilotinib, olaparib, osimertinib, palbociclib, pazopanib, pomalidomide, regorafenib, ruxolitinib, sorafenib, sunitinib, tegafur-uracil, thalidomide, topotecan, trametinib, vandetanib, vemurafenib, and venetoclax
Minimal emetogenic agents	Atezolizumab, bevacizumab, bleomycin, daratumumab, durvalumab fludarabine, ipilimumab, nivolumab, pembrolizumab, ramucirumab, rituximab, trastuzumab, vinblastine, vincristine, and vinorelbine	

Pathophysiology

Chemotherapy-induced nausea and vomiting is regulated by central pattern generator (vomiting center), nucleus tractus solitarius and area postrema (chemoreceptor trigger zone), higher brainstem and cortical structures, and GI tract (via vagus and splanchnic nerves). Acute CINV is mediated mainly by peripheral pathway which is predominantly mediated via serotonin receptors located in GI tract. Delayed CINV is mediated mainly by central pathway which is predominantly mediated via substance P and neurokinin 1 (NK1) receptors located in the brain. Anticipatory emesis is mediated by higher brainstem and cortical structures.

Treatment

Drugs used in CINV are *5-HT3 receptor antagonists*: *First-generation*: Dolasetron, granisetron, and ondansetron *and second-generation*: Palonosetron. *Neurokinin-1 receptor antagonists*: Aprepitant, fosaprepitant, netupitant, and rolapitant. *Glucocorticoids:* Dexamethasone. *Atypical antipsychotic*: Olanzapine. *Dopaminergic antagonist*: Phenothiazines, metoclopramide, and butyrophenones. *Cannabinoid:* Dronabinol. *Antihistaminic*: Diphenhydramine and hydroxyzine. *Benzodiazepine:* Lorazepam. Others: Thalidomide, scopolamine, etc.

In cases of breakthrough CINV (nausea and vomiting which occurs despite optimal antiemetic prophylaxis and requires rescue therapy) and refractory CINV (nausea and vomiting which occurs despite optimal antiemetic prophylaxis and requires rescue therapy) other causes of nausea and vomiting such as GI obstruction/paresis, brains metastases, dyselectrolemia, uremia, and drugs like opioids must be ruled out. After ruling out other causes an agent from different class of antiemetic should be added. Complementary therapies acupuncture, behavioral therapy, ginger, etc., can also be used.

Chemotherapy-related Diarrhea

Diarrhea is defined as abnormal increase frequency, water content, and weight (>300 g/day) of the stool. Acute diarrhea: <2 weeks; persistent diarrhea: 2–4 weeks; and chronic diarrhea: >4 weeks.

Chemotherapy-induced diarrhea: Fluoropyrimidines (5-fluorouracil and capecitabine) and irinotecan. Targeted therapy-associated diarrhea: Gefitinib, afatinib, erlotinib, sorafenib, sunitinib, everolimus, bortezomib, cetuximab, and panitumumab. Others such as immunotherapy-associated diarrhea, radiotherapy-induced diarrhea, neutropenic colitis, *Clostridium difficile* diarrhea, enteral feeding, and celiac plexus block.

It can occur by any one of the following mechanism or combination of them: Increased secretion (fluid and electrolytes) and abnormal absorption; osmotic diarrhea; increased GI motility; infection; and inflammation. Few specific mechanisms are:

- *Fluoropyrimidine*: Diarrhea occurs due to the relative increase in number of immature crypt cells due to its mitotic arrest leading to defects in its absorption and secretion.
- *Irinotecan*: Acute diarrhea occurs due to inhibition of acetylcholine esterase leading to increase in cholinergic transmission while delayed diarrhea occurs by from deconjugation by intestinal bacteria of irinotecan metabolite, leading to its direct toxic effect on intestinal epithelium leading to defects in its absorption and secretion.
- *Targeted therapy*: Altered gut motility, colonic crypt damage, changes in the intestinal microflora, and altered colonic transport.

Diarrhea may be associated with pain abdomen. Features of infection, dehydration, and electrolyte imbalance may be present. Diarrhea can lead to dehydration, electrolyte imbalance, and malnutrition

Grading

It is graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 as below.

- Grade 1: Increase of <4 stools/day or mild increase in ostomy output over baseline
- Grade 2: Increase of 4–6 stools/day or moderate increase in ostomy output over baseline
- Grade 3: Increase of ≥7 stools/day or severe increase in ostomy output over baseline, limiting self-care activities of daily living, and requiring hospitalization
- Grade 4: Life-threatening consequences and urgent intervention required
- Grade 5: Death

Patient is said to have complicated diarrhea if any of the following risk factor is present: Grade 3/4 diarrhea or grade 1/2 diarrhea with ≥1 of the following feature: Abdominal cramps, nausea/vomiting grade ≥2, deteriorating or decreased performance status, fever, suspected sepsis, neutropenia, blood in stools, dehydration, chest pain, and history of admission for chemotherapy-induced diarrhea.

Diagnostic workup includes CBC, stool routine and culture, stool for *Clostridium difficile* toxin, comprehensive metabolic panel along with magnesium, abdominal imaging like CT if needed (fever, bloody diarrhea, or peritoneal signs), infective workup if needed (fever and suspected sepsis), and endoscopy if needed (refractory diarrhea, chronic diarrhea, or bloody diarrhea).

Treatment

Common drugs used in its management are opioids (loperamide), somatostatin analogs (octreotide), uridine triacetate, budesonide, antibiotics, and other agents.

Extravasation of Chemotherapy

Extravasation of chemotherapy refers to inadvertent leakage of chemotherapy into the tissue around it from a blood vessel or tube. Based on local toxicity chemotherapeutic agents are divided as:

- *Vesicants*: Dactinomycin, daunorubicin, doxorubicin, epirubicin, trabectedin, vinblastine, and vincristine.
- *Irritants*: Ado-trastuzumab emtansine, bendamustine, bleomycin, bortezomib, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, docetaxel, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, liposomal doxorubicin, oxaliplatin, paclitaxel, and topotecan.
- *Neutral***:** Arsenic trioxide, asparaginase, eribulin, monoclonal antibodies, methotrexate, and pemetrexed.

Vesicants cause tissue necrosis. Irritants cause inflammation and concentrated large volumes can also result in necrosis. Initially at the site of extravasation and surrounding tissue there may be redness, tingling, burning sensation, pain or discomfort, and swelling. Later there may be blistering, ulceration, or necrosis. *Diagnostic workup includes* peripheral extravasation clinical examination which is usually sufficient, but in selected cases ultrasound (quantify volume and determine margin) may be needed.

In central venous access device extravasation, a chest radiograph or CT scan should be obtained. Management strategy for chemotherapy extravasation is summarized in **Box 2**.

Cytokine Release Syndrome

Cytokine release syndrome (CRS) refers to an acute cytokine-mediated systemic inflammatory syndrome which is characterized by fever and multiorgan dysfunction. It is seen with chimeric antigen receptor (CAR) T-cell therapy, therapeutic antibodies, and haploidentical allogeneic transplantation mainly. It is also seen with severe viral infection.

BOX 2: Management of extravasation of chemotherapy.

Peripheral line extravasation

- Stop the injection immediately, and leave the cannula in place
- Elevate the afflicted limb
- Aspirate as much fluid as possible through the cannula and also try to draw back about 3–5 mL of blood. Then remove cannula
- Mark the extravasation area with a pen
- Identify class of agent extravasated
- In vinca alkaloids (vinblastine and vincristine): Local injection hyaluronidase, hot packs, and hydrocortisone cream
- In anthracyclines (daunorubicin, doxorubicin, and epirubicin): Cold pack, topical dimethyl sulfoxide + hydrocortisone cream, and intravenous dexrazoxane
- In dactinomycin: Cold pack, topical dimethyl sulfoxide + hydrocortisone cream
- In taxanes (docetaxel and paclitaxel): Cold pack, local injection hyaluronidase, and topical hydrocortisone cream
- In irritant drugs other than taxanes including trabectedin and neutral drugs: Cold packs and topical hydrocortisone cream
- Surgical referral may be sought in case of large volume subcutaneous extravasation

Central line extravasation

- Stop the injection immediately, but leave the catheter in place.
- Aspirate as much fluid as possible through the catheter
- Identify class of agent extravasated
- Start fluids, antibiotics, and analgesics. In extravasation into chest also start supplemental oxygen and antipyretics
- In anthracyclines: Intravenous dexrazoxane
- Urgent surgical referral (pleura—thoracentesis and chest tube; mediastinum—thoracoscopy or thoracotomy; and subcutaneous—drainage)

Pathophysiology

Supraphysiologic response to immune therapy that activates or engages T cells and/or other immune effector cells associated with increased levels of inflammatory cytokines. In the setting of T cell-engaging immunotherapies, CRS is triggered by release of interferon gamma (IFN-γ) by activated T cells or tumor cells. IFN-γ activates macrophages, which produce excessive interleukin (IL)-6, tumor necrosis factor alpha (TNF-α), and IL-10. IL-6 binds to the soluble form of the IL-6 receptor (IL-6R) that has been cleaved by metalloproteinases, and the IL-6 and IL-6R complex binds to gp130 and activates cell types that ordinarily do not express membrane-bound IL-6R. IL-1, 5, 8, and 10 and granulocyte-macrophage colony-stimulating factor are also elevated in CRS and which also contribute to the pathophysiology of CRS.

Clinical Presentation

Onset of symptoms after therapy: CAR-T-cell therapy: 1–14 days, therapeutic antibodies: minutes to hours, haploidentical allogeneic transplantation: 1–3 days. Clinical presentation can range from mild flu-like symptoms to a severe life-threatening systemic inflammatory response syndrome.

Grading

Common Terminology Criteria for Adverse Events (version 5) has classified CRS as below.

- Grade 1: Fever with or without constitutional symptoms
- Grade 2: Hypotension responding to fluids and hypoxia responding to <40% oxygen
- Grade 3: Hypotension managed with one pressor and hypoxia requiring ≥40% oxygen
- Grade 4: Life-threatening consequences and urgent intervention indicated
- Grade 5: Death

Management

- Depends on **grade, etiology, and comorbidities.**
- All patients should also undergo infectious disease workup to rule out any infection and if present/suspected, should be treated in lines of FN.
- *Supportive*: Antihistamines, antipyretics, and IV fluids with close monitoring.
- *Tocilizumab*: **Anti-IL-6**; dose: In <30 kg patient—12 mg/kg and ≥30 kg patient—8 mg/kg (maximum: 800 mg). If there is no clinical improvement after the first dose, it may be repeated after an interval of at least 8 hours and should not exceed four doses in total.
- *Steroid*: Usually hydrocortisone 100 mg q8 hourly or dexamethasone 10 mg up to q6 hourly or methylprednisolone 1 mg/kg/day.
- *Resistant CRS*: Anti-IL-6, e.g., siltuximab, clazakizumab, anti-IL-1RA, e.g., anakinra, anti-TNF alpha, e.g., etanercept, antithymocyte globulin, alemtuzumab, cyclophosphamide, ruxolitinib, and ibrutinib.

SUMMARY

With advances in therapeutics and enhanced survival of cancer patients, complications of malignancies are an increasingly common reason for admission in emergency department. Every healthcare provider should be aware and able to recognize oncologic emergencies. Emergencies in oncology can be life-threatening, complications can arise in a known malignancy or individual not previously diagnosed with cancer, or these events can happen during treatment. These life-threatening oncologic emergencies may not have characteristic signs and symptoms, so high degree of suspicion is crucial while dealing with malignancy related complications. Oncologic emergencies should be treated promptly in emergency department.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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143 CHAPTER

Thrombocytopenia, Bleeding, and Coagulopathy

Ragesh Radhakrishnan Nair, Isha Gambhir

INTRODUCTION

Normal coagulation process involves the balance between procoagulant pathway (clot formation) and the anticoagulant pathway (clot dissolution). The normal clot formation starts as a cascade of events leading to activation of clotting factors and thus causing thrombus formation. The inhibitory pathway of coagulation system prevents the abnormal clot propagation. The various prothrombotic and antithrombotic factors are shown in **Table 1**. Normal coagulation system involves the initial or the primary hemostasis by platelet plug formation and then the activation of clotting factors called the clot propagation.

PRIMARY HEMOSTASIS

It is the platelet plug formation, which involves complex interactions between platelets, vessel wall, and adhesive proteins. The subendothelial layer is highly thrombogenic and contains collagen, von Willebrand factor (vWF), and other proteins such as laminin, thrombospondin, and vitronectin that are involved in platelet adhesion and once there is injury this subendothelial layer is exposed.

TABLE 1: Prothrombotic and antithrombotic factors in the body.

Site	*Prothrombotic factors*	*Antithrombotic factors*
Vessel wall	Exposed endothelium	Thrombomodulin
	Tissue factor	
	Collagen	
Circulating factors	Platelets	Heparin
	Platelet activating factors	Antithrombin
	Clotting factors	Protein C and S
	Fibrinogen	Plasminogen
	Prothrombin	Tissue plasminogen activator
	von Willebrand factor	

In contrast, the endothelial lining also has antithrombotic properties due to multiple factors such as negatively charged heparin-such as glycosaminoglycans, neutral phospholipids, synthesis and secretion of platelet inhibitors, coagulation inhibitors, and fibrinolysis activators.

Platelets are anucleate, disk-shaped cells which play an important role in initial platelet plug formation by providing the phospholipid rich plasma membrane which is an important component in activation of coagulation factors. Normally platelets do not adhere to intact endothelial surface, but after injury the subendothelial surface is exposed leading to binding platelets to collagen and vWF plays the intermediary role in this process. Platelets have these two important granules:

1. Alpha (α) *granules*: Contain P-selectin, fibrinogen, fibronectin, factor V, factor VIII, platelet factor IV, platelet-derived growth factor, and tumor growth factor-α (TGF-α)
2. *Delta* (δ) *granules or dense granules*: Contain adenosine triphosphate (ATP), adenosine diphosphate (ADP), calcium (Ca), serotonin, histamine, and epinephrine.

The platelet plug formation involves three steps:

1. *Platelet adhesion*: After vascular injury, the subendothelial layer is exposed, leading to binding of collagen to platelet surface receptors GPIb and promotes platelet adhesion to the subendothelial layer, and this binding is facilitated by vWF which acts as a bridge.
2. *Platelet secretion*: The binding of platelets to subendothelial layer causes the activation of platelets and thus the granules to release their contents and calcium which causes further aggregation of platelets. These granules are also responsible for activation of coagulation system.
3. *Platelet aggregation*: Secretion of granule content causes release of thromboxane A2 (TxA2) which leads to platelet aggregation. TxA2 along with ADP causes platelets to aggregate which leads to platelet plug formation and thus sealing the injury. ADP binding also causes a conformational change in GPIIb/IIIa receptors and thus facilitating binding to fibrinogen. Thrombin in turn converts fibrinogen to fibrin which further stabilizes the clot.

COAGULATION CASCADE

The second phase of hemostasis is the cascade of coagulation factor activation leading to conversion of soluble fibrinogen to fibrin strand which is involved in clot formation. Majority of coagulation factors are proenzymes called zymogens which becomes activated in coagulation cascade. Most of the factors are produced by liver except factor III, IV, and VIII. The various coagulation factors and their properties are mentioned in the **Table 2**. Normal coagulation cascade involves activation of factor X by the extrinsic or intrinsic pathway (tenase complex). Activated factor X with factor V forms the prothrombinase complex which in turn converts prothrombin to thrombin which converts soluble fibrinogen to fibrin monomer which polymerizes to form the firm clot [basic conceptual (**Fig. 1**)].

TABLE 2: Coagulation factors.

No.	*Name*	*Function*	*Half-life (in hours)*
I	Fibrinogen	Converted to fibrin	90
II	Prothrombin	Activates I, V, VII, VIII, XI, XIII, protein C, and platelets	60
III	Tissue factor	Cofactor of VII	-
IV	Calcium	Act as coenzyme	-
V	Proaccelerin and labile factor	Cofactor of X-prothrombinase complex	15
VI	None		
VII	Stable factor and proconvertin	Activates IX and X	4–6
VIII	Antihemophilic factor A	Cofactor of IX-tenase complex	10
IX	Antihemophilic factor B and Christmas factor	Activates X: Tenase complex with factor VIII	20–24
X	Stuart–Prower factor	Forms prothrombinase complex with factor V	40
XI	Plasma thromboplastin antecedent		45
XII	Hageman factor	Activates factor XI and prekallikrein	-
XIII	Fibrin-stabilizing factor	Fibrin polymerization	200
XIV	Prekallikrein (F Fletcher)	Serine protease	35
XV	HMWK (F Fitzgerald)	Cofactor	150
XVI	vWF	Binds to factor VIII, collagen, and mediates platelet adhesion	12
XVII	Antithrombin III	Inhibits IIa, Xa, and other proteases	72
XVIII	Heparin cofactor II	Inhibits IIa	60
XIX	Protein C	Inactivates Va and VIIIa	0.4
XX	Protein S	Cofactor of protein C	-

(HMWK: high-molecular-weight kininogen; vWF: von Willebrand factor)

Process of Coagulation Cascade

Coagulation process starts immediately once there is any injury to the vessel wall causing exposure of the endothelium to the blood coagulation system which includes platelets and coagulation factors. The normal coagulation process first involves platelet plug formation by platelet activation adhesion and aggregation as already explained and later the formation and maturation of fibrin.

Once the endothelium is damaged it leads to exposure to platelets which causes the first step of coagulation called the primary hemostasis and then simultaneously the secondary hemostasis also starts involving the release of tissue factor (TF) from the endothelium which activates the factor VII which is considered as the first step in the activation of the coagulation cascade which in turn activates the factor X. This activation of factor X through the TF pathway is also called the extrinsic tenase complex and is now considered as the primary stimulus for the activation of the secondary hemostasis. The coagulation factors circulate in the blood in inactive form called zymogens and are named as roman numerals and once activated they are added by lower case letter a. The main role of TF pathway is to produce thrombin burst.

The intrinsic pathway also called the contact activation pathway involves the formation of complex by high-molecular-weight kininogen (HMWK), factor XII, and prekallikrein when it comes in contact with the collagen. Once factor XII is activated it further activates XI to Xia which further activates factor IX which act as cofactor for factor VIIIa and act as intrinsic tenase complex which activates factor X to Xa. This division of coagulation pathway in extrinsic and intrinsic type is not absolutely clear, in fact this division was based on laboratory tests as intrinsic pathway is activated after contact with glass and extrinsic pathway is activated by adding thromboplastin which is a mixture of TF and phospholipid. The formation of tenase complex leads to activation of factor X which with the help of factor V and calcium forms the prothrombinase complex which converts prothrombin to thrombin which in turn convert the soluble fibrinogen to fibrin. This pathway is called the final common pathway.

In fact thrombin is not only generated by common pathway, it is also released by activated platelets which are involved in platelet plug formation. Thrombin also activates coagulation

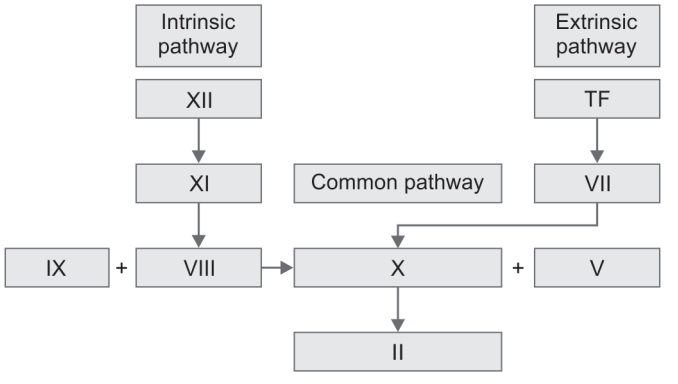

FIG. 1: Basic concepts of coagulation pathway.

factors VIII, V, and XIII and the anticoagulant protein C with the help of thrombomodulin. Role of factor XIII is to crosslink fibrin monomers and thus stabilizes the clot.

The *new model of coagulation system* involves around the cell-based coagulation system mainly the extravascular tissues providing the TFs and the platelets. It constitutes two phases; the first initiation phase which causes the release of TF leading to activation of extrinsic pathway leading to 5% of thrombin production and then the propagation phase wherein the intrinsic pathway is activated leading to 95% of thrombin generation. The other aspect is the platelet activation following tissue injury and thus causing platelet plug formation and also thrombin generation.

In fact the primary step of secondary hemostasis starts with the activation of extrinsic pathway and the intrinsic pathway further facilitates thrombin generation needed for clot propagation. *The newer model has the following steps:*

1. *Initiation*: It involves binding of TF in damaged vessel to factor VIIa which activates factor IX and factor X. This activation of factor IX by TF-VIIa complex serves as the bridge between classical extrinsic and intrinsic pathways. Factor Xa then binds to factor II to form thrombin. Thrombin generation through this reaction is not robust and can be effectively terminated by TF pathway inhibitor.
2. *Amplification*: Thrombin produced in the initiation phase further activates factor V and factor VIII, which serves as a cofactor in prothrombinase complex and augments the activation of factor II by FXa and of FXa by FIXa, respectively. This mainly involves the intrinsic pathway.
3. *Propagation*: The enzyme complexes such as tenase and prothrombinase on platelet surface produces massive amount of thrombin and platelet activation, which produces the firm clot.
4. *Stabilization*: Thrombin also activates factor XIII (fibrin stabilizing factor) which covalently links fibrin polymers and provides strength and stability to fibrin incorporated in platelet plug.

Along with the activation of coagulation cascade there is also simultaneous activation of anticoagulant pathway mainly via the antithrombin. It is serine protease inhibitor which mainly hydrolyses thrombin, factor IXa, Xa, Xia, and XIIa and thus limits abnormal propagation of thrombus. The other important anticoagulant pathway is TF pathway inhibitor which directly inhibits the TF and the tissue plasminogen activator which converts plasminogen to plasmin which degrades fibrin.

APPROACH TO THROMBOCYTOPENIA

Any patient with platelet counts $<150 \times 10^9$/L needs evaluation for thrombocytopenia. Thrombocytopenia can mild (platelet count: 100–149 $\times 10^9$/L), moderate (59–99 $\times 10^9$/L), or severe (50×10^9/L). The etiology of the thrombocytopenia can be primarily hematological or maybe the manifestation of primarily nonhematological disorder. In the emergency and critical care setting, it is important to find out the cause so as to not to miss serious hematological disorders such as acute leukemias or other thrombocytopenic emergencies like thrombotic thrombocytopenic purpura (TTP). Nonhematological illnesses like sepsis causing thrombocytopenia or disseminated intravascular coagulation (DIC) should also not be missed as they can be catastrophic. The focus of the chapter will be approach to thrombocytopenia in the critical care and emergency setting. The context of the patient's admission is very important in delineating the cause of thrombocytopenia such as sepsis or trauma which can per se lead to thrombocytopenia. It is very important to find out preexisting thrombocytopenia from the past records/history which can point out to previously existing recognized or unrecognized cause of thrombocytopenia such as immune thrombocytopenia, myelodysplastic syndrome, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection, or chronic liver disease causing hypersplenism.

There are certain thrombocytopenic emergencies which have to be ruled out, especially when the thrombocytopenia is the isolated abnormality. Causes like drug-induced immune thrombocytopenia (DITP) cause severe thrombocytopenia with high risk of bleeding. The detailed review of current and past drug history including herbal medications is crucial. Common medications such as rifampicin and beta-lactam antibiotics can lead to DITP. The onset of thrombocytopenia is 1 week after the onset of drug intake. Certain drugs such as abciximab and eptifibatide can cause DITP even within 1–2 days. In DITP, platelets typically fall below 20×10^9/L. Treatment involves stopping the suspected drug (which may be sometimes essential or sometimes optional) and replacing the suspected essential drugs with a different class of drug as substitute. In case of bleeding, intravenous immunoglobulin (IVIG) may also be given.

In heparin-induced thrombocytopenia (HIT), platelet activating antibodies are formed which bind to the complex of heparin and platelet factor 4 (PF4) (present on the platelets). This phenomenon leads to drop in platelet counts by 50% classically usually after 5 days of initiating heparin. The platelet count nadir is classically $>20 \times 10^9$/L in patients with HIT. Interestingly the patient with HIT is predisposed to develop thrombosis in spite of having thrombocytopenia. The site of thrombosis can be both venous as well as arterial. The thrombosis can involve cerebral cortical veins and other unusual sites such as splanchnic vessels. The culprit heparin may be unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). The 4Ts scoring system may be helping in suspecting HIT. The 4Ts scoring system consist of the degree of platelet call and the nadir, the timing of platelet fall with relation to heparin administration, the presence of thrombosis and presence of other causes of thrombocytopenia. A low T score <4 may help in looking for other causes of thrombocytopenia in the patient. It is important to make a suspicion of HIT clinically as laboratory facilities may not be locally available at all centers to confirm the diagnosis rapidly. Laboratory diagnosis will help to confirm the clinical diagnosis or exclude the diagnosis. The tests done include PF4/heparin immunoassays [e.g., PF4/heparin enzyme-linked immunosorbent assay (ELISA)] and functional assays. The treatment consists of immediate stopping of all heparin (UFH or LMWH) in any forms including heparin intravascular catheter flushes. Patients will need immediate starting of anticoagulation to prevent thrombosis or treat thrombosis, if already present. The anticoagulants which may be used include bivalirudin, argatroban, and fondaparinux. There is emerging data for use of oral novel anticoagulant such as dabigatran and rivaroxaban preferably once the acute phase is resolved as evident by normalization of platelet counts. Warfarin also may be started after the acute

phase is resolved along with bridging with other anticoagulants as per protocol. Early use of warfarin without proper bridging can be deadly and catastrophic due to prothrombotic status due to initial depletion of protein C. When a patient presents with thrombosis in three or more vascular territories a suspicion of catastrophic antiphospholipid antibody (APLA) syndrome should always be considered. The associated thrombocytopenia may be many times mild. Appropriate diagnosis with relevant history of miscarriages, thrombosis in the past along with the identification of APLAs such as anticardiolipin antibodies, anti-beta-2-glycoprotein, and lupus anticoagulant. Patients with immune thrombocytopenic purpura (ITP) may present to the emergency with bleeding such as gastrointestinal (GI) bleeding, mucocutaneous bleeding, or intracranial bleeding and low platelet counts. Patients with ITP may also incidentally be detected of low platelets in routine check-up or for some other disorder. They may reach hospital emergency out of panic but without any symptoms. The blood tests usually depict isolated thrombocytopenia and peripheral smear shows no abnormality apart from low platelets. Bone marrow examination reveals no abnormal cells. In case of severe bleeding manifestations such as intracranial bleeding, GI bleeding, or platelets $<10 \times 10^9$/L patients would require immediate treatment with IVIG along with corticosteroids. Usually after administration of IVIG, platelets start to rise within 24–48 hours. Patients of acute leukemia such as acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) may present to emergency or critical care department with various manifestations including bleeding manifestations due to thrombocytopenia. They may present with fever due to underlying infection (bacterial or fungal) or fever due to disease per se, fatiguability due to anemia, and bony pains due to marrow infiltration. The diagnosis is very critical as if missed can lead to mortality in a potentially curative disorder with proper treatment. Complete hemogram may show evidence of high total leukocyte count (TLC) or sometime low TLC. There may be thrombocytopenia and anemia. Peripheral smear may show evidence of blasts in the smear. Further tests such as bone marrow examination along with flow cytometry will help in confirming the diagnosis. Patients require immediate referral by a hematologist for the treatment of the acute leukemia. The most sinister of all leukemia to cause bleeding is acute promyelocytic leukemia (APL) which can lead to serious bleeding such as intracranial bleeding due to concurrent presence of thrombocytopenia and deranged coagulation parameters with DIC. Peripheral smear shows evidence of promyelocytes in the peripheral smear. Similarly patients with myelodysplastic syndrome may present to the emergency room (ER) or the intensive care unit (ICU) with bleeding due thrombocytopenia along with or without other cytopenia. Peripheral smear may show evidence of dysplasia. Aplastic anemia may have pancytopenia with severe thrombocytopenia which may be associated with catastrophic bleeding such as intracerebral bleeding or GI bleeding. Bone marrow examination will be diagnostic with evidence of hypocellularity in aplastic anemia, Patients with malignancies may present to ER with bleeding due to chemotherapy-induced thrombocytopenia or marrow infiltration by the tumor. Patients may present to critical care division with thrombocytopenia due to a potentially lethal condition known as hemophagocytic lymphohistiocytic syndrome with associated other features such as fever, hepatosplenomegaly, hemophagocytosis in the marrow, cytopenia, and high ferritin in blood.

Disorders such as TTP or hemolytic uremic syndrome (HUS) are microangiopathic hemolytic anemia which may present to the ER or the ICU with thrombocytopenia, anemia, features of hemolysis, renal dysfunction (especially in HUS), and neurological manifestation (especially in TTP). Peripheral smear shows presence of schistocytes due to the presence of microangiopathic hemolysis. Acquired TTP is due to presence of anti-ADAMTS13 antibodies, which can be demonstrated by serological testing as well as low ADAMTS13 level. TTP requires immediate plasma exchange and glucocorticoids. Any delay in administering plasma exchange may lead to fatal outcomes. HUS can be typical HUS (due to enteric infection with strains of *Escherichia coli* that produce Shiga-like toxins) or atypical HUS due to genetic mutations leading to dysregulation of the complement system. Treatment of typical HUS is typically supportive. Treatment of atypical HUS is generally with eculizumab.

Pregnancy may be associated with thrombocytopenia which can bring the patient to the ER or the ICU. This thrombocytopenia can be due to gestational thrombocytopenia which is usually mild thrombocytopenia usually occurring from second trimester onwards and usually resolves postpartum. Pregnant women also can present with thrombocytopenia related previously existent ITP. The treatment may require IVIG and or prednisolone as deemed necessary by the hematologist. Patients may present with preeclampsia or HELLP syndrome which may have thrombocytopenia. Thrombotic microangiopathy such as TTP and atypical HUS may present for the first in the course of the pregnancy. During pregnancy patients may have develop DIC due to amniotic fluid embolism, puerperal sepsis, postpartum hemorrhage, or retained products of conception. This DIC is accompanied by not only thrombocytopenia but also coagulation parameter derangement.

Patients with tropical infections such as dengue, malaria, and scrub typhus may present with concurrent thrombocytopenia. Other infections such as hepatitis C, HIV, and Epstein–Barr virus (EBV) infections may also cause thrombocytopenia.

Management of Thrombocytopenia

General management of patients with severe thrombocytopenia should avoid contact sports. Antiplatelets and anticoagulants should be used with caution to avoid bleeding in patients with thrombocytopenia on a case-to-case basis in association with the hematologist. Patients presenting to the emergency or the ICU with thrombocytopenia may sometimes need invasive procedures. It is imperative to maintain platelet count in preparation for any invasive procedure to decrease the risk of bleeding. In patients without bleeding, prophylactic platelet transfusion is used in most afebrile patients with platelet counts below 10,000/μL to prevent spontaneous bleeding. Platelets are transfused in patients with fever or sepsis and platelet counts <20,000/μL. In patients with APL, the target platelet count is >50,000/μL, especially in the presence of coexisting coagulopathy. The preferred product for transfusion is single donor apheresis product which usually contains $3–4 \times 10^{11}$ platelets. In all conditions, attempt to identify the

underlying disease process causing the thrombocytopenia and addressing that disease process is the most important step in the management of thrombocytopenia.

DISORDERS OF COAGULATION

Basic Tests of Coagulation

It is critical to have a basic understanding about the various coagulation laboratory tests for the diagnosis and management of disorders of coagulation. The basic tests are prothrombin time (PT), activated partial thromboplastin time (aPTT), Fibrinogen assays, thrombin time (TT), and lupus anticoagulant assay. Next level of tests include coagulation factor activity assays, mixing studies, and inhibitor assays. Isolated prolongation of the PT (extrinsic coagulation pathway) most often reflects a deficiency of vitamin K-dependent factors due to reasons such as warfarin, vitamin K deficiency, or decreased hepatic synthesis. Reduced quantities of factor VIII, IX, XI, and XII (intrinsic coagulation pathway) cause isolated prolongation of aPTT. Deficiency or inhibition of a factor in the common pathway (factors X, V, II, and fibrinogen) cause combined prolongation of the PT and aPTT. Fibrinogen assays are prolonged in fibrinogen deficiencies. Presence of thrombin inhibitors such as heparin and dabigatran inhibit thrombin, and prolong TT. Mixing study is used in the setting of prolonged aPTT or prolonged PT to determine whether the prolongation is due to deficiency of coagulation factors or to a presence of inhibitors. Inhibitors like certain antifactor antibodies cause inhibition of coagulation factors. Correction of PT/aPTT with mixing studies indicates factor deficiency while noncorrection suggests the presence of inhibitors. Inhibitor assay determines the presence of coagulation cascade inhibitors and its titers. Lupus anticoagulant is present in patients with APLA, in which antiphospholipid antibodies result in prolongation of aPTT and usually without bleeding manifestations, but with thrombotic manifestations.

Von Willebrand Disease

Von Willebrand disease (vWD) is one of the common disorders of bleeding presenting to the healthcare setting with symptoms of mucocutaneous bleeding such as bruising, epistaxis, menorrhagia, or GI bleeding. It is characterized by quantitative or qualitative reduction in the vWF. They may also present to the critical care unit with profuse bleeding following surgery such as dental surgery and tonsillectomy. They may also come to notice in preoperative check in the form coagulation laboratory report abnormality done as part of preoperative clearance. The cases are usually hereditary with predominantly being autosomal dominant. There is also an acquired variant of vWD due to conditions such as aortic stenosis, autoantibodies to vWF, and in other conditions like hypothyroidism. The diagnostic assays for vWD include quantitative measurement of vWF (vWF:Ag) which is reduced to 30 IU/dL, vWF activity—ristocetin cofactor assay (vWF:RCo) which is reduced in the patients and factor 8 levels which may also be reduced (as normally vWF protects factor 8 from proteolysis). Management is done in collaboration with a hematologist with the help of plasma-derived vWF concentrates or using agents like desmopressin which lead to increased release of vWF from the storage pool into the circulation.

Hemophilia

Hemophilia A and hemophilia B is due to the congenital deficiency of factor VIII and factor IX, respectively. Usually the presentation is that a child presenting to the emergency because of acute joint pain due to joint bleeding, hematomas in the muscle, intracranial bleeding, profuse bleeding following procedures such as circumcision, and later on with permanent sequelae like joint damage. Many of the patients may have family history of similar disorder in X-linked recessive pattern. Diagnosis is usually established by a prolonged aPPT and demonstration of low levels of factor VIII in hemophilia A, and low level of factor IX in hemophilia B. The treatment involves urgent replacement in case of bleeding with appropriate factor concentrate; in this era with help of recombinant factor VIII in hemophilia A and recombinant factor IX in hemophilia B. The dose and duration of treatment depends on the type of concentrate and the severity of bleeding. Preoperative doses and postoperative doses may be required in patients requiring surgery to prevent catastrophic bleeding. Some patients with hemophilia who are given exogenous factor develop antibodies which inhibit the factor (known as inhibitors). In these patients the factors may not work and patient often require other agents such as recombinant factor VII or activated prothrombin complex concentrate (aPCC)-factor eight inhibitor bypass activity (FEIBA) in case of bleeding or for purposes of surgery. Hence it is also important to send inhibitor assay in a patient who comes to the emergency with bleeding manifestations; else the factor concentrates which the medical team gives maybe of no use in patients with inhibitors. Rarely patients with pregnancy, malignancy, or connective tissue disorders can present with acquired hemophilia due to development of antibodies against endogenous factor VIII. They will be diagnosed with prolonged aPTT with positive inhibitor assay in the setting of major bleeding such as intracranial bleeding or muscle hematoma.

There are several rare disorders due to congenital deficiency of other factors such as factor II, VII, X, V, and XIII which is beyond the scope of discussion here. They may present with bleeding manifestations such as intracranial bleeding, umbilical stump bleed (factor XIII deficiency), postsurgical bleeding (factor XI), or other nonbleeding symptoms such as miscarriages (fibrinogen deficiency or factor XIII deficiency), splenic rupture, and thrombosis in fibrinogen deficiency. The clue to their existence will be by the past history of bleeding and abnormal coagulation parameters such as prolonged PT and prolonged aPTT in association with normal TT in factor II, factor X, and factor V deficiency. In factor VII deficiency there would be isolated PT prolongation. In fibrinogen deficiency there would PT, aPTT, TT prolongation along with low fibrinogen levels as per fibrinogen assay. In factor XIII deficiency there would be normal aPTT, TT, PT, and fibrinogen level but clot solubility test would be abnormal. In isolated factor XI deficiency, there would be isolated prolongation of aPTT. Treatment of these rare factor deficiencies will be to given specific factor concentrates wherever available or fresh frozen plasma (FFP) in close association with a hematologist.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is due to abnormal activation of intravascular coagulation along with fibrinolysis

BOX 1: Major causes of disseminated intravascular coagulation (DIC).

- Sepsis
- Crush injury
- Severe head injury
- Cancer procoagulant (Trousseau's syndrome)
- Acute leukemia, especially promyelocytic
- Amniotic fluid embolism
- Abruptio placentae
- Acute hemolytic transfusion reaction (ABO incompatibility)
- Snake and viper venoms
- Heat stroke
- Burns

activation leading to DIC with concurrent fibrinolysis. This can lead to bleeding due consumption and depletion of coagulation factors along with accelerated fibrinolysis. The activation of intravascular coagulation can also lead to thrombosis. It usually occurs due to a systemic abnormal exposure of procoagulant in conditions such as sepsis, malignancy such as APL, trauma, intrauterine uterine death of fetus, and viper bite (**Box 1**). Clinically it can present with the underlying condition along with features of bleeding from cannula sites, catheters site, mucous membranes, and sometimes with organ dysfunction with renal dysfunction and liver function abnormalities. Sometimes, especially in chronic DIC as in malignancies like the DIC associated with pancreatic cancer presentation can be due to thrombosis. Laboratory abnormalities in various permutations and combinations reflect the systemic activation of coagulation along with concurrent activation of fibrinolysis as shown by prolonged PT/aPTT/low fibrinogen levels/increased D-dimer/thrombocytopenia/evidence of microangiopathic hemolysis in the peripheral smear. The treatment involves that of treating the underlying condition such as antibiotics for sepsis. Prevention of bleeding includes prophylactic platelet transfusion with target platelet counts above 20,000/μL in the absence of bleeding. In the presence of bleeding or in the preparation of an invasive procedure, it is important to keep platelets above 50,000/μL. In presence of bleeding, fibrinogen has to be maintained above 100 mg/dL with the help of cryoprecipitate and if PT/aPTT is prolonged then FFP should be transfused.

Coagulation Abnormalities in Liver Diseases

In liver, being the site of production of the procoagulant factors (except factor VIII) and most anticoagulants, there is usually reduction of the synthesis of both the procoagulant and the anticoagulant factors, thereby leading to the rebalancing of the hemostasis. The measurement of PT/aPTT/fibrinogen will reveal deficiency in these factors, but in view of reduction in anticoagulant factors such as protein C, antithrombin which is also produced in the liver is prothrombotic, hence the high PT/aPTT and low fibrinogen level may mislead the treating team to believe that patient is at increased risk of only bleeding. In fact in this rebalanced hemostasis, the risk of bleeding or thrombosis depends on the tilt of this rebalancing towards thrombosis or bleeding. Hence in a nonbleeding patient with liver disease, not planned for any invasive procedure, giving FFP just for elevated PT is pointless. For patients with nonvariceal bleed, vitamin K must be supplemented, platelets to be maintained above 50,000/μL, and cryoprecipitate to be given to maintain fibrinogen level above 100 mg/dL. In case bleeding is still persistent then FFP can be given. In case of variceal bleeding, standard treatment of variceal bleeds along with above measures are done. Preparation for invasive procedure will require platelet transfusion to maintain platelet above 50,000/μL, cryoprecipitate maintain fibrinogen level above 100 mg/dL, optimization of renal status, treatment of infection, etc. Viscoelastic testing such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM) can be used to optimize management and prevention of bleeding in patients with chronic liver disease. Treatment of thrombosis is chronic liver disease has to be in close association with a liver specialist in collaboration with a hematologist in view of increased risk of bleeding, both variceal and nonvariceal. Measures such as prophylaxis with beta-blockers may be needed to reduce the bleeding risk in patients with varices who need anticoagulants to be used in thrombosis such as portal vein thrombosis, deep venous thrombosis (DVT), and other thrombotic states.

Treatment of Bleeding Due to Anticoagulants

Use of anticoagulants for various conditions like DVT may lead to bleeding complications. The treatment of the bleeding complications include stopping of the anticoagulant and use of reversal agents. The reversal agents used depends on the anticoagulant used. For heparin (UFH) and LMWH protamine is used for reversal. In case of bleeding due to warfarin FFP is used. For patients on direct oral anticoagulants with bleeding FFP/protamine is of no use. For dabigatran-related bleeding idarucizumab is the medication of choice for reversal. For anti-factor Xa, direct oral anticoagulants such as apixaban and rivaroxaban andexanet alpha or if not available prothrombin complex concentrates may be used in appropriate settings.

SUMMARY

There is large diversity in the spectrum of bleeding disorders. Thus, it is very important for the team of critical care/emergency care/hematologist to work in close collaboration for the diagnosis and immediate and long-term management of these patients. Special emphasis is to be laid on the immediate recognition of some of these medical emergencies, which without appropriate treatment can be fatal.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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Blood Transfusion Therapy and Related Complication

Aseem Kumar Tiwari, Geet Aggarwal

INTRODUCTION

The transfusion of the blood components in emergencies, if not done rationally, can increase the morbidity and mortality of patients. The immediate availability of blood components for life-threatening hemorrhages requires a rapid and focused approach as excessive bleeding threatens the survival of patients. Early recognition of major blood loss and immediate effective interventions are vital to avoid hypovolemic shock and its consequences. One of the effective interventions is the rapid provision of blood components, for which effective communication between emergency team and blood bank is a must. Transfusion support is vital for any patient in hemorrhagic shock. The transfusion of the right component to the right patient in the right quantity and at the right time has been the guiding principle for resuscitating emergency/trauma patients. The emergency team and blood bank also need disaster preparedness, presently, more than ever before. The entire chapter has been dealt with in five major sections: (1) Responsibility of emergency and blood bank team, (2) Transfusion approach in emergency and massive transfusion protocol (MTP), (3) Use of specific blood components, (4) Adverse effects of blood transfusion, and (5) Hemovigilance.

RESPONSIBILITY OF EMERGENCY AND BLOOD BANK TEAM

Responsibility of Emergency Team (Ordering Blood Component)

Every hospital should have a written protocol for ordering blood component in an emergency which should be clear and simple so that everyone understands and follows them. Simplified protocol given by the World Health Organization (WHO) in clinical use of blood is as follows:

- Insert an intravenous (IV) cannula. Use it to take the blood sample for compatibility testing, set up an IV infusion of normal saline or a balanced salt solution (e.g., Ringer's lactate or Hartmann's solution). Send the blood sample to the blood bank as quickly as possible.
- Clearly label the blood sample tube and the blood request form. If the patient is unidentified, which may happen in a disaster-like situation or road traffic accident, use some form of emergency identification system (e.g., emergency admission number). Use the patient's name, only when you are sure that you have the correct information. If you are not sure then an identifier like "*Unknown 1", "Unknown 2", and so on,* can be used. Preferably two identifiers should be used; so along with "Unknown 1" you can use patient's hospital enrollment/registration number (for example, patient id: *12345*).
- If you have to send another request for another blood component for the same patient within a short period, use the same identifiers which were used in the first request form (and blood sample) so the blood bank staff know they are dealing with the same patient. In the interim, even if the real name is identified it should not be used until the patient has stabilized clinically.
- If there are several staff members working with emergency cases, one person should take charge of ordering blood components and communicating with the blood bank about the particular patient(s). This is especially important if several injured patients are involved at the same time.
- Tell the blood bank how quickly the blood is needed for each patient. Communicate using words that have been previously agreed with the blood bank to explain how urgently blood is required. For example, we follow the terminology of immediate, urgent, and routine. Immediate, urgent, and routine denotes 5 minutes, 15 minutes, and 30 minutes, respectively.
- Make sure that emergency team and the blood bank staff know:
  - Who is going to bring the blood to the patient (e.g., General duty assistant at authors' institute)
  - Where the patient will be: Example, emergency room, operating theatre, and delivery room
- The blood bank may send group O (and possibly RhD negative) blood, especially if there is any risk of errors in patient identification. During an acute emergency, this may be the safest way to avoid a serious mismatched transfusion.

Responsibility of Blood Bank (Issuing Blood in Emergency)

In critical patients, the emergency physician may ask for O negative or group-specific uncross-matched blood. In such situations, the request may contain a signed statement from the emergency medical team indicating that clinical status of patient is too critical to wait for completion of pretransfusion compatibility testing. However, signed statement is not necessary before an immediate/urgent transfusion and does not preclude blood bank to issue blood in emergency. Every hospital needs to have a written emergency protocol. The emergency protocol at authors' institute is as follows.

Emergency Protocol

Blood bank should keep aside at least two O negative units for any exigency. Turnaround time (TAT)-based approach is suggested which matches the degree of urgency in transfusing blood components to a patient in an emergency setting. It has been divided in three categories: immediate, urgent, and routine.

Immediate Transfusion (TAT-5 Minutes)

- Issue uncross-matched group O red blood cells (RBCs) if the patient's blood group is unknown.
- Use RhD negative blood if the recipient's Rh status is unknown, especially if the patient is female (in childbearing age group).

Urgent Transfusion (TAT-15 Minutes)

Issue group-specific uncross-matched if the patient's blood group is known or can be typed, quickly.

Routine Transfusion (TAT-30 Minutes)

Issue group-specific cross-match compatible blood.

When blood is requested in emergency, blood bank should take the following steps:

- Document on the unit as "Uncross-matched" or "Compatibility testing not completed" at the time of issue of unit in the immediate and urgent protocol.
- Complete the compatibility tests promptly, even after issue. If any incompatibility is detected during the completion of compatibility tests, the emergency medical team should be notified and blood transfusion should be stopped.
- O RhD negative units should be issued only in emergency situations where the recipient blood group is unknown at the time of transfusion, up to two units; thereafter group-specific blood unit to be issued (as the patient should have had their blood group tested by this time). This is important to conserve precious O RhD negative inventory.

Blood Check at Administration

Final administration check of the blood unit must be done by trained and competent emergency physician or her/his trained team member. All patients receiving transfusion must be positively identified by last name, first name, and unique identification number and must match the details on blood component label and document(s). All blood components should be administered using standard blood administration set with an integral mesh filter (170–200 μ).

TRANSFUSION APPROACH AND MASSIVE TRANSFUSION PROTOCOL

Trauma patients generally present with varying grades of hemorrhage and shock. The approach with respect to blood component transfusion to such patients can only be understood if we understand various classes of hemorrhage which have been classified as follows:

- *Class I hemorrhage*: Blood volume loss of up to 15%. The heart rate is minimally elevated or normal, and there is no change in blood pressure, pulse pressure, or respiratory rate.
- *Class II hemorrhage*: There is a 15–30% blood volume loss and is manifested clinically as tachycardia (heart rate of 100–120 beats/min), tachypnea (respiratory rate of 20–24 breaths/min), and a decreased pulse pressure, although systolic blood pressure changes minimally if at all. The skin may be cool and clammy, and capillary refill may be delayed.
- *Class III/IV hemorrhage*: It involves a 30–40%/>40% blood volume loss, resulting in a significant drop in blood pressure and at times even changes in mental status.

While no treatment is necessary in Class I, Class II requires crystalloids; e.g., Ringer's lactate solution, which rapidly distributes between the intra- and extravascular spaces. Volume of crystalloid needed to restore intravascular volume is three times the estimated blood loss. Blood components are required only in Class III and Class IV hemorrhages. Earlier there was a traditional approach to give crystalloids and RBCs and transfuse fresh frozen plasma (FFP) only when >5–10 RBC units were transfused. However, this approach has given way to a newer approach described below.

Newer Approach—Transfusion for Severe Ongoing Hemorrhage (Class III/IV)

If the bleeding in trauma patients is unlikely or difficult to be controlled quickly, immediate transfusion of blood components in a 1:1:1 ratio of RBC, FFP, and platelets should be considered. In simple terms, if the emergency team recognizes that the patient will require four or more units of RBCs in 1 hour (or >10 units in 12–24 h), they should start transfusing four unit of RBCs, four units of FFP, and six units of random donor platelets (RDP) [or one unit of single-donor apheresis platelets (SDP) as one unit of SDP (also called apheresis platelets) is equivalent to six units of RDP]. Hypothermia must be controlled during transfusions with the help of inline warmers.

Studies supporting newer approach of 1:1:1 blood component transfusion are as follows:

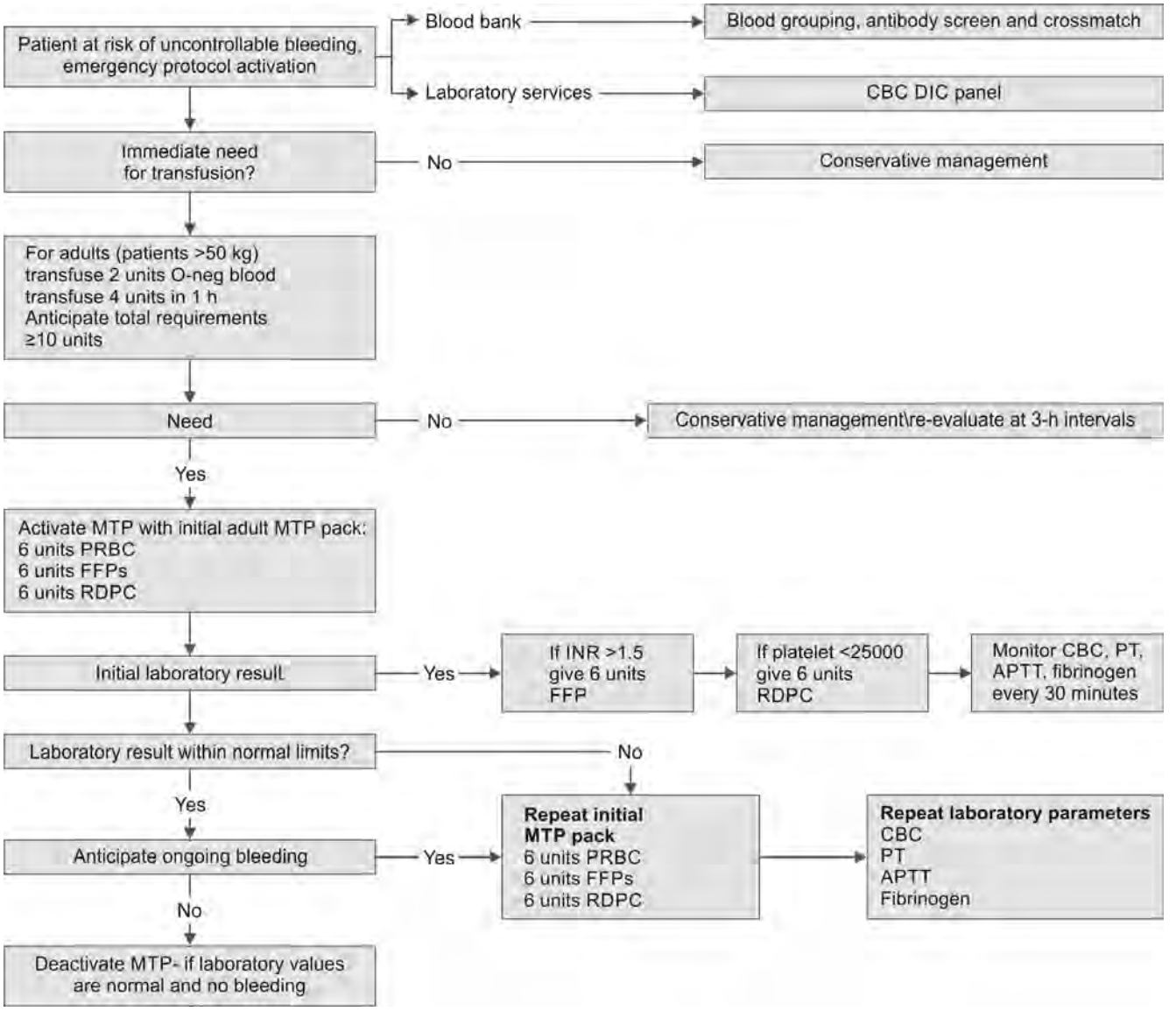
- A trial that randomly assigned 680 patients with major bleeding from severe trauma to receive transfusion of one unit versus two units of RBC for every unit of FFP and platelets (i.e., FFP to platelets to RBC of 1:1:1 vs. 1:1:2) found slightly better outcomes with the 1:1:1 approach. Patients assigned to 1:1:1 were more likely to have adequate hemostasis (86 vs. 78%) and had fewer exsanguination deaths at 24 hours (9 vs. 15%). Overall mortality at 1 day and 30 days were not different between the groups, although there was a trend favoring 1:1:1 at both time points. Adverse events were also similar between the groups.

- A retrospective study of 246 patients who presented to an army combat support hospital in Iraq has produced some data to evaluate the merits of this regimen. When patients who received massive transfusion were stratified by transfusion therapy regimen, patients who received a high ratio of FFP to RBCs (median of 1:1.4) had a survival rate of 81%, compared with 66% for those with an intermediate ratio (median 1:2.5) and 35% for those who received a low ratio of FFP to RBCs (median of 1:8).
- In a retrospective study of 467 massively transfused trauma patients, 30-day survival was increased in patients transfused at a high FFP:RBC ratio (i.e., ≥1:2) as well as in those transfused at a high platelet:RBC ratio (i.e., ≥1:2). The combination of high FFP and high platelet to RBC ratios was associated with decreased truncal hemorrhage and increased 6-hour, 24-hour, and 30-day survivals, with no change in deaths due to multiple organ failure.
- In a retrospective study of 694 massively transfused trauma patients who did not receive fresh whole blood, those receiving a high ratio of apheresis platelets (equivalent to six units of RDP) per stored RBC unit (i.e., ratio ≥1:8) had a higher 24-hour survival (95%) compared with those receiving a medium (i.e., ratio 1:16 to 1:8, 87%) or a low ratio (i.e., <1:16, 64% percent) [6]. On multivariate analysis, higher FFP:RBC ratios and higher SDP:RBC ratios were both independently associated with improved survival at both 24 hours and 30 days.

Massive transfusion protocol should be in place in every hospital and this protocol should be activated as soon as the emergency team recognizes the presence or likelihood of severe, ongoing hemorrhage. One example of MTP followed at authors' institute adapted from publication in journal of American College of Surgeons is shown in **Flowchart 1**.

ROLE OF SPECIFIC BLOOD COMPONENTS

The decision to transfuse the blood components should not depend only on transfusion triggers but should depend



(APTT: activated partial thromboplastin time; CBC: complete blood count; DIC: disseminated intravascular coagulation; FFPs: fresh frozen plasmas; INR: international normalized ratio; MTP: massive transfusion protocol; PRBC: packed red blood cell; PT: prothrombin time; RDPC; random donor platelet concentrate)

FLOWCHART 1: Massive blood transfusion protocol.

on clinical condition of patient, rate of ongoing bleeding, cardiopulmonary status, and operative intervention. The ultimate goal of blood component transfusion is to restore volume and oxygen-carrying capacity. Role of whole blood and different blood components in emergency situation are summarized in **Table 1** and described in the text below.

Transfusion of Whole Blood

Whole blood has high levels of potassium, ammonia, and hydrogen ions and has no clotting factors. With the advent of blood component therapy, the use of whole blood has become obsolete. Although it provides volume expansion along with increased oxygen-carrying capacity, it may cause volume overload and dilutional coagulopathy in patients.

Transfusion of Red Blood Cells

Red cell transfusion always remains an important unanswered question and often depends on clinical circumstances. In trauma patients if hemodynamics does not improve after administration of 2–3 L of crystalloid, two units of RBCs should be transfused. Further transfusions will depend on response to the initial transfusion.

Anti-human globulin (AHG) cross-matched compatible with antibody screen negative RBCs are best, but take considerable time. If the patient's condition warrants, emergency physician can transfuse immediately using type O RhD positive or type O RhD negative for males and type O Rh negative for girls and women of childbearing age, until group-specific uncross-matched or group-specific cross-matched blood is available.

- ABO-patients with blood type B or A may receive O RBC while type AB recipients can receive A or B RBCs. Patient should be switched back to original ABO type if blood bank inventory permits, and the patient is stable with bleeding stopped. This is important as the type B patient (or A patient) who received type O RBC, do not get too much passively transferred anti-B (or anti-A) from the donors.
- Rh negative individual may be switched to Rh positive RBCs, but should be avoided in women of childbearing potential. It can be done if RhD negative patient is likely to receive massive RBC transfusion that will deplete the existing ABO compatible and ABO inventory. Rh immunoglobulins (RhIg) prophylaxis can be given to prevent anti-D formation in childbearing females following Rh incompatible transfusion.

Transfusion of Clotting Factors: Fresh Frozen Plasma, Cryoprecipitate, and Platelets

Transfusion of intravenous crystalloid and RBC in hemorrhage increases the risk of coagulopathy due to dilution of clotting factors and platelets and also due to hypothermia. For bleeding patients (>4 units of RBCs transfused in the first few hours or chest tube continues to drain >200 mL of blood per hour) we suggest using 1:1:1 ratio approach of RBC, FFP, and RDP. This means 1 RBC:4 FFPs:6 RDP for an adult patient. If SDP is used; one SDP unit would be equivalent to six units of RDP.

When to transfuse cryoprecipitate will depend on assessment of fibrinogen levels. Fibrinogen concentration below 100 mg/dL is generally treated with 10 units of cryoprecipitate (each unit of cryoprecipitate raises the fibrinogen level by about 5 mg/dL).

TABLE 1: Use of specific blood components.

Component	*Shelf life*	*Storage condition*	*Approximate volume per unit*	*Dose*	*Trigger/indication for transfusion*	*Effect*
Red blood cell (RBC)	21–42 days (longer shelf life if suspended in additive solution)	2–8°C	• 250 mL ± 10% from 450 mL bag • 150 mL ± 10% from 350 mL bag	• 5 mL/kg (child) • 3–5 mL/kg (adult)	Hemoglobin (Hb) <8 g/dL	Raises hemoglobin by 1 g% or hematocrit by 3%
Random donor platelets (RDP)	5 days	20–24°C on flat agitator	50–70 mL	1 unit per 10 kg body weight 6 units (adult)	Platelet <20,000/μL	Raises platelet count by 30,000–50,000/mm^3, but less in many cases
Apheresis or single donor platelet (SDP)	5 days	20–24°C on flat agitator	250–350 mL	1 unit per adult	Platelet <20,000/μL	Raises platelet count by 30,000–50,000/mm^3, but less in many cases
Fresh frozen plasma (FFP)	1 year	<–30°C	• 180–220 mL from 350 mL bag • 220–300 mL from 450 mL bag	10–15 mL FFP/kg (all patients)	Used for coagulation factor replacement	Raises most coagulation factors by 25%
Cryoprecipitate	1 year	<–30°C	15–20 mL	1 unit per 5 kg 10 units (adult)	Used for replacement of fibrinogen, FXIII, FVIII, or von Willebrand factor (vWF)	Raises fibrinogen level by 50–100 mg%

Fresh frozen plasma can be transfused irrespective of Rh status of blood component, for example, A positive can be safely transfused to A negative recipient. If ABO blood group compatible FFPs are not available, use "universal plasma", group AB plasma.

Thawed plasma can be kept at 4°C for 24 hours. This plasma has decreased levels of labile factors such as FVIII and FV, but other factor levels are sufficient. It saves time in urgent transfusion settings.

Cryoprecipitate can be safely transfused across the ABO and Rh blood groups. Thawed plasma is a good alternative in emergency transfusion.

Platelets (RDP) can be safely transfused across the ABO and Rh blood group. While in apheresis transfusing O platelets to non-O blood group recipient has to be done cautiously since they may contain high titer iso-agglutinins. In such cases, it is a good idea to remove plasma to reduce transfer of iso-agglutinins.

ADVERSE EFFECT OF BLOOD TRANSFUSION

Blood transfusion can be associated with various adverse effects. These adverse effects can be either acute and arise during or shortly after the transfusion or delayed that may present after few days to months or years. Therefore, decision to transfuse blood must be based on a careful assessment of the risks and benefits to the patient, and with the knowledge and skills to recognize and treat any adverse reactions or complications that may arise. Transfusion reactions can be classified in (**Table 2**) simple categories (acute and delayed) in order to help you to recognize them, understand their underlying causes and when they may occur, and know how to prevent, manage, and record them.

Acute Complications of Blood Transfusion

Acute transfusion reactions occur during or shortly after (within 24 h) the transfusion. The WHO has broadly categorized acute transfusion reactions according to their severity and the appropriate clinical response: mild, moderate-to-severe, and life-threatening transfusion reactions.

- *Category 1: Mild reactions*
  - Mild hypersensitivity: Allergic and urticarial reactions
- *Category 2: Moderate-to-severe reactions*
  - Moderate-to-severe hypersensitivity (severe urticarial reactions)
  - Febrile nonhemolytic reactions: Antibodies to white cell or platelet antigens; antibodies to proteins, including immunoglobulin A (IgA)
- *Category 3: Life-threatening reactions*
  - Acute intravascular hemolysis
  - Bacterial contamination and septic shock
  - Fluid overload
  - Anaphylactic reactions
  - Transfusion-associated acute lung injury (TRALI)
  - Transfusion-associated circulatory overload (TACO)

Delayed Complications of Transfusion

Delayed transfusion reaction occurs days to month even years after transfusion. As with acute transfusion reactions, the consequence may be severe but often treatable. Delayed reactions can be classified into following types:

- Transfusion-transmitted infections
- Alloimmunization [against red cell or human leukocyte antigen (HLA)]
- Delayed hemolytic reaction
- Post-transfusion purpura
- Graft-versus-host disease
- Iron overload (in patients who receive repeated transfusions)

Management of Adverse Transfusion Reaction

When an acute reaction first occurs, it may be difficult to decide on its type and severity as the signs and symptoms may not initially be specific or diagnostic. However, with the exception of allergic urticarial and febrile nonhemolytic reactions, adverse reactions are potentially fatal and require urgent treatment. It is essential to monitor the transfused patient closely in order to detect the earliest clinical evidence of an acute transfusion reaction. In an unconscious or anaesthetized patient, hypotension and uncontrolled bleeding may be the only signs of an incompatible transfusion. In a conscious

TABLE 2: Guidelines for recognition of adverse transfusion reaction.

Category	*Symptoms*	*Signs*	*Possible cause*
Category 1 (mild)	Pruritus (itching)	Localized cutaneous reactions—urticaria and rash	Hypersensitivity/allergic (mild)
Category 2 (moderate-to-severe)	Anxiety; pruritus; palpitation; mild dyspnea; and headache	Flushing; urticaria; rigors; fever; restlessness; and tachycardia	• Hypersensitivity/allergic (moderate-to-severe) • Febrile nonhemolytic reaction • Possible contamination with pyrogen/bacteria
Category 3 (life-threatening)	Anxiety; chest pain; pain near infusion site; respiratory distress; pain in loin/back; headache; and dyspnea	Rigors; fever; restlessness; hypotension (>20% fall in systolic BP); tachycardia (>20% rise in heart rate); hemoglobinuria (red urine); and unexplained bleeding (DIC)	• Acute intravascular hemolysis • Bacterial contamination/septic shock • Anaphylaxis • TRALI • TACO

(BP: blood pressure; DIC: disseminated intravascular coagulation; TACO: transfusion-associated circulatory overload; TRALI: transfusion-associated acute lung injury)

patient undergoing a severe hemolytic transfusion reaction, signs and symptoms may appear very quickly—within minutes of infusing only 5–10 mL of blood. Close observation at the start of the infusion of each unit is essential. If an acute transfusion reaction is suspected, stop the transfusion immediately. Check the blood unit labels and the patient's identity. If there is any discrepancy, consult the blood bank. Management steps for blood transfusion reaction are summarized in **Box 1**.

HEMOVIGILANCE (HEMOVIGILANCE PROGRAM OF INDIA)

On December 10, 2012, a centralized hemovigilance program was launched in India. Hemovigilance Program of India (HvPI) was planned jointly by Indian Pharmacopoeia Commission (IPC) and the National Institute of Biologicals (NIB), Noida. The program was launched to assure patient safety and promote public health through a well-structured program for monitoring of adverse transfusion reactions associated with blood and blood products. The Transfusion Reaction Reporting Form (TRRF), guidance document, standardized definitions of transfusion reactions, and the Haemo-Vigil software for online reporting of transfusion reactions were approved. The key objectives outlined in the HvPI are:

- Monitor transfusion reactions,
- Create awareness among healthcare professionals,
- Generate evidence-based recommendations,
- Advise the Central Drugs Standard Control Organization (CDSCO) for safety-related regulatory decisions,
- Communicate findings to all key stakeholders, and
- Create national and international linkages.

BOX 1: Guidelines for management of acute transfusion reaction.

Category 1: Mild

- Slow the transfusion
- Administer antihistamine IM (e.g., chlorpheniramine 0.1 mg/kg or equivalent)
- If no clinical improvement within 30 min or if signs and symptoms worsen, treat as Category 2

Category 2: Moderate-to-severe

- Stop the transfusion. Replace the infusion set and keep IV line open with normal saline
- Notify the doctor responsible for the patient and the blood bank immediately
- Send blood unit with infusion set, freshly collected urine and new blood samples (one clotted and one anticoagulated) from vein opposite infusion site with appropriate request form to blood bank and laboratory for investigations
- Administer antihistamine IM (e.g., chlorpheniramine 0.1 mg/kg or equivalent) and oral or rectal antipyretic (e.g., paracetamol 10 mg/kg: 500 mg to 1 g in adults). Avoid aspirin in thrombocytopenic patients
- Give IV corticosteroids and bronchodilators if there are anaphylactoid features (e.g., bronchospasm and stridor)
- Collect urine for next 24 h for evidence of hemolysis and send to laboratory
- If clinical improvement, restart transfusion slowly with new blood unit and observe carefully
- If no clinical improvement within 15 min or if signs and symptoms worsen, treat as Category 3

Category 3: Life-threatening

- Stop the transfusion. Replace the infusion set and keep IV line open with normal saline
- Infuse normal saline (initially 20–30 mL/kg) to maintain systolic BP. If hypotensive, give over 5 min and elevate patient's legs
- Maintain airway and give high flow oxygen by mask
- Give adrenaline (as 1:1,000 solution) 0.01 mg/kg body weight by slow intramuscular injection
- Give IV corticosteroids and bronchodilators, if there are anaphylactoid features (e.g., bronchospasm and stridor)
- Give diuretic: e.g., furosemide 1 mg/kg IV or equivalent
- Notify the doctor responsible for the patient and the blood bank immediately
- Send blood unit with infusion set, fresh urine sample and new blood samples (one clotted and one anticoagulated) from vein opposite infusion site with appropriate request form to blood bank and laboratory for investigations
- Check a fresh urine specimen visually for signs of hemoglobinuria (red or pink urine)
- Start a 24-h urine collection and fluid balance chart and record all intake and output. Maintain fluid balance
- Assess for bleeding from puncture sites or wounds. If there is clinical or laboratory evidence of DIC, give platelets (adult: 5–6 units) and either cryoprecipitate (adult: 12 units) or fresh frozen plasma (adult: 3 units). Use virally-inactivated plasma coagulation products, wherever possible
- Reassess. If hypotensive: Give further saline 20–30 mL/kg over 5 min; give inotrope, if available
- If urine output falling or laboratory evidence of acute renal failure (rising K^+, urea, and creatinine): Maintain fluid balance accurately. Give further furosemide. Consider dopamine infusion, if available

  Seek expert help: The patient may need renal dialysis
- If bacteremia is suspected (rigors, fever, collapse, and no evidence of a hemolytic reaction), start broad-spectrum antibiotics IV to cover pseudomonas and gram positives

(BP: blood pressure; DIC: disseminated intravascular coagulation; IM: intramuscular; IV: intravenous)

Awareness about the hemovigilance program and its objectives was generated through hemovigilance newsletters, scientific publications, and organizations of continuing medical education (CME) programs across the country. Reporting under HvPI is voluntary. There has been a gradual increase in blood center enrolment with HvPI since its inception, and till year 2018, 716 out of 2,903 licensed blood banks (24.6%) were enrolled. Overall risk of adverse reactions, according to HvPI data, is 1 in 1,000 or 8.4 per 10,000 blood component transfusions.

SUMMARY

Safe and effective replacement of blood or one of its components in critically ill anemic or bleeding patients is main goal of transfusion therapy. The indications for transfusions in emergency department and intensive care unit should be clearly mentioned in their manual, and only the required blood components are replaced using appropriate dosages. In view of limited resources of blood products they should be given only when indicated, using the minimal dosage required and after carefully considering possible alternatives. The indications and efficacy of transfusing platelets, leukocytes, and other plasma proteins are limited although red blood cells and plasma clotting factors are crucial. By prior compatibility testing acute hemolytic transfusion reactions can be avoided; other transfusion reactions cannot be predicted by compatibility testing. By using appropriate clinical and laboratory parameters, the effectiveness and survival of transfused blood cells and plasma proteins should be monitored during and after transfusion.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Therapeutic Plasmapheresis

Rahul Solanki, Devendra Richhariya

INTRODUCTION

Plasmapheresis, which literally means withdrawal or removal of plasma, is a procedure in which plasma is separated from the blood cells and when is replaced with fresh frozen plasma, a blood product or a plasma substitute (colloid or crystalloid such as albumin) is termed as plasma exchange. The replacement solution used depends on the severity and type of disease, tolerability of the patient, and some other factors. Saline is relatively safe for small volume exchange or even in larger quantities. The plasma protein fraction (PPF) is superior to fresh frozen plasma. The PPF is free of the risk of hepatitis. When added with albumin but supplementation with calcium and potassium is necessary as their content is low in it. A vasoactive substance bradykinin is present in PPF, which may cause severe adverse reactions. Dextran may be used for volume replacement; these solutions reduce platelets aggregation thus help in reduced clot formation. Up to 1,000 mL of this solution is usually well tolerated. Anticoagulant used in centrifugation technique is citrate while heparin is used in membrane filtration technique. Plasmapheresis is a method of treating number of diseases of frequently uncertain etiology and poorly understood pathogenesis for which there is no adequate therapy. Removal of some toxic substances or auto antibodies accumulated in the plasma can have therapeutic effect.

HISTORY

Hendon (1902s) was the first to conduct research on the therapy method of hemapheresis by withdrawing blood from animals to be washed and reinjected. Fleig (1909) after Hendon used this method for the treatment of human uremia. Abel et al. (1914) have explained the removal of plasma technique through the treatment of poisoned dogs whose kidneys had been removed. At the end of 1940s and early 1950s, simultaneously the appearance of plastic advanced blood bag and advanced refrigerated centrifuge, hemapheresis was used more broadly as a treatment method. In 1950s, Dr Edwin Cohn had established the using a continuous flow centrifuge with >60 years since it was invented by De Laval for use in the dairy industry to prepare blood products and improve the effectiveness of a therapeutic plasmapheresis during the Second World War. In 1962, Judson provided a device for separation of leukocytes from the whole blood, device consists of disposable plastic tubes that were sterile previously, and worked with a steady stream of closed system and it was the first device that enables functionality to provide the processing of large volumes of blood. This device is capable of exchanging plasma, collecting platelets, granulocytes, lymphocytes, and erythrocytes. In 1988, Cobe Company began selling a new device as SPECTRA. This type of devices is automatically equipped with computer systems that can platelet aphaeresis with minimal contamination of white blood cell. Moreover, SPECTRA have been moving for medical procedures affairs that are easily transferred to the patient's room. Subsequent development of the basic principles established by the people, eventually leading to the construction of several kinds of semiautomatic separation devices for clinical applications in blood that the wider use of plasmapheresis was followed as a method of treatment. Continuation of this trend depends on the development of consumer devices and software whatever needs to be more selective separation of blood components, and other ingredients can be returned to the donor or patient. Plasmapheresis was divided generally into two groups; plasma products by donor plasmapheresis and therapeutic plasmapheresis.

INDICATIONS

Autoimmunity is a condition in which the body produces an immune response against its own tissue constituents. It is most commonly treated with medications that suppress the immune system. Immunosuppressive drugs are like a double-edged sword, though they are most beneficial in autoimmune disease, they bring a series of adverse reactions which sometimes may become intolerable to the patient. The demand for a procedure that would cut out the adverse effects of immunosuppressants and at the same time treats autoimmune diseases. Apheresis is derived from the Greek, meaning "withdrawal". After the blood is withdrawn from the body, the blood components can be separated by either filtration or centrifugation. Filtration systems allow plasma removal (plasmapheresis) with retention of blood cells. Centrifugal systems are more versatile,

allowing plasmapheresis or selective removal of cell types (e.g., plateletpheresis). The plasma exchange involves removal of plasma and replacement of it with various fluids, whereas plasmapheresis involves only the removal of plasma.

Plasmapheresis has been used with good effect in the following disease: Myasthenia gravis, thrombocytopenic purpura, Guillain–Barré syndrome, rheumatoid arthritis, insulin-dependent diabetes mellitus, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, erythema multiforme, psoriasis, multiple myeloma, hypercholesterolemia, severe sepsis and shock, and neuromyelitis of the eye. The appropriate use of therapeutic plasma exchange is based on two societies (**Tables 1** and **2**), i.e., American Association of Blood Banks (AABB) and American Society for Apheresis (ASFA).

TECHNIQUES

Techniques used in plasmapheresis are centrifugation technique and membrane filtration technique (**Figs. 1** and **2**).

Centrifugation Techniques

This technique includes continuous flow technique and intermittent flow technique.

Continuous Flow Technique

In this technique, the withdrawal of blood is fed continuously into a rapidly rotating bowl in which red cells, leukocytes, plasma, and platelets are separated in to different layers. Any of these layers are removed and the remainder is returned to the patient with the replacement fluid. The advantage of this procedure is that it is faster and completely automated. But it requires the use of a dual lumen catheter and the equipment is immobile. It is an expensive technique. The anticoagulant used in this technique is citrate.

Intermittent Technique

In this technique, blood is drawn in successive batches and separated. This cycle is repeated as often as necessary to remove the desired volume of plasma (i.e., 1–1.5 plasma volume). The equipment is portable unlike that in the continuous flow technique and a single needle peripheral venous puncture is sufficient. The limitations of this technique include the time taken, i.e., it takes >4 hours for one cycle and a large extracorporeal blood volume is required (>225 mL).

Membrane Filtration Technique

This technique is used as an alternative to centrifugation technique. The patient's blood is pumped through a parallel plate or hollow fiber filter at a continuous flow rate (50–200 mL/min). The membranes have pores of 0.2–0.6 μm diameter which is sufficient to allow passage of plasma while retaining cells. Plasma is thus collected and separated from the blood. The average time required for membrane filtration is <3 hours. In general, the plasma can be removed at a rate of 30–50 mL/min. Unlike the intermittent technique, a large vein catheter is required. The anticoagulant used in this technique is heparin.

TABLE 1: Indications of therapeutic plasmapheresis (ASFA and AABB classification) in neurologic diseases.

Disease	*Indication category*
• Guillain–Barré syndrome • Chronic inflammatory demyelinating • Polyradiculoneuropathy • Polyneuropathy with IgG/IgA monoclonal protein • Polyneuropathy with IgM monoclonal protein	I
• Stiff-person syndrome • Idiopathic inflammatory demyelinating disease • Sydenham's chorea • PANDAS	II
• Myasthenia gravis • Lambert–Eaton myasthenia syndrome • Paraneoplastic neurologic syndrome • Multiple sclerosis • Refsum's disease • Rasmussen's encephalitis	III
Polymyositis or dermatomyositis	IV

(AABB: American Association of Blood Banks; ASFA: American Society for Apheresis; Category I: standard acceptable therapy; Category II: sufficient evidence to suggest efficacy usually as adjunctive therapy; Category III: inconclusive evidence of efficacy or uncertain risk/benefit ratio; Category IV: lack of efficacy in controlled trials; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)

TABLE 2: Indications of therapeutic plasmapheresis therapy (ASFA and AABB classification) in blood disease and dysproteinemia.

Disease	*Indication category*
• Post-transfusion purpura • Thrombocytopenic purpura	I
• ABO-incompatible marrow transplant • Coagulation factor inhibitors • Cryoglobulinemia • Hyperviscosity/multiple myeloma • Immune thrombocytopenia purpura	II
• Aplastic anemia • Autoimmune hemolytic anemia • Hemolytic uremic syndrome • Platelet alloimmunization • Pure red cell aplasia • Red cell alloimmunization	III

(AABB: American Association of Blood Banks; ASFA: American Society for Apheresis; Category I: standard acceptable therapy; Category II: sufficient evidence to suggest efficacy usually as adjunctive therapy; Category III: inconclusive evidence of efficacy or uncertain risk/benefit ratio; Category IV: lack of efficacy in controlled trials)

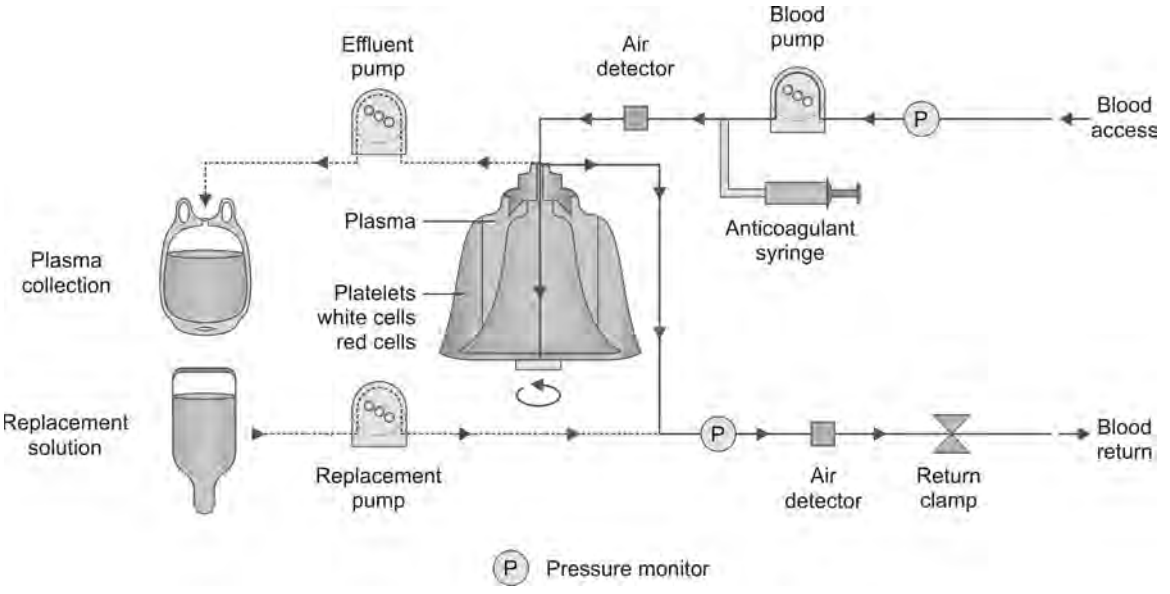

FIG. 1: Centrifugation technique.

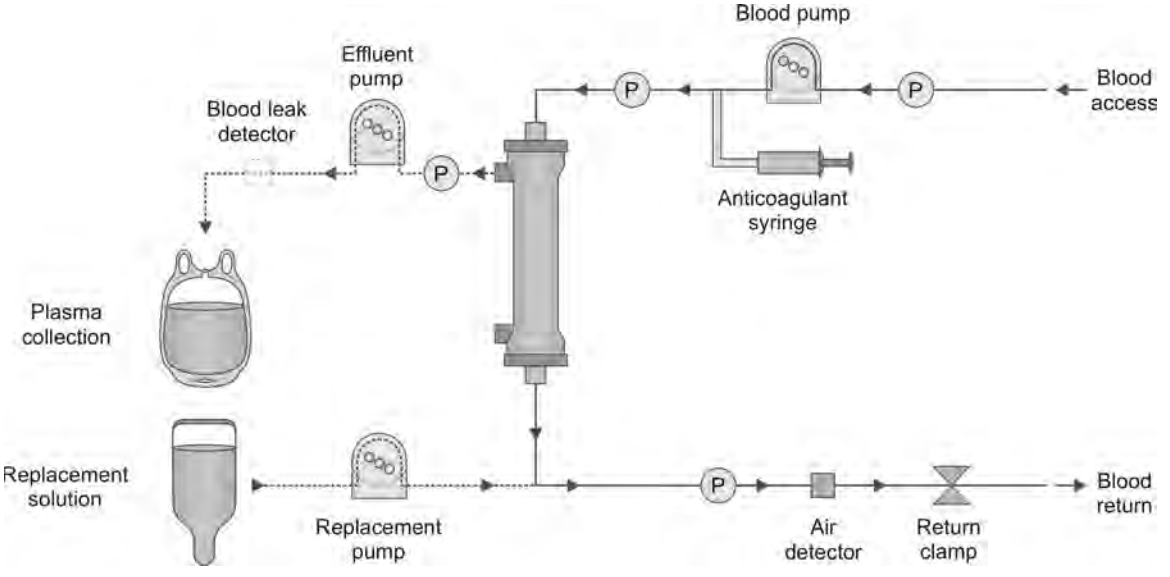

FIG. 2: Membrane filtration technique.

Patient Preparation

The patient should be asked to avoid caffeine-containing liquids 24 hours before the treatment due to their diuretic action. A balanced diet should be given before treatment. Patient should empty the bladder prior to the procedure. Comfortable clothing with loose fitting sleeves that pull easily above the elbow will make it easier to place the needle in each arm.

Procedure

A needle is inserted in to a vein in each arm; patient has to stabilize his arm during insertion of the needle. Blood is taken from one arm and circulated through cell separators following one of the previously mentioned techniques. To replace the plasma that is removed, a plasma substitute is given with returned blood cells (**Table 3**). The treatment takes several hours and it can be done on outpatient basis. The number of times the treatment is needed varies greatly depending on the disease and person's general condition (**Table 4**). An average course of plasmapheresis is 6–10 treatments over 2–10 weeks. Most patients begin to improve with in the first few days of the treatment. Patients who have received three to four exchanges over a week would remain healthy for 1–2 months.

COMPLICATIONS

The complications which may occur during or after the procedure include a drop in blood pressure, bleeding due to the use of anticoagulants, risk of infection due to placement of central venous catheter, allergic reaction to the solution, and temporary suppression of the immune system. Most of the complications are reversible and there is no major effect on vital organs.

TABLE 3: Advantages and disadvantages of any replacement fluids in therapeutic plasma exchange.

Replacement fluid	*Advantages*	*Disadvantages*
Crystalloids	• Low cost • Hypoallergenic • No viral risk	• 2–3 volumes required • Hypooncotic • No coagulation factors • No immunoglobulins
Albumin	• Iso-oncotic • No contaminating "inflammatory mediators" • No viral risk	• High cost • No coagulation factors • No immunoglobulins
Hydroxyethyl starch (HES)	• Moderate cost • Iso-oncotic • No contaminating "inflammatory mediators"	• No coagulation factors • Long-term residual levels of HES contraindicated with renal failure • Possible coagulopathy
Plasma	Maintain normal levels of immunoglobulins, complement antithrombin and other proteins	• Viral transmission risk • Citrate load • ABO incompatibility risk • Allergic reaction • Sensitization

TABLE 4: The final target of plasmapheresis therapy.

Substance to removed	*Treatment volume (mL/kg)*	*Treatment interval (hours)*	*Treatment endpoint*
Autoantibodies	40–60	24–48	Four to six treatment
Immune complexes	40–60	24–48	Treat till response
Paraproteins	40–60	24	Treat till response
Toxins	40–60	24–72	Treat till response
TTP/HUS	40	24	Treat till remission
Immunologic rebound	40–60	24–48	Two to three treatment followed by immunosuppressive medication

(HUS: hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura)

SUMMARY

Plasmapheresis is a valuable treatment in patients with autoimmune diseases in which all other treatment modalities have failed. Hence, it can be employed as a treatment of choice in certain autoimmune diseases involving the oral cavity in which the adverse effects of other treatment modalities outweigh the therapeutic effects. This area holds scope for further studies and trials thereby providing patients with untreatable diseases a new treatment modality with fewer side effects and faster recoveries.

MULTIPLE CHOICE QUESTIONS

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146 CHAPTER

Sickle Cell Disease

Devendra Naik

INTRODUCTION

Sickle cell disease (SCD) is an inherited blood disorder which is more commonly seen among people of African, Arabian, and Indian origin. SCD occurs in heterozygous form in about 8% of American blacks and in homozygous form in 1 in 400. The disease is largely not documented in India. The sickle hemoglobin (Hb) was first described in India in the tribals of Nilgiri hills in 1952. Emergency physicians need to be familiar with SCD and its complications as this can be one of the most common causes of emergency department (ED) visits.

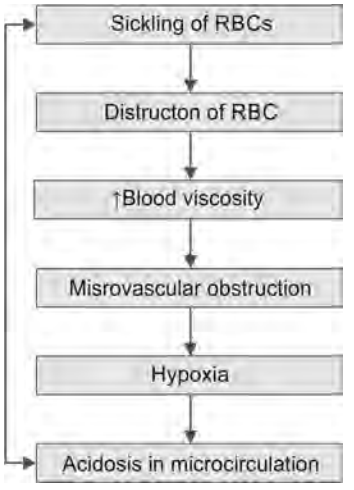
PATHOPHYSIOLOGY

The characteristic in SCD is red blood cells (RBCs) containing at least one abnormal Hb, hemoglobin S (HbS). The normal adult Hb (HbA) consists of a pair of alpha and beta chains. The Hb of sickle cell anemia (HbSS) consists of a pair of alpha chains and a pair of sickle beta chains whereas Hb of sickle cell trait (HbS) consists of a pair of alpha chains, one normal beta chain and one sickle beta chain.

The abnormal HbS results from an adenine-to-thymine deoxyribonucleic acid (DNA) substitution in the beta globin chain of Hb. Donut-shaped RBCs with normal Hb are quite flexible so that they move through arterioles and capillaries. RBCs containing HbS are stiff and sickle shaped. Sickle shape of the RBC results in premature destruction of RBC (life span of about 20 days) thereby increasing the blood viscosity which leads to microvascular obstruction. Hypoxia caused by microvascular obstruction causes acidosis in the microcirculation. This acidosis leads to further sickling (**Flowchart 1**). In the initial period, the sickling is reversible as HbS is reoxygenated. The red cell membrane will be permanently damaged due to repeated episodes of distortion and RBC remains irreversibly sickled. Many organ systems will be affected due to this chronic, ongoing hemolysis, and periods of microvascular occlusion which leads to tissue ischemia.

CLINICAL FEATURES

Sickle cell disease has been a repeated, painful, and frustrating problem for the patients. A study suggests that as many as 35% of a sickle cell population are recurrent ED visitors. SCD is characterized by *two major clinical manifestations—hemolysis and acute events of vaso-occlusions.* The hallmark and the most common reason for ED visits is *the painful vaso-occlusive crisis.* Precipitating factors are preceding infection, exposure to cold, altitude, dehydration, and trauma. Multiorgan failure is seen in a small proportion of patients with vaso-occlusive crisis. Systemic manifestations of vaso-occlusive crisis of SCD are summarized in **Table 1**.



(RBCs: red blood cells)

FLOWCHART 1: Pathophysiology of sickle cell disease.

Acute Painful Episodes

Acute pain in back and extremities is classical presentation due to vaso-occlusive crisis of SCD. Bone pain is quite common during sickle cell crisis usually involving the back and extremities. This pain would be diffuse without local signs of inflammation. Hence, if there are local signs it suggests infection. The humeral or femoral heads are most commonly affected. Managing the pain in priority basis is utmost important (**Box 1**).

Children may present with acute abdomen with acute splenic enlargement due to intrasplenic sickling and vascular obstruction. The child may be in shock. These children have increased susceptibility to infection. Most of these patients with

TABLE 1: Systemic manifestations of sickle cell disease.

Organ system	*Manifestations*
Skin	Stasis ulcers
Central nervous system	Cerebrovascular accident
Eye	Retinal hemorrhage and retinopathy
Cardiac	Congestive heart failure
Pulmonary	Pulmonary embolism, infection, and infarction
Vascular	Occlusive events at any site
Liver	Intrahepatic cholestasis, hepatic sequestration, and hepatic infarct
Gallbladder	Bilirubin gallstones due to hemolysis
Spleen	Acute sequestrations—acute abdomen
Urinary	Hematuria and urinary tract infection
Genital	Impotence, decreased fertility, and priapism
Skeletal	Bone infarcts leading to osteomyelitis and septic necrosis
Placenta	Fetal wastage
Erythrocytes	Anemia due to chronic hemolysis

BOX 1: Management of acute painful episode in sickle cell disease.

***Types of pain in sickle cell disease*:**

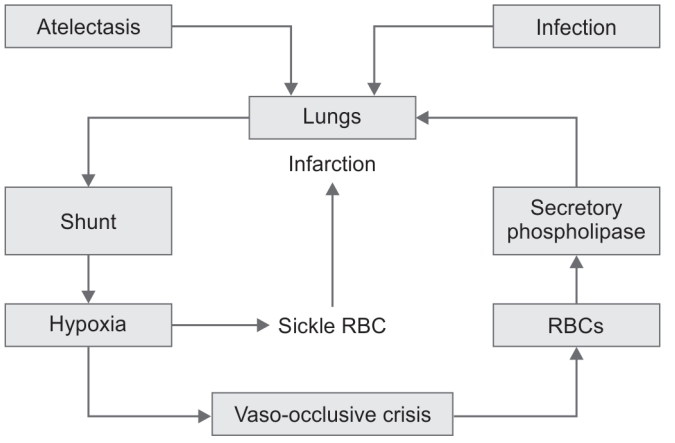
- Usually symmetric back pain and extremities pain
- Acute flare up of chronic pain—of bone and joints (chronic ulcer, osteomyelitis, and avascular necrosis of joints bone infarction)
- Neuropathic pain-burning paresthesia hyperalgesias

***Management of acute painful episodes*:**

- Triage the patient according to pain
- Opioid analgesics within 30 min, morphine 0.1 mg/kg by intravenous (IV)/oral routes avoid intramuscular route
- Adjuvant agents such as acetaminophen and nonsteroidal anti-inflammatory agents
- Other therapy; IV fluids and oxygen (in hypoxic patient, if saturation <92%)
- Laboratory—complete blood count, reticulocyte liver function test, lactate levels, and electrolytes
- Experimental therapy—steroids, nitric oxide, and possible future role of ketamine

SCD coming to ED are having a defined pain patterns. Enquiry into family history, previous pain episodes, and history of chronic anemia are very important. Adult patients commonly have a youthful appearance with long and thin extremities.

The emergency physician needs to be vigilant in differentiating uncomplicated crises from other more serious pathologic conditions. Investigations may be required to rule out other causes of acute abdomen or acute chest pains or neurological complications. The use of tissue plasminogen activator (tPA) for thrombolysis in acute nonhemorrhagic strokes is similar to acute strokes without SCD. Chronic organ system damage is common in these patients. Hence, quick review of these conditions is necessary during every ED visit. The common causes of mortality in patients with SCD are cardiopulmonary disease, chronic renal failure, acute stroke, and recurrent infections.



(RBCs: red blood cells)

FLOWCHART 2: Pathogenesis of acute chest syndrome.

Acute Chest Syndrome

It is defined as a chest X-ray (CXR) showing a new infiltrate along with one of these symptoms—fever, cough, wheezing, chest pain, or tachypnea. Acute chest syndrome (ACS) is an important cause of mortality in patients with SCD in the US. The precipitating etiology of ACS may be pulmonary infections, infarction in the ribs, pulmonary infarction, and fat emboli (**Flowchart 2**). Two most common organisms identified are *Chlamydia pneumoniae* (adults) and *Mycoplasma pneumonia* (children).

Supplemental oxygen, empirical antibiotics cephalosporin, and macrolide covering *Chlamydia* and *Mycoplasma* are initial management. Incentive spirometry and judicious use of pain control medications and IV fluids is also recommended. Improved outcomes have been reported with mechanical ventilation use. Role of anticoagulation, nitrous oxide steroid either unclear or in experimental stage can also be used. Extensive lung involvement in X-ray chest, low platelets count, and cardiac disease as comorbidity are the bad prognostic factors.

Abdominal Crisis

Constant abdominal pain is a common complaint during episodes of acute sickle cell crisis. This has to be differentiated from focal abdominal problem such as appendicitis. Jaundice and abdominal pain may be because of hepatic infarction. There may be anemia with elevated reticulocyte count, hepatomegaly, and right upper quadrant pain. Pigment-related cholelithiasis is common due to chronic hemolysis and increased bilirubin turnover. The spleen is particularly susceptible to infarction and sequestration during these vaso-occlusive episodes. The spleen might become essentially nonfunctional over time, due to microinfarction. This pushes these patients at risk for serious infections and overwhelming sepsis, especially in children.

Aplastic Crisis

These patients have a chronic hemolytic state. Aplastic crisis happens due to significant reduction in the RBC production leading to rapid drop in Hb level along with decreased reticulocytes. The Hb level will be unusually low and reticulocyte count of <0.5% (baseline Hb in SCD 6–9 g/dL and reticulocyte 5–15%). The leukocyte and platelet counts will be within normal limits. This is usually a self-limiting syndrome.

Acute Stroke

Both ischemic as well as hemorrhagic strokes are common in patients with SCD. The children with sickle cell anemia have >200 times greater risk of stroke than those without this disorder. It is unfortunate that these children are at 70–90% risk for recurrent stroke. Hence, chronic transfusion therapy is indicated in these children to prevent the recurrent strokes.

Fever and Infections

These patients are in a sort of immunocompromised state as they are functionally asplenic after their early childhood. They are susceptible to infections from *Haemophilus influenzae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Salmonella typhimurium, Streptococcus aureus*, and *Escherichia coli.*

APPROACH TO SICKLE CELL DISEASE PATIENT IN EMERGENCY DEPARTMENT

Sickle cell disease patient present to ED mostly due to various complications so main challenges to emergency physician is to understand different pathophysiology. Immediate challenge is to know if any acute anemic crisis.

In Presence of Anemia

Due to increased hemolysis and RBC destruction, all patients with SCD usually are moderately anemic. A drop of 2 g/dL from baseline is considered acute. Aplastic crisis or sequestration/hemolysis need to be differentiated. Obtain the reticulocyte count. A low reticulocyte count indicates an aplastic crisis. Bone marrow production is reduced; there is a high reticulocyte count. Splenic sequestration progresses rapidly. It may manifest with left upper quadrant pain and splenomegaly and can progress to shock. These patients are critically ill. Abdominal pain is not a reliable indicator. Bedside ultrasound may be useful in assessing for splenomegaly by measuring size. This sequestration is more common in children.

Hemolysis

Hemolytic crisis will cause an elevation in lactate dehydrogenase (LDH), aspartate aminotransaminase/alanine aminotransferase, and bilirubin. This elevation will differentiate it from splenic sequestration.

In Absence of Anemia

There is presence of cardiopulmonary symptoms and ACS. Diagnostic criteria are any combination of fever, shortness of breath, hypoxia, and/or chest pain with new infiltrate on CXR.

Absence of Cardiopulmonary Symptoms—Vaso-occlusive Crisis

This condition causes ischemic pain. Bones, joints, and muscles are commonly affected. Rarely, it can cause myonecrosis. Creatine phosphokinase may be used in the appropriate setting. Ensure patients are not developing osteomyelitis, septic arthritis, avascular necrosis, or another emergent cause. Ask patients if their pain is similar or different than usual. Patients are at a higher risk for infarction because of sickling of cells. Providers must have an increased suspicion of embolic disease in patients with SCD, as they are at higher risk for: (1) stroke, (2) pulmonary thrombosis or pulmonary embolism (PE), (3) venous thromboembolism, (4) renal infarction, (5) priapism, (6) splenic infarction and chronic microvascular infarctions (often reduce or eliminate splenic function reducing immune function), and (8) hepatic infarction (may be difficult to differentiate from hepatitis or biliary disease).

MANAGEMENT

Due to availability of antenatal and neonatal screening and parental education, majority of the patients would be aware of the diagnosis. So history and clinical examination play an important role in diagnosing these conditions during the acute episodes in the ED.

Investigations

Complete blood count, reticulocyte count, LDH, serum electrolytes, renal function tests—creatinine, urea, and urine analysis, liver function tests, chest radiograph, ultrasound abdomen, blood cultures, and imaging of the brain in stroke symptoms.

General Management

Bed rest, fluids—oral or IV depending on hydration status, 5% dextrose in half normal saline, oxygen—if hypoxia present (<92%), encourage deep breathing, incentive spirometry, and hydroxyurea (10–30 mg/kg/day)—helps by increasing HbF.

Pain Management

Use analgesics as appropriate to the degree of pain, paracetamol, oral or IV for mild pain, nonsteroidal anti-inflammatory drugs (NSAIDs) for moderate pain (if no renal insufficiency), opioids for moderate-to-severe pain—titrated doses (morphine 0.1 mg/kg every 15–30 min), and intranasal fentanyl 2 μg/kg, especially in children.

Adjuvant Therapy

Antibiotics—empirical broad-spectrum antibiotics, blood transfusion—exchange transfusion is more advantageous, and surgery—splenectomy, *consider* anxiolytic antiemetic medication to prevent constipation.

Other Therapies

Considered 5-azacytidine, an antitumor drug 5-deoxyazacytidine (decitabine), IV steroids (dexamethasone), bone

marrow transplantation, gene therapy, combination of clotrimazole and magnesium, and poloxamer 188, an artificial surfactant.

Specific Treatment

- *Aplastic crisis*: Bone marrow suppression is often self-limited, but patients with SCD may not be able to tolerate an acute drop in RBC production. Packed RBC (PRBC) transfusion is indicated if Hb drops >2 g/dL from baseline. This condition is usually self-limited and resolves in 1 week.
- *Splenic sequestration*: Initially, fluid resuscitate if patients are in shock to bridge to transfusion, as fluids may help the spleen release sequestered RBCs. Perform a PRBC transfusion to goal Hb of 6–8 g/dL. Rule out precipitating pathology, such as infection. Splenectomy is not routinely indicated.
- *Hemolysis*: This condition is often self-limited. PRBC should be performed if transfusion is required, though often it is not. Rule out precipitating pathology.
- *Acute chest syndrome*: Aggressive pain treatment can be required to reduce splinting and increase tidal volume. This treatment will lead to improved respiratory mechanics and help improve oxygenation, potentially helping reduce sickling. Opioids are the preferred method of pain control. Although aggressive treatment is recommended, caution must be used to avoid over sedation causing hypoventilation. Anti-inflammatories may be used, though with caution. Patients with SCD have microvascular renal disease, even in the setting of normal creatinine due to chronic renal vasculopathy from SCD. Begin incentive spirometry on admission. It reduces splinting, increases tidal volume, and is an affective adjunct to pain medications in the treatment of ACS. Bronchodilators are indicated if wheezing is present. Supplemental oxygen is recommended only if patients are hypoxic. Administer antibiotics to cover for infection. Typically, a macrolide plus third generation cephalosporin are used. There is not, however, clear evidence for a specific antibiotic choice. Perform parenteral hydration. The goal of hydration in the treatment of ACS, or really any SCD complication, is to decrease plasma viscosity. Hypotonic solutions are preferred. Hydration is only indicated for patients with hypovolemia or examination findings suggesting dehydration. Hypotonic solutions create an osmotic gradient that allows fluid to be taken up by the RBCs, rehydrating the RBCs, and reducing sickling. D5 1/4 normal saline should be given at 1.0–1.5 times the maintenance rate. Avoid normal saline bolus, as it may precipitate ACS. Normal saline, or any normotonic/hypertonic IV fluid, can have the opposite effect, drawing fluids out of RBCs and worsening sickling, which may worsen ACS. Perform exchange transfusion. This transfusion method removes sickled cells while maintaining blood viscosity. Removing sickled cells reduces microvascular occlusion, whereas the transfusion of normal cells improves oxygen carrying capacity and reduces tissue hypoxia. It is thought to be lifesaving, but there is limited evidence on its efficacy.
- *Vaso-occlusive pain crisis*: Pain crisis is a common reason for a visit to the ED; patients are generally on outpatient pain medications and have written plans for treating pain exacerbations. Many patients may have developed a tolerance to opioids because of routine use and will require more aggressive treatment. Opioid medications are preferred. Morphine 0.1 mg/kg every 15–30 minutes. Hydromorphone 0.015 mg/kg every 15–30 minutes. Intranasal fentanyl 2 μg/kg may be a useful adjunct, especially in children. Ketamine 0.3 mg/kg may be a useful adjunct in opioid-tolerant patients. Use caution with anti-inflammatory drugs because of underlying renal dysfunction. Many patients know dosing regimens that work for them. Because of this, their requests for specific medications can be interpreted as drug seeking. Evidence has borne out that although some patients with SCD may be seeking opiates for elicit purposes, most are not. Supplemental oxygen and hydration are often not necessary. Supplemental oxygen is only needed if patients are hypoxic. IV hydration is not routinely needed. If indicated, oral hydration is preferred. Gentle IV hydration can be used if indicated. Avoid boluses if possible.

Ensure pain (i.e., chest pain, abdominal pain, and headache) is not a result of another pathologic process. Embolic disease patients are at much higher risk for embolic diseases, such as stroke, PE, and renal/splenic/hepatic infarction. Have a high index of suspicion when patients with SCD present with signs and symptoms concerning for any of these embolic pathology despite their age or lack of other risk factors. Treatment depends on the type of infarction and often involves routine care indicated for the specific condition; however, gentle hydration and exchange transfusion may be useful adjuncts in these cases as well.

SUMMARY

Sickle cell disease is one of the common genetic disorders. The most common reason for ED visits among these patients is acute painful episodes. A brief history about pattern of previous episodes is important. The emergency physician must be vigilant to look for other emergent conditions causing similar painful crisis and also conditions such as ACS, PE, and cerebrovascular accident (CVA) must be considered. Early and aggressive pain management and hydration are the key priorities in the ED (**Table 2**). Disposition has to be planned accordingly considering the individual patient's pain control and ruling out other conditions. Advice on discharge should include oral analgesics, regular ophthalmology consultation, vaccination, and antibiotic prophylaxis appropriate for splenectomies patients during invasive procedures like dental extraction. A good coordination with hematology and other outpatient teams is of utmost importance for follow-up and long-term management of patients with SCD.

TABLE 2: Summary of treatment options in sickle cell disease.

General	*Pain control*	*Adjuvants*	*Others*
• Bed rest • Hydration • Oxygen • Hydroxyurea • Deep breathing	• Paracetamol • NSAID • Morphine • Fentanyl	• Antibiotics • Transfusion • Splenectomy • Anxiolytics • Antiemetics • Laxatives	• 5-azacytidine • 5-deoxyazacytidine • IV dexamethasone • Bone marrow transplantation • Gene therapy • Combination of clotrimazole and magnesium • Poloxamer 188

(IV: intravenous; NSAID: nonsteroidal anti-inflammatory drug)

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Thrombotic Microangiopathies

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INTRODUCTION

Thrombocytopenia can be a life-threatening condition; it may be the first presentation of the patient's primary disease or an aggravated underlying disorder. When presented to the emergency, an emergency physician should have a strong clinical suspicion for thrombocytopenia evaluation, risk assessment and should warrant early diagnostic evaluation, stabilization, and admission for further observation.

Platelet production from the megakaryocyte in the bone marrow is stimulated by thrombopoietin. A single megakaryocyte produces about 5,000–10,000/mm^3 platelets in which two-thirds enter the circulation pool and release platelet-derived growth factor and chemotactic agents stimulating extracellular matrix formation and clot propagation in their 7–10-day lifespan. Clearance of platelets occurs in the liver and spleen.

Thrombocytopenia is defined as a platelet count of <150,000/mm^3. Clinically significant thrombocytopenia occurs when there is a drop in the platelet count to <100,000/mm^3 and bleeding occurs when the platelet count drops below 30,000/mm^3.

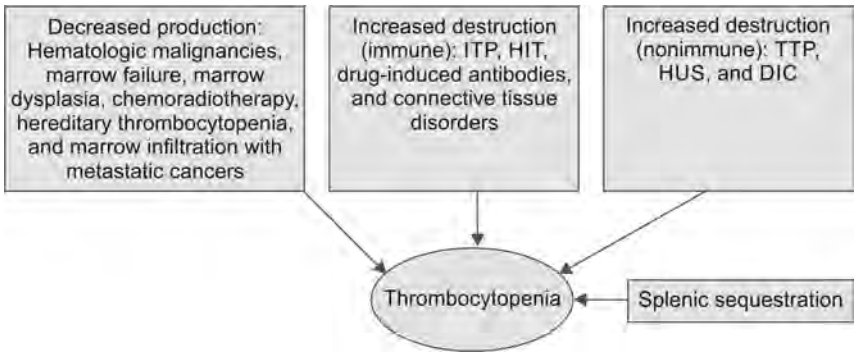
A sudden drop in the platelet count >50% even within the normal range should raise clinical suspicion and requires further evaluation.

Thrombocytopenia can result from three mechanisms; decreased production, splenic sequestration, and increased destruction as described in **Figure 1**. It is important for the emergency physician to be aware about important diagnostic clues (**Table 1**) for evaluation of the thrombocytopenia (**Flowchart 1**).

This chapter focuses on life-threatening diseases with thrombocytopenia as the underlying pathophysiology resulting predominantly from platelet destruction such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), idiopathic thrombocytopenic purpura (ITP), disseminated intravascular coagulation (DIC), hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, heparin-induced thrombocytopenia (HIT) evaluating their clinical presentations, differentials, stabilizations, management, and also approach to thrombocytopenia.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura is a systemic disease characterized by platelet aggregation into thrombi leading to occlusion of body's microvasculature. Both TTP and HUS

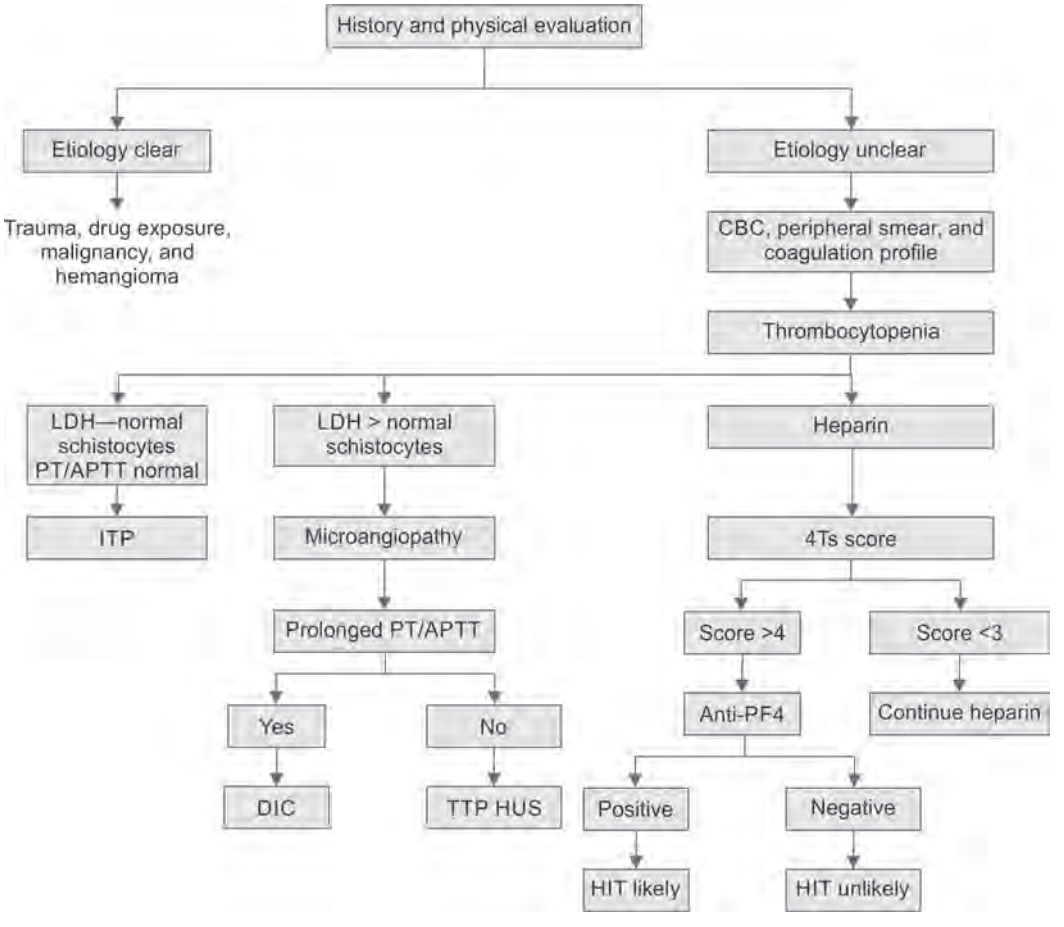

Decreased production: Hematologic malignancies, marrow failure, marrow dysplasia, chemoradiotherapy, hereditary thrombocytopenia, and marrow infiltration with metastatic cancers
Increased destruction (immune): ITP, HIT, drug-induced antibodies, and connective tissue disorders
Increased destruction (nonimmune): TTP, HUS, and DIC
Thrombocytopenia
Splenic sequestration

(DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia; HUS: hemolytic uremic syndrome; ITP: idiopathic thrombocytopenic purpura)

FIG. 1: Causes of thrombocytopenia.

TABLE 1: Diagnostic clues to thrombocytopenia.	
Clinical setting	***Differential diagnosis***
Cardiac surgery	CABG, HIT, TTP, and dilutional thrombocytopenia
Sepsis syndrome	DIC, pulmonary artery catheters, Sepsis, Hemophagocytic syndrome, and mechanical ventilation
Pulmonary failure	DIC, H1N1 infection, Hantavirus, Pulmonary Syndrome, and mechanical ventilation
Mental status changes	Seizures and ehrlichiosis
Renal failure	TTP, dengue, HIT, and DIC
Cardiac failure	HIT, drug induced, and pulmonary artery catheter
Postsurgery	Dilutional, drug induced, HIT, and TTP
Pregnancy	HELLP syndrome, fatty liver of pregnancy, and TTP/HUS
Acute liver failure	Splenic sequestration, HIT, drug induced, and DIC

(CABG: coronary artery bypass graft; DIC: disseminated intravascular coagulation; HELLP: hemolysis, elevated liver enzymes, and low platelet count; HIT: heparin-induced thrombocytopenia; HUS: hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura)



(APTT: activated partial thromboplastin time; CBC: complete blood count; DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia; HUS: hemolytic uremic syndrome; ITP: idiopathic thrombocytopenic purpura; LDH: lactate dehydrogenase; PF4: platelet factor 4; PT: prothrombin time; TTP: thrombotic thrombocytopenic purpura)

FLOWCHART 1: Thrombocytopenia evaluation.

are associated with platelet aggregation in the microvascular circulation mediated by von Willebrand factor (vWF) and microangiopathic hemolytic anemia which occurs from red blood cell (RBC) fragmentation during travel through the partially occluded arterioles and capillaries. TTP predominantly affects females over 40 years of age.

Causes

Idiopathic (most common), infections—human immunodeficiency virus (HIV), pregnancy, malignancy, bone marrow transplantation, drug therapy *[quinine, oral contraceptive (OC) pills, clopidogrel, ticlopidine, trimethoprim, pegylated*

interferon, and simvastatin], chemotherapy, Pancreatitis, Autoimmune disease *[systemic lupus erythematosus (SLE) and antiphospholipid syndrome].*

Pathophysiology

There are three pathophysiology processes give rise to TTP.

1. *Deficiency of ADAMTS-13*: ADAMTS-13 is produced by the hepatic stellate cells, glomerular podocytes and vascular endothelial cells. Normally regulates the cleaving of large vWF multimers into smaller proteins, the deficiency of which leads to accumulation of vWF which attracts and binds platelets.
2. *Accumulation of vWF,* which is an ultra-large multimers that can spontaneously aggregate platelets.
3. *Widespread platelet aggregation* leads to subsequent thrombi in the microvasculature and ultimately end-organ damage.

Clinical Features

Any patient presenting with a classic pentad of fever, hemolytic anemia, thrombocytopenia, renal impairment, and neurologic manifestations should be suspected for TTP.

- *Central nervous system (CNS)*: Headache, seizures, visual changes, and aphasia
- *Gastrointestinal (GI) symptoms*: Pain abdomen, nausea, vomiting, and diarrhea
- *Cardiovascular/respiratory*: Chest pain, dyspnea, and fever
- *Bleeding*: Hematuria, epistaxis, bruising, ecchymosis, petechiae, purpura, menorrhagia, and bleeding gum
- *End-organ damage*: Shearing of RBCs across the microthrombi produces the microangiopathic hemolytic anemia causing jaundice and dark-colored urine. Accumulation of microthrombi in the CNS, renal arterioles, and capillaries promotes tissue ischemia and necrosis with resultant end-organ damage such as seizures, stroke, focal neurological deficits, coma, and acute renal injury.

Diagnosis

Diagnosis is based mostly on the clinical presentation. Laboratory testing is aimed at assessing the degree of end-organ damage, ruling out other causes of thrombocytopenia and identifying an infectious or immune inciting event.

- *Complete blood count with peripheral smear*: Microangiopathic hemolytic anemia, thrombocytopenia, decreased hematocrit, and elevated reticulocyte count. Peripheral smear reveals schistocytes (fragmented RBCs due to the shear mechanism).
- *Complete metabolic panel with liver function tests*: Elevations in lactate dehydrogenase (LDH), serum K^+, and total bilirubin raises suspicions of hemolytic anemia due to release from fragmented RBCs. HUS presents with more severe renal impairment than TTP.
- *Coagulation profile [prothrombin time/partial thromboplastin time/international normalized ratio (PT/PTT/INR)]*: TTP can be distinguished from DIC by a normal coagulation profile.
- *Lactate dehydrogenase level*: Elevations in LDH should raise suspicions of hemolytic anemia and is a prognostic factor in TTP.
- *Decreased haptoglobin, increased free hemoglobin, and hemoglobinuria are suggestive of intravascular hemolysis.*
- Elevated troponin levels in acute idiopathic TTP are due to end-organ damage caused by thrombosis of coronary vasculature.
- *Other tests*: Direct Coombs test, urine pregnancy test, complete urine examination, HIV, hepatitis (A, B, and C), thyroid function tests, autoimmune screening, blood cultures, and type and screen for plasma exchange therapy (PET).

Management of Thrombotic Thrombocytopenic Purpura

Primary Treatment is Plasma Exchange Therapy

Plasma exchange therapy replaces the ADAMTS-13, removes the causative antibody and achieves a normal platelet count. Plasmapheresis is performed daily at 40 mL/kg or 1–1.5 times a patient's plasma volume and then either tapered to an alternate day plasmapheresis or stopped once normal counts are reached for 2–3 consecutive days and LDH levels are normalized. PET is more effective than PIT due to its ability to give very large volumes of fresh frozen plasma (FFP) and removal of inhibitory antibodies, disease remission, and all-cause mortality.

First-line Therapy

PET with FFP: 1–1.5 plasma volume exchanges per day with FFP (2 plasma volume exchanges in refractory cases).

Second-line Therapy

Fresh frozen PIT: FFP can be infused at 15–30 mL/kg.

Adjunctive Therapies to PET

Glucocorticoids**,** methylprednisolone 1 g/day, or prednisone 1 mg/kg/day. Rituximab in consultation with hematology at 375 mg/m^2 every week for 4 weeks.

Plasma Infusion Therapy

When PET is not available immediately, then plasma infusion therapy (PIT) can be used as a stop-gap measure and provides the required ADAMTS-13 activity, start plasma infusions at a rate of one unit every 4 hours. PIT leads to fluid overload and must be used with caution in renal and heart diseases. In patients with plasma allergy, consider factor VIII concentrates infusion containing ADAMTS-13 activity.

Cases of malignancy-induced TTP should be aimed at treating the underlying cause as PET/PIT is not beneficial. Discontinue the inciting drug in cases of drug-associated TTP. Platelet transfusions are considered only in cases of life-threatening bleeding as platelet transfusions may worsen the disease by causing accumulation of raw material leading to thrombosis in the microvasculature. Consider corticosteroids, rituximab, and cyclosporine in cases of autoimmune TTP with the advantage of reduction in relapses and refractory cases. If there are cases of TTP in pregnancy then consider early delivery in consultation with gynaecologist. Timely diagnosis and initiation of therapy is paramount to a favorable prognosis. Mortality is as high as 90% in untreated TTP whereas prompt recognition and initiation of treatment reduces the mortality

to as low as 20%. TTP relapse is defined as onset of a new case >30 days after completion of remission and seen in 20–50% of cases, most often within 2 years of the initial episode. Patients with ADAMTS-13 activity levels <10% are at increased risk for relapse.

HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia due to microvascular thrombosis, and renal failure. HUS is divided into typical and atypical HUS.

Typical HUS usually effects 1 week to 4 years age group and causative agents being Shiga toxin-producing *Escherichia coli* O157:H7 (most common), *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter*. Manifests as infectious bloody diarrhea and comes to medical attention with renal failure. Extrarenal manifestations include thrombocytopenia, neurological involvement as seizures, deranged liver function tests, and pancreatitis. Supportive treatment and dialysis are helpful. Recurrence is uncommon.

Atypical HUS effects older children and adults and is due to defective complement system activation. Causative agents include *Streptococcus pneumoniae*, Epstein–Barr virus (EBV), bone marrow transplantation, and chemotherapeutic agents and have a prominent extrarenal symptomatology without bloody diarrhea. Prognosis is worse for atypical HUS. Supportive treatment dialysis ± plasmapheresis is required. Recurrence is common.

Pathophysiology

Predominantly transmitted via food or water. Once ingested the virulent factors associated with Shiga toxin-producing *E. coli* O157:H7 allow invasion of intestinal epithelial cells, subsequent transmural migration, and produce the characteristic hemorrhagic colitis. Toxin-mediated microvascular injury promotes platelet aggregation and thrombus formation at the injury site.

Once absorbed into the systemic circulation, the Shiga toxin binds with receptors on the epithelial and endothelial cells of the glomerulus, renal tubules, colon, cerebrum, and the pancreas creating a vicious cycle of thrombosis and microangiopathic hemolytic anemia via shearing of RBCs over the microthrombi contributing to tissue ischemia and necrosis.

Clinical Features

Hemolytic uremic syndrome typically sets in 2–14 days after the diarrhea develops, so the patients present during the diarrheal phase of illness with abdominal cramps with or without bloody diarrhea and often without fever.

Laboratory Evaluation

For patients with bloody and nonbloody diarrhea, stool testing reveals inflammatory colitis. Electrolytes, urinalysis (RBC casts and protein), and renal function panels to detect nephropathy and associated dyselectrolytemia.

Management

Typical HUS is treated with supportive care and pain management with careful maintenance of fluid and electrolytes.

TABLE 2: Differentiating features between TTP and HUS.

	TTP	*HUS*
Clinical features	• Mostly nonspecific symptoms • Neurological features are common—aphasia, diplopia, and clumsiness • Minor purpura related to thrombocytopenia	• Bloody diarrhea, abdominal pain, nausea, and vomiting • Kidney injury is more common than TTP • Neurologic symptoms are less common than TTP
Lab findings	• Anemia, thrombocytopenia, and schistocytes on smear • Low ADAMTS-13 activity	Anemia, thrombocytopenia, schistocytes on smear, and inflammatory colitis
Treatment	Urgent plasma exchange	• Typical HUS (Shiga toxin associated) supportive care Atypical HUS (complement associated), PET, and eculizumab (anticomplement therapy) • PET, and eculizumab (anticomplement therapy)

(HUS: hemolytic uremic syndrome; PET: positron emission tomography; TTP: thrombotic thrombocytopenic purpura)

Control the hypertension with nifedipine and nicardipine. RBC or platelet transfusion is required in cases of significant anemia or profound thrombocytopenia. Hemodialysis when clinically indicated. Severe extrarenal manifestations can be treated with plasma exchange. Antimotility agents and antibiotics are contraindicated as they increase the risk of HUS by increasing Shiga toxin expression from the bacteria. Atypical HUS is often hard to distinguish from TTP and should be treated as a close TTP variant with PET therapy. Eculizumab (C5 inhibitor) is being used in atypical HUS and reduces the incidence of renal failure. Typical HUS is associated with acute renal failure in 55–70% of patients and almost 85% of the patients have recovered kidney function. Mortality in typical HUS is about 5–15%. Atypical HUS has a poor outcome and is associated with permanent renal failure and neurologic damage.

It is often difficult to differentiate atypical HUS from TTP (**Table 2**) in emergency setting. If any one of diagnoses is considered a team of hematologist, nephrologist, neurologist critical care blood bank team should be involved in managing the critically ill patient.

IMMUNE THROMBOCYTOPENIC PURPURA

Immune thrombocytopenic purpura is an acquired immune-mediated syndrome characterized by thrombocytopenia and bleeding tendencies, despite which the circulating platelets are functional. ITP is characterized by antiplatelet antibodies to platelet surface glycoprotein IIb/IIIa ultimately resulting in

peripheral platelet destruction. Idiopathic with no underlying cause termed as *primary ITP* while *secondary ITP* is associated with underlying cause or medication induced. Primary ITP further subdivide to acute ITP (duration of illness 3 months) and chronic illness (>12 months). This process is likely to be multifactorial whereby a genetic predisposition causes an alteration in the immune response and peripheral tolerance. The immunoglobulin G (IgG) autoantibodies from the patient's B-lymphocytes directed against the platelet membrane glycoprotein IIb/IIIa cause peripheral platelet destruction and inhibition of megakaryocyte platelet production ultimately leading to thrombocytopenia.

Causes

Causes of ITP are as follows:

- *Medications*: Acetaminophen, acetazolamide, allopurinol, amiodarone, ampicillin, aspirin, carbamazepine, cephalexin, chlorothiazide, chlorpheniramine, cimetidine, diazepam, digoxin, diphenylhydantoin, furosemide, gentamicin, heparin, lidocaine, methicillin, methyldopa, minoxidil, morphine, penicillin, phenylbutazone, procainamide, quinidine, quinine, ranitidine, rifampin, spironolactone, tricyclic, antidepressants, trimethoprim-sulfamethoxazole, valproic acid, and vancomycin
- *Underlying conditions*: Live vaccinations (i.e., mumps, measles, and rubella), *Helicobacter pylori*, *Cytomegalovirus*, hepatitis C virus (HCV), HIV, antiphospholipid syndrome, SLE, Evans syndrome, posthematopoietic cell transplantation, chronic lymphocytic leukemia, and low-grade lymphoproliferative disorders

Clinical Presentation

Mucocutaneous bleeding is the most common clinical presentation. Epistaxis and gingival bleeding and menorrhagia in childbearing women are other presentations. Petechial or purpuric rashes in the dependent lower extremities and areas of constriction, receding in crops over days. Chronic ITP patients present as paradoxical thrombosis. Otherwise normal physical examination except for bruises and petechiae.

Laboratory Workup

Complete blood count reveals anemia, thrombocytopenia, and large well-granulated platelets on peripheral smear. Rh testing for treatment with anti-Rh(D). Direct Coombs test to exclude concurrent autoimmune hemolytic anemia. Hepatitis C and HIV testing to rule out secondary causes of ITP. Bone marrow evaluation in complex/atypical cases/elderly (>60 years)/those with diagnostic uncertainty.

Diagnosis

No definitive diagnostic test for ITP exists and the diagnosis is primarily by exclusion of an underlying cause and is characterized by isolated thrombocytopenia.

Management

Goal of therapy is to treat symptomatic bleeding and maintain platelet count >30,000/mm^3. Life-threatening bleeding with a platelet count <30,000/mm^3 where there is an urgent need to achieve hemostasis, administer IV corticosteroids and IV immunoglobulins concomitantly and repeat platelet transfusions until hemostasis is achieved. Consider emergent splenectomy when other treatment options have exhausted. Treatment strategies are summarized in **Table 3**.

Complications

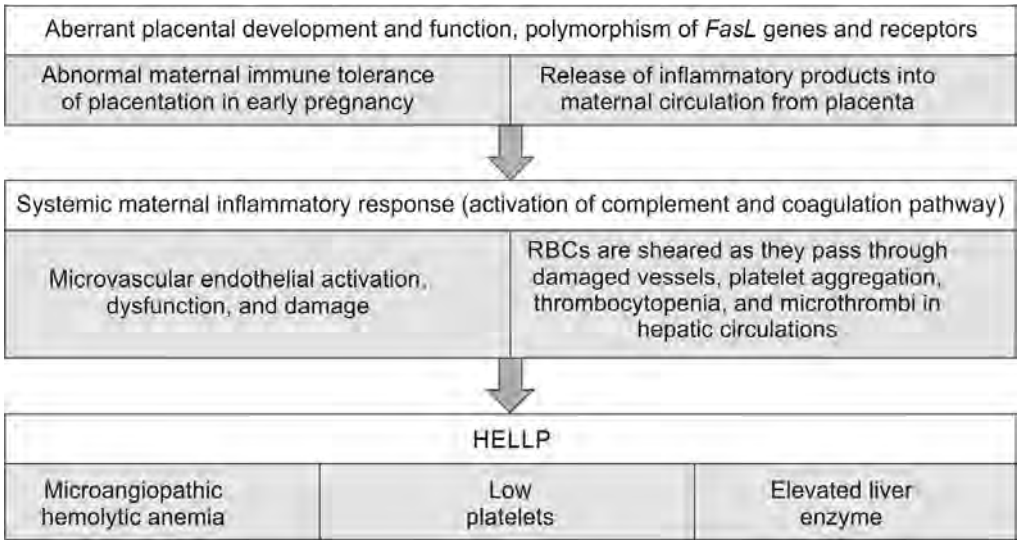
Life-threatening spontaneous bleeding [intracerebral (IC) bleed and GI bleed] are more significant with a platelet count <10,000/mm^3. Hypotension, transfusion reactions, transient neutropenia, acute kidney injury, infection, and aseptic meningitis with intravenous immunoglobulin (IVIG) infusion are other complications. Mortality from hemorrhage is approximately 1% in children and 5% in adults. Patients with bleeding tendencies and with moderate-to-severe thrombocytopenia need to be admitted for close monitoring and initiation of therapy. Patients with new-onset thrombocytopenia and those with poor patient follow-up need to be considered for admission to determine the clinical course and platelet trends. Asymptomatic patients with platelet counts >30,000/mm^3 can be considered for outpatient management.

HELLP SYNDROME

HELLP stands for hemolysis, elevated liver enzymes, and low platelet count and describes a variant of preeclampsia. Presents in pregnancy after 20 weeks of gestation and can be life-threatening. Family history, advanced maternal age, and

TABLE 3: Treatment of idiopathic thrombocytopenic purpura (ITP) with life-threatening bleed and thrombocytopenia.

First line: Corticosteroids are the first line of treatment for primary ITP	*Second line: Monoclonal antibodies*	*Third line: Thrombopoiesis stimulating agents*
• Prednisolone 1 mg/kg daily for 4–6 weeks and taper after obtaining response (or) • Dexamethasone 40 mg/day PO/IV for 4 days (or) • Methylprednisolone 30 mg/kg IV with rapid taper every third day to 1 mg/kg daily • Response to corticosteroids occurs in 4–14 days and peaks at 7–28 days • IVIG 1 g/kg daily for 1–2 days, response occurs at 1–3 days and peaks at 2–7 days • Single dose anti-Rh(D) 50–75 µg/kg IV in Rh(+)ve patients and have not undergone splenectomy • Platelet transfusion if bleeding actively	• Rituximab 375 mg/m^2/week for 4 weeks, which acts by blunting the autoimmune destruction of platelets • Splenectomy	• Thrombopoietin mimetics and thrombopoietin receptor agonists such as romiplostim and eltrombopag to stimulate platelet production • Cyclophosphamide, cyclosporine, azathioprine, eltrombopag, romiplostim, and vincristine


Aberrant placental development and function, polymorphism of FasL genes and receptors
Abnormal maternal immune tolerance of placentation in early pregnancy
Release of inflammatory products into maternal circulation from placenta
Systemic maternal inflammatory response (activation of complement and coagulation pathway)
Microvascular endothelial activation, dysfunction, and damage
RBCs are sheared as they pass through damaged vessels, platelet aggregation, thrombocytopenia, and microthrombi in hepatic circulations
HELLP
Microangiopathic hemolytic anemia
Low platelets
Elevated liver enzyme

(HELLP: hemolysis, elevated liver enzymes, and low platelet count; RBCs: red blood cells)

FIG. 2: Pathophysiologic mechanism of HELLP.

past pregnancy with preeclampsia are few risk factors for HELLP syndrome. Pathophysiologic mechanism of HELLP is summarized in **Figure 2**.

Patient presents with complaints of right upper quadrant abdominal pain, headache, blurred vision, nausea, vomiting, malaise, and flu-like symptoms. On examination, weight gain, edema, hypertension, mucosal bleeding, hematuria, and petechiae/purpura are the findings. Since HELLP syndrome is common in pregnancy and gives rise to various complications as follows:

- *Maternal complication:* Placental abruption, DIC, renal failure, pulmonary edema, liver hematoma, liver failure, severe ascites, cerebral edema, and cerebral hemorrhage.
- *Neonatal complications:* Perinatal death, preterm delivery, thrombocytopenia, intraventricular hemorrhage, respiratory distress syndrome (RDS), patent ductus arteriosus, and bronchopulmonary dysplasia.

HELLP syndrome should be differentiated from *conditions related to pregnancy* such as acute fatty liver of pregnancy and benign thrombocytopenia of pregnancy; *hepatobiliary conditions* such as hepatitis, cholangitis, cholecystitis, pancreatitis; and *other platelets disorders* such as ITP, TTP, HUS, SLE, antiphospholipid antibody (APLA), hemorrhagic, or septic shock.

Diagnostic Workup

The first sign of HELLP is a decrease in the platelet count followed by abnormal liver function test. *Complete blood count* reveals anemia, decrease in hematocrit, platelets <100,000 µL/mL, increased reticulocyte count, decreased haptoglobin due to marrow release of immature cells, and hemolysis.

- *Peripheral smear:* Hemolysis, schistocytes, and burr cells
- *Liver function test*: Unconjugated bilirubin > 1.2 mg/dL, aspartate aminotransferase (AST) >70 IU/L, LDH > 600 IU/L or more than two times the upper limit of the normal
- *Renal function test*: Increased serum levels of creatinine and uric acid due to glomerular endotheliosis and impaired renal tubular secretion
- *Imaging:* Subcapsular liver hematoma or frank liver rupture

Management

Definitive treatment of HELLP syndrome is the delivery of the baby. Seizure prophylaxis and blood pressure (BP) control are among the first-line agents in the management of HELLP syndrome.

Seizure management—$MgSO_4$: Loading dose 4–6 g IV over 20 minutes followed by continuous infusion of 2 g/h to be continued for 24 hours after delivery. *BP control*: Target systolic blood pressure (SBP) < 160 mm Hg or diastolic blood pressure (DBP) < 105 mm Hg. *Hydralazine*: 5 mg IV every 15 minutes up to a maximum dose of 20 mg/h (or) labetalol 20–40 mg IV every 15 minutes up to a maximum dose of 240 mg/h.

Corticosteroids are considered beneficial in thrombocytopenia as they decrease the inflammatory response that leads to platelet activation, aggregation, destruction, and improve neonatal outcomes accelerating fetal lung maturity. Betamethasone: 12 mg IM every 12th hourly (or) dexamethasone: 12 mg IV every 12th hourly. Any patient seen in the emergency department suspected of HELLP syndrome requires consultation with obstetrics and admission for an extended period of observation with repeated laboratory evaluation and fetal monitoring and delivery.

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation is an acquired, systemic process of overstimulation of the coagulation pathway resulting in thrombosis followed by consumption of platelets and coagulation factors with concomitant activation of fibrinolytic system resulting in breakdown of fibrin clots and subsequent bleeding. DIC can be classified into acute and chronic. Acute and decompensated DIC when the generation of clotting factors cannot match the excessive consumption. Chronic and compensated DIC when the generation of clotting factors matches the consumption. Precipitating factors which may give rise to DIC are summarized in **Table 4**.

TABLE 4: Precipitating factors of DIC.

Conditions	*Comments*
Infection (bacterial, viral, and fungal)	Most common cause, endotoxins stimulate monocytes and endothelial cells to express tissue factor
Carcinoma, adenocarcinoma, and lymphoma	Malignant cells cause endothelial damage and allow expression of tissue factor
Acute leukemia	DIC is common with promyelocytic leukemia, blast cells release procoagulant enzymes
Trauma	DIC with brain injury, crush injury, burns, hypothermia, hyperthermia, rhabdomyolysis, fat embolism, and hypoxia
Organ injury: Liver disease and pancreatitis	• Acute DIC can occur in setting of acute hepatic failure, tissue factor is released from the injured hepatocytes • Pancreatitis can activate the coagulation cascade
Pregnancy	Placental abruption, amniotic fluid embolus, septic abortion, and IUFD
Vascular disease	Large aortic aneurysms, giant hemangiomas, vasculitis, and multiple telangiectasias
Envenomation	Venom damages the endothelial cells
Acute lung injury (ALI) or ARDS	Microthrombi are deposited in the small pulmonary vessels and patients develop acute lung injury
Transfusion reactions, such as acute hemolytic reaction	DIC with severe bleeding, shock, and acute renal failure

(ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; IUFD: intrauterine fetal demise)

Pathophysiology

The precipitating factors causing widespread activation of intrinsic coagulant pathway lead to marked imbalance between procoagulant and anticoagulant processes resulting in unopposed thrombin generation and diffuse fibrin clot formation and intravascular deposition with subsequent microvascular occlusion and tissue hypoxia ultimately leading to multiple organ death syndromes as described in **Flowchart 2**. Production of thrombin and fibrin indirectly activates tissue plasminogen activator and counter-regulatory fibrinolytic system. When hyperfibrinolysis occurs, the hemostatic clots dissolve and bleeding ensues. Bleeding is due to a combination of factor depletion, platelet dysfunction, thrombocytopenia, and excessive fibrinolysis.

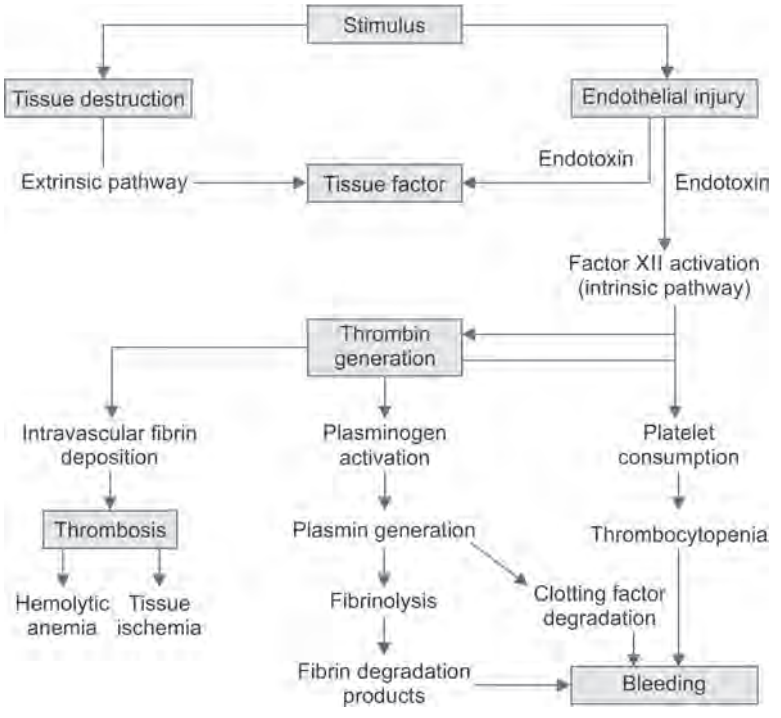
Clinical Presentation

A clinical suspicion for DIC is paramount in establishing the diagnosis. Rapid onset of bleeding from more than three unrelated sites is highly suggestive of DIC.

- *End-organ damage*: Cutaneous gangrene, thrombotic purpura, and purpura fulminans
- *Bleeding*: Petechiae, ecchymosis, GI bleed, and intracranial bleed
- *Nervous system*: Headache, delirium, neurologic deficits, and coma
- *Multiorgan involvement*: Acute renal failure, acute RDS, liver failure, and shock
- *Thromboembolism:* Venous, arterial, and nonbacterial thrombotic endocarditis

Laboratory Evaluation

A compatible underlying condition and laboratory studies (**Table 5**) consistent with increased activation of coagulation and thrombin generation [elevated PT, activated partial thromboplastin time (APTT), fibrin degradation product (FDP),



FLOWCHART 2: Pathophysiology of disseminated intravascular coagulation (DIC).

TABLE 5: Laboratory abnormalities in DIC.

Platelet count	*Usually low or dropping*
Prothrombin time	Prolonged
Fibrinogen < 100 mg/dL	Correlates with severe DIC
FDPs and D-dimer	Elevated
APTT	Usually prolonged
Thrombin clotting time	Prolonged
Fragmented blood cells	Should be present
Factor II, V, VII, and IX	Low

(APTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulation; FDPs: fibrin degradation products)

and D-dimer] and excessive fibrinolysis (decreased fibrinogen, antithrombin III, and platelets). International scoring system (**Table 6**) is helpful for the diagnosis and severity of DIC. Patient must be screened with a DIC screening panel composed of PT, APTT, platelet count, fibrinogen, and D-dimer.

Differential Diagnosis

Disseminated intravascular coagulation should be differentiated from *primary fibrinolysis*—a rare syndrome where fibrinolysis occurs without the production of thrombin and *severe liver disease.* D-dimer assay is normal or minimally elevated in both primary fibrinolysis and liver disease but significantly elevated in DIC.

Treatment

Identification and treatment of underlying disorder that is driving the thrombin generation is the hallmark for the management of DIC. Treat the precipitating disorder: volume resuscitation, antibiotics, and external cooling. Guidelines for transfusion of various blood products described in **Box 1**. Acute DIC requires admission, aggressive resuscitation, and treatment of underlying cause. DIC from sepsis has a significantly higher death rate than DIC associated with trauma.

Prognosis is poor and mortality is 50%. Approach to DIC is summarized in **Flowchart 3**.

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia is a syndrome that occurs due to the formation of IgG or IgM autoantibodies directed against the heparin-platelet factor 4 complex that activates platelets producing thrombocytopenia and a tendency for thrombosis. Type I is a benign nonimmune mediated and Type II is a life-threatening. Incidence of HIT is influenced by the heparin preparation used, dose, patient characteristics, and increases with the duration of heparin exposure (heparin treatment for >4 days, incidence is 15% and treatment <4 days, incidence is 0.2%). Frequency of HIT is less with low-molecular-weight heparin (LMWH) (1%) when compared to unfractionated heparin (UFH) (1–5%). HIT can be predicted by using the 4Ts score described in **Table 7**.

TABLE 6: International Society on Thrombosis and Hemostasis scoring system for diagnosis of DIC.

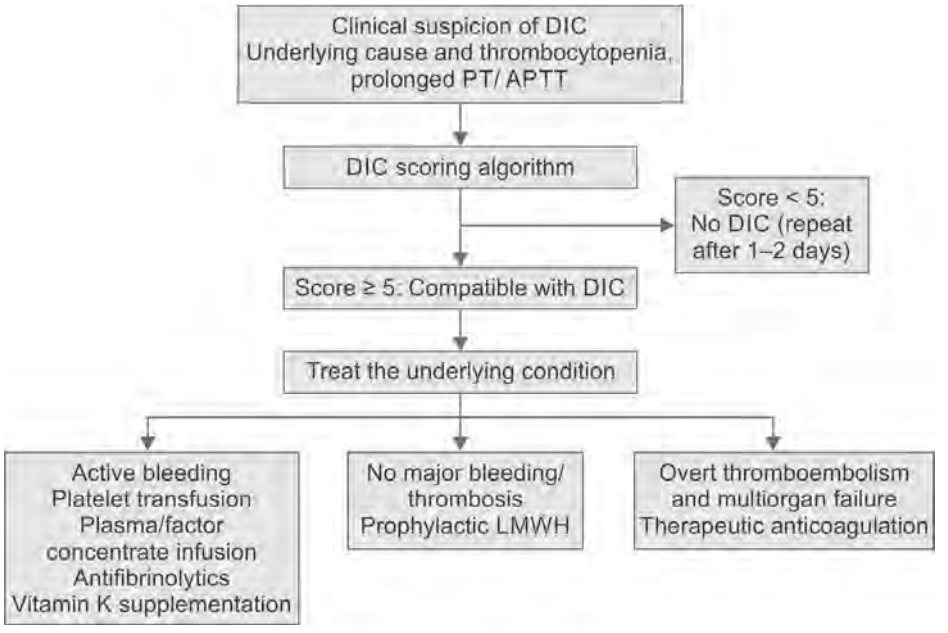
Tests	*Points*
Platelet count	
• >100,000/mm^3	0
• 50,000–100,000/mm^3	1
• <50,000/mm^3	2
Fibrin markers (D-dimer and FDPs)	
• Normal	0
• Mildly elevated	2
• Markedly elevated	3
Prothrombin time prolongation	
• <3 seconds	0
• 3–6 seconds	1
• >6 seconds	2
Fibrinogen level	
• >100 mg/dL	0
• <100 mg/dL	1
• A score of ≥ 5 is compatible with overt DIC	
• A score of <5 is suggestive of nonovert DIC	
• Higher scores correlate with a higher 28-day mortality	

(DIC: disseminated intravascular coagulation; FDPs: fibrin degradation products)

BOX 1: Guidelines for transfusion of various blood products in patients at high risk of bleeding.

- Consider platelet transfusion when there is a high risk of spontaneous bleeding (platelet count <20,000/mm^3) or active bleeding. Platelets <50,000/μL, give platelet concentrates or one unit of SDPs
- Fibrinogen 80–100 mg/dL, give 10 units of cryoprecipitate. Transfuse FFP/cryoprecipitate when fibrinogen level < 100 mg/dL
- Hematocrit below 30%, give red cells
- Prothrombin time more than twofold the upper limit of normal and APTT abnormal, give two to four units of FFP. Vitamin K for prolonged PT
- When risk of hypervolemia due to FFP administration, consider prothrombin complex concentrates
- In case of thromboembolic disease, retained products of conception, purpura fulminans consider heparin/LMWH as it augments antithrombin III activity and prevents conversion of fibrinogen to fibrin
- Consider tranexamic acid for trauma-related DIC

(APTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulation; FFP: fresh frozen plasma; LMWH: low-molecular-weight heparin; PT: prothrombin time; SDPs: single donor platelets)



(DIC: disseminated intravascular coagulation; LMWH: low-molecular-weight heparin)

FLOWCHART 3: Approach to DIC.

TABLE 7: Prediction (4Ts score) for heparin-induced thrombocytopenia (HIT).

Points	***2***	***1***	***0***
Thrombo-cytopenia	>50% fall from the baseline and 20–100 × 10^9/L	30–50% fall or 10–19 × 10^9/L	<30% fall or <10 × 10^9/L
Timing of platelet fall	Onset within 10 days of heparin	Counts fall after day 10	Counts fall <5 days and no recent heparin
Thrombosis	New thrombosis or skin necrosis	Progressive or recurrent thrombosis	None
Other cause for thrombo-cytopenia	None	Possible	Definite

Test score high probability: score 6–8; intermediate probability: score 4–5; low probability: score 0–3. Patients with a low probability score are very unlikely to have HIT and can forgo PF4-heparin antibody testing and empiric therapy. Patients with intermediate and high scores should receive empiric therapy until definitive testing can be obtained.

Patients are often asymptomatic with unexplained thrombocytopenia. One of the earliest clues is an anaphylactoid reaction such as fever, chills, hypertension, tachycardia, dyspnea, and chest pain within 30 minutes of receiving an IV bolus of heparin and should be evaluated for HIT. Paradoxical venous thrombosis with thrombocytopenia involving the skin (cutaneous necrosis), major arteries (ischemic limbs), and veins (recurrent venous thrombosis or pulmonary embolism).

Diagnosis is confirmed by history of heparin exposure and unexplained thrombocytopenia. HIT should be suspected when there is a sudden onset of thrombocytopenia with either at least 50% drop in the platelet count from the baseline or platelet count falling to < 100 × 10^9/L in patients receiving heparin in any form. Baseline platelet count to be obtained, repeated at 24 hours and every 2–3 days during treatment with heparin. Serotonin release assay is gold standard which is a platelet aggregation assay. Enzyme-linked immunosorbent assay (ELISA) immunoassay detects anti-heparin PF4 antibodies.

Treatment

First step in the therapy of HIT consists of discontinuing all forms of heparin including heparin-bonded catheters, heparin IV locks, and heparin flushes. Consider platelet transfusion only in case of life-threatening bleeding due to risk of perpetuating thrombus. Transition to warfarin or thrombin specific inhibitors such as dabigatran (Pradaxa) or rivaroxaban (Xarelto) should be made once the patient is stabilized and the platelet counts are >150,000/mm^3.

The platelet counts return to normal within 4–6 days of discontinuing heparin. Protamine is not effective against the immune mediated response. Treatment of HIT is summarized in **Box 2**.

SUMMARY

Thrombotic microangiopathies (TTP, HUS, HELLP, ITP, HIT, and DIC) are life-threatening conditions and emergency physician should be aware of their clinical feature and management strategies to recognize these conditions in early stage so that life-saving treatment can be initiated in emergency department. Thrombotic microangiopathies are summarized in **Table 8.**

BOX 2: Treatment of heparin-induced thrombocytopenia (HIT).

***Argatroban*:**

A synthetic thrombin inhibitor

- Initial dose of 2 µg/kg/min adjusted to an APTT of 1.5–3 times normal
- In severe liver disease at 0.5 µg/kg/min adjusted to an APTT of 1.5–3 times normal
- In MODS at 1 µg/kg/min adjusted to an APTT of 1.5–3 times normal
- Post-CABG 0.5–1 µg/kg/min adjusted to an APTT of 1.5–3 times normal
- Indications: Prevention and treatment of thrombosis in HIT

***Bivalirudin*:**

Semisynthetic direct thrombin inhibitor

- Bolus: 1 mg/kg
- Infusion: 2.5 mg/kg/h for 4 hours and then 0.2 mg/kg/h for 14–20 hours
- Renal adjustments:
  - For creatinine clearance of 30–59 mL/min, decrease dose by 20%
  - For creatinine clearance of 10–29 mL/min, decrease dose by 60%
  - For creatinine clearance of <10 mg/min, decrease dose by 90%

Indications: Percutaneous coronary intervention in patients with or without HIT

***Lepirudin*:**

Direct inhibitor of thrombin: Initial IV bolus of 0.4 mg/kg IV bolus

- Continuous infusion: Initial rate determined by renal function
- GFR > 60 mL/min: 0.10 mg/kg/h, GFR 45–60 mL/min: 0.075 mg/kg/h
- GFR < 45 mL/min: Lepirudin not recommended (consider argatroban)

***Fondaparinux*:**

Indirect anti-Xa inhibitor

- 7.5 mg every 24 hours (consider 5 mg in patients under 50 kg and 10 mg in patients over 100 kg)
- *Perform APTT at 4-hour interval until steady state within the therapeutic range (1.5–2 times patient baseline APTT is achieved)*

(APTT: activated partial thromboplastin time; CABG: coronary artery bypass graft; GFR: glomerular filtration rate; MODS: multiple organ dysfunction syndrome)

TABLE 8: Summary of thrombotic microangiopathies.

	TTP	*HUS*	*ITP*	*DIC*	*HELLP*	*HIT*
Pathogenesis	ADAMTS-13 deficiency	• Typical HUS: Shiga toxin-producing bacteria • Atypical HUS: Defective complement activation and regulation	Immune-mediated platelet destruction and inhibition of production	Activation of coagulation cascade with thrombin production	Unknown	Antibodies destroy heparin platelet factor 4 complex
Features	MAHA with thrombocytopenia No other cause	Same as TTP + renal failure, predominantly effects children with diarrhea, and renal failure	Isolated thrombocytopenia with normal smear	Consumptive coagulopathy due to an underlying pathologic abnormality	MAHA with elevated liver enzymes and low platelets associated with pregnancy	Drug exposure, immune-mediated thrombocytopenia, and thrombosis
Laboratory	• CBC with peripheral smear: Thrombocytopenia, anemia, and red cell fragmentation • LDH: Elevated	Stool: Shiga toxin-producing *Escherichia coli*	• CBC with smear: Isolated thrombocytopenia, no red cell fragmentation • Diagnosis of exclusion	CBC with smear: Thrombocytopenia, anemia, red cell fragmentation, elevated PT and APTT, D-dimer, decreased fibrinogen	• CBC with smear: Thrombocytopenia, anemia, red cell fragmentation • Increased AST or ALT • Positive UPT	CBC with smear: Isolated thrombocytopenia with a >50% decrease in the platelet count in first 5–10 days of initiation of heparin

Continued

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	TTP	*HUS*	*ITP*	*DIC*	*HELLP*	*HIT*
Treatment	• Plasma exchange therapy • Glucocorticoids • Prednisolone or methyl-prednisolone	• Typical HUS: Supportive care • Atypical HUS: Treat like TTP	• Methylpred-nisolone or prednisone • IVIG • Platelet transfusion or splenectomy	• Treat underlying cause • Administer platelets/FFP/ cryoprecipitate in serious bleeding	• BP control (labetalol or hydralazine) • Prevent seizures ($MgSO_4$) • Definitive care is delivery of fetus	Discontinuation of heparin and anticoagulation with nonheparin containing anticoagulant

(APTT: activated partial thromboplastin time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BP: blood pressure; CBC: complete blood count; DIC: disseminated intravascular coagulation; FFP: fresh frozen plasma; HELLP: hemolysis, elevated liver enzymes, and low platelet count; HIT: heparin-induced thrombocytopenia; HUS: hemolytic uremic syndrome; ITP: idiopathic thrombocytopenic purpura; IVIG: intravenous immunoglobulin; LDH: lactate dehydrogenase; MAHA: microangiopathic hemolytic anemia; PT: prothrombin time; TTP: Thrombotic thrombocytopenic purpura; UPT: urine pregnancy test)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Approach to Skin Diseases in Emergency

Ramanjit Singh, Nidhi R Sharma

INTRODUCTION

Dermatology is considered to be primarily an outpatient specialty. Dermatological diseases account for 8–20% of the patients visiting emergency outpatient department globally. This chapter will help in recognizing dermatological emergencies because recognition of specific skin signs, early diagnosis, hospitalization, monitoring, and multidisciplinary care can reduce associated morbidity and mortality. Proper history taking and examination is an important part to start while approaching a dermatology patient in an emergency department (ED).

HISTORY TAKING

- Onset and duration of the disease
- *Nature of spread*: Generalized or is it localized
- Asymptomatic or associated with symptoms such as pain, itching, and burning sensation
- Associated complaints such as fever, joint pain, and oral ulcers
- First episode or recurrence nature of it
- Any aggravating or relieving factor
- Similar complaints in family or close contacts
- *Triggering factors*: Drug intake, vaccination, excessive sunlight exposure, food, and chemical exposure
- Prior history of travel
- Previous history of drug or food allergies or any chronic disease
- Treatment history or any investigations done specifically skin biopsy of the skin condition patient has landed into ED

EXAMINATION OF THE PATIENT

It can be divided into two parts—general and systemic examination and dermatological examination.

General and Systemic Examination

It is similar to general and systemic examination like in other patients presenting in ED. Check for patient's vital signs and symptoms to rule out sepsis or anaphylaxis. Systemic examination should be done to rule out respiratory disease/cardiovascular/neurological/gastrointestinal involvement, involvement of lymph nodes along with pallor, icterus, clubbing, and cyanosis should be checked, and check for joint involvement.

Dermatological Examination

The clinical diagnosis of skin diseases is accomplished by understanding the morphology of the lesion along with distribution, color, arrangement, and body site. Thorough examination of rash should be done after undressing the patient in a proper light. A small magnifying lens can be used for better visualization. Inspect all skin and mucous membranes including hair, nail, scalp, and mucous membranes. Palpation of the skin augments the visual clues. Lesions should be palpated after wearing the gloves to see the texture of the lesion, if it is blanching or it bleeds on touch. Skin lesions can be classified into two types:

1. *Primary skin lesion*: It is the initial lesion, occurring early in a disease that has not been altered by trauma, manipulation, medication, secondary infection, or natural regression.
2. *Secondary skin lesion*: This is a lesion that arises later during the course of a disease or is created by scratching or secondary infection.

Tables 1 to **3** depict the basic morphology of primary, secondary, and special lesions. **Table 1** summarizes the primary skin lesions and **Table 2** summarizes secondary skin lesion.

DIAGNOSTIC TESTS

Simple diagnostic tests and cytology can aid in the rapid and reliable diagnosis or to rule the disease:

- KOH mount can diagnose fungus and molluscum contagiosum.
- Gram stain can aid in diagnosis of the type of bacterial infection.
- Tzanck smear will diagnose herpes or acantholytic cells (in case of blistering disease).

- Skin scrapings can help in diagnosing of mites such as scabies and pediculosis.
- Woods light or lamp produces invisible long wave ultraviolet radiation. It is a quickest technique for diagnosing erythrasma due to *Corynebacterium* infection (coral red fluorescence), fungal infection due to *Malassezia* infection (dull yellow fluorescence), *Pseudomonas* infection (yellow/green fluorescence), and porphyria cutanea tarda (orange/red color and urine fluorescence).
- Serological test to rule out syphilis [venereal disease research laboratory/treponema pallidum hemagglutination (VDRL/TPHA)], systemic lupus erythematous, and acquired human immune deficiency virus.

TABLE 1: Primary skin lesions. ***(For color version, see plate 19 to 21)***

S. No.	*Type of lesion*	*Description*	*Example*
1.	Macule	A circumscribed area of skin or mucous membrane different in color or texture from its neighboring tissue, measuring <1 cm in diameter.	
2.	Patch	A circumscribed area of skin or mucous membrane different in color or texture from its neighboring tissue, measuring >1 cm in diameter.	
3.	Papule	A small solid, elevation of the skin <1 cm in diameter.	

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S. No.	Type of lesion	Description	Example
4.	Plaque	A solid elevated area of skin >1 cm in diameter, where the horizontal dimensions are more than vertical.	
5.	Nodule	A solid elevated area of skin >1 cm in diameter, which can be observed as an elevation or can be palpated.	
6.	Vesicle	A circumscribed elevated area of skin <1 cm in diameter, containing fluid other than pus.	
7.	Bulla	A circumscribed elevated lesion of >1 cm in diameter containing free fluid other than pus.	

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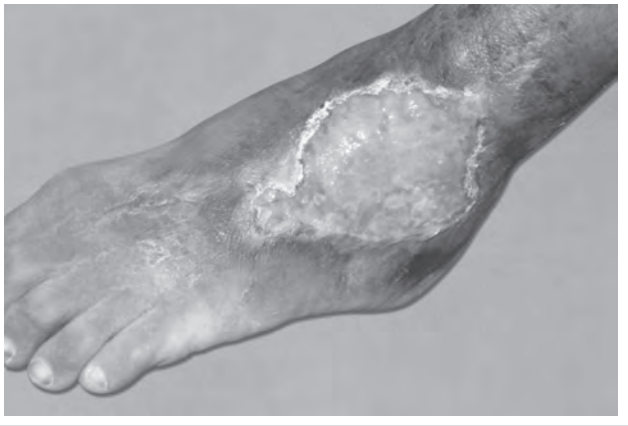
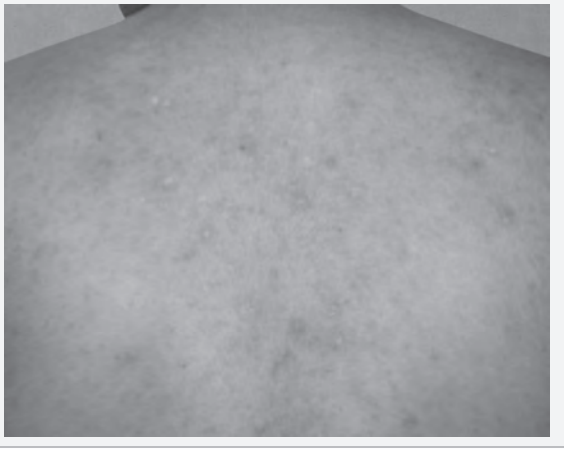
S. No.	Type of lesion	Description	Example
8.	Pustule	A circumscribed area of the skin of any size containing visible purulent exudate.	
9.	Cyst	A closed cavity or sac with an epithelial, endothelial, or membranous lining, containing fluid or semisolid material.	
10.	Wheal	An elevated, evanescent compressible area due to dermal edema. It is pale and often surrounded by a dermal flare.	

- Skin biopsy is indicated in case of doubtful cases which cannot be confirmed by clinical examination.
- Complete panel of relevant investigations need to be performed to rule out systemic involvement.

Few pointers to aid in diagnosis: Fever with leukocytosis is mostly seen in cases of infection or autoimmune disease. Drug rashes may have elevated transaminases along with eosinophilia in drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Thrombocytopenia along with disseminated intravascular coagulation (DIC) and acute kidney disease may be indicative of bacteremia/toxic shock syndrome.

TABLE 2: Secondary skin lesion. ***(For color version, see plate 22 and 23)***

S. No.	*Type of lesion*	*Description*	*Example*
1.	Erosion	Loss of whole or part of the epidermis, but with the dermis left intact, and which heals without scarring.	
2.	Ulcer	A breach in continuity of the epidermis and at least a part of dermis, associated with necrosis of tissue and which heals with scarring.	
3.	Excoriation	Loss of substance of skin produced by scratching (linear erosions).	
4.	Scale	Visible exfoliation of skin.	

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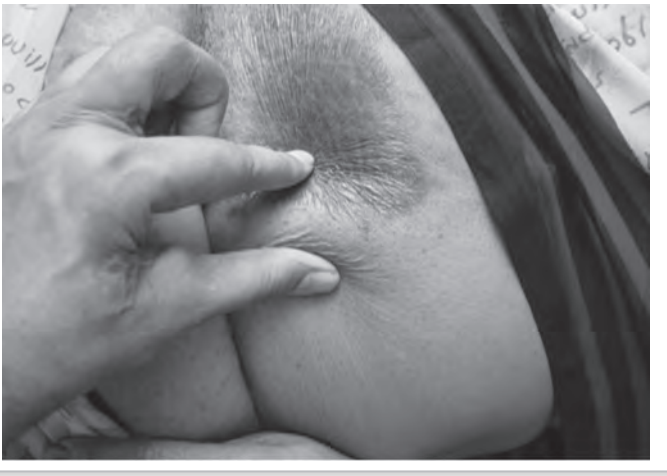
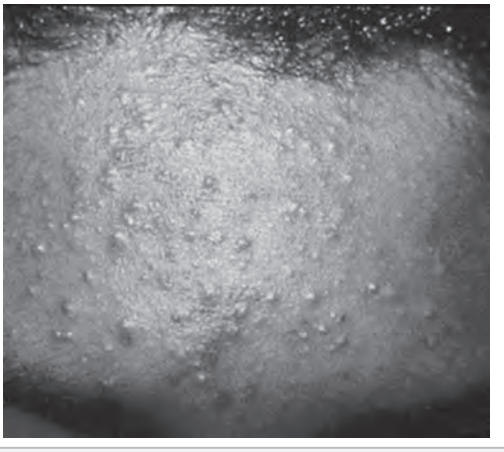
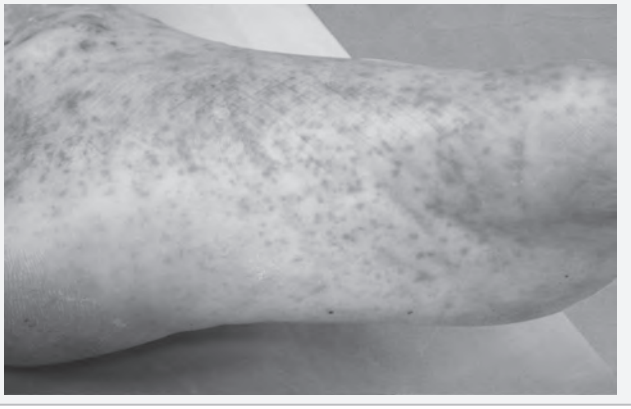
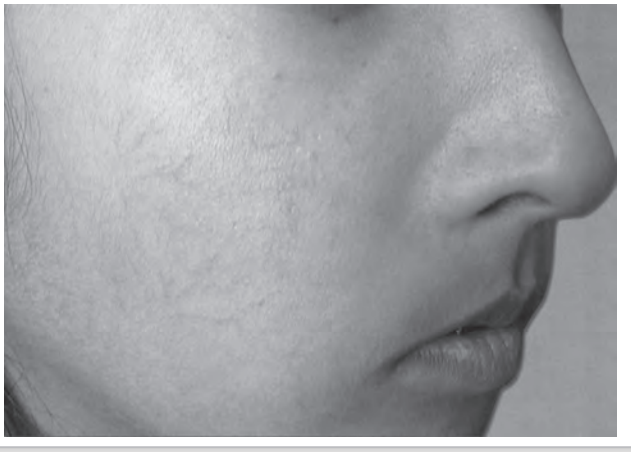
S. No.	Type of lesion	Description	Example
5.	Crust	Accumulation of dried up exudate, secretion, or hemorrhage on the skin surface as a result of its disruption.	
6.	Scar	A visible alteration in the appearance of the skin due to fibrous tissue replacing normal tissues destroyed by disease or injury.	
7.	Lichenification	Thickening of the skin with exaggeration of its normal marking often as a result of chronic scratching or rubbing.	
8.	Sclerosis	Circumscribed or diffuse hardening of skin usually due to fibrosis.	

BEDSIDE TESTS IN DERMATOLOGY

Few bedsides tests that are specific to the dermatological conditions can be done by the physician while examining the patient, as they can help in confirmation of the disease or help in differentiating from other skin disease.

- *Asboe-Hansen Sign*: There is enlargement of bulla by applying finger pressure to small, intact, and tense bulla. It is seen in pemphigus and bullous pemphigoid.
- *Auspitz sign*: There is pinpoint bleeding on removal of scales from the lesions of psoriasis by using blunt end of

TABLE 3: Special lesions. ***(For color version, see plate 24 and 25)***

Special lesions		
Burrow	A passage or a tunnel in the skin that houses a parasite, e.g., scabies.	
Comedones	A plug of keratin or a sebum in a dilated pilosebaceous orifice, e.g., acne vulgaris.	
Purpura	Discoloration of skin due to extravasation of blood. • If >2 cm in diameter—ecchymosis • If <2 cm (pin point)—petechiae • If linear, it is called vibex	
Telangiectasias	Permanent dilatation of capillaries.	

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Special lesions		
Fissure	A small linear gap or slit in the skin surface.	
Sinus	A closed cavity or channel that permits the escape of pus or fluid.	
Milium	A tiny white superficial cyst with an epidermal lining containing keratin.	

pin or glass slide. It is more specific to psoriasis, but it can also be seen in Darier disease and actinic keratosis.

- *Carpet tag sign*: The adherent scale is removed from the lesions of discoid lupus erythematosus, the under-surface of the scale shows horny plugs that have occupied patulous hair follicles.
- *Cullen's sign*: It is seen as periumbilical ecchymosis in cases of acute hemorrhagic pancreatitis and ruptured ectopic pregnancy.
- *Dermographism*: When normal skin is stroked with a dull object, it becomes raised and inflamed to assume the shape of the stroke. It is commonly seen in physical urticaria.
- *Diascopy*: It is a refinement in which a piece of clear glass or plastic is pressed against the skin while the observer looks directly at the lesion under pressure. It is to determine if skin redness is due to blood within vessels (erythema) or extravasated into the skin (petechiae and purpura). The former will blanch with pressure, the latter will not.

- *Forchheimer sign*: It presents as dull red macules or petechiae seen on the soft palate during the prodromal period. It is seen in 20% cases of rubella and can also be seen in infectious mononucleosis.
- *Nikolsky sign*: It refers to easy peeling of skin on applying tangential pressure over a bony prominence and is classically seen in pemphigus, toxic epidermal necrolysis (TEN), and staphylococcal-scalded skin syndrome.
- *Nose sign*: It is seen in exfoliative dermatitis in which there is complete absence of erythema and scaling of the nose and perinasal areas.

EVALUATION OF THE NATURE OF DISEASES

- Dermatological diseases without systemic involvement or complications
- Dermatological diseases with systemic involvement or complications
- Primary systemic diseases with related cutaneous disorders
- Systemic diseases with unrelated cutaneous disorders

Studying in detail on each topic or disease is beyond the scope of this chapter. Hence, we will discuss common rashes seen in pediatric and adult patient presenting in ED. Major groups of dermatologic emergencies include:

- Vesiculobullous disorder and drug reaction
- Infections
- Autoimmune disorders
- Inflammatory cutaneous disorders
- Environmental disorder

VESICULOBULLOUS DISORDERS

- Erythema multiforme (EM) major
- *Stevens–Johnson syndrome (SJS)*: It is considered to be a severe form of EM
- *TEN*: It is considered to be more severe form of SJS
- Generalized bullous fixed drug eruption
- Pemphigus vulgaris
- Bullous pemphigoid
- DRESS syndrome

Table 4 depicts differentiation between EM, SJS/TEN, and bullous fixed drug eruption while **Table 5** presents differentiation between pemphigus vulgaris and bullous pemphigoid.

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS/DRUG-INDUCED DELAYED MULTIORGAN HYPERSENSITIVITY

It is a severe idiosyncratic drug reaction, usually occurs 2–8 weeks after initiating the offending drug. Clinical manifestations include fever, rash, lymphadenopathy, hematological findings (eosinophilia, leukocytosis, etc.), and visceral involvement mainly abnormal liver function tests, which can mimic viral hepatitis. The cutaneous manifestations typically consist of an urticarial, maculopapular eruption and, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma.

INFECTIOUS DISEASES

Major cutaneous patterns of presentation include:

- *Petechial/purpuric lesions*: Chronic gonococcal septicemia, meningococcemia, subacute and acute bacterial endocarditis, Rocky Mountain spotted fever, and dengue hemorrhagic fever
- *Vesicular*: Herpes zoster, varicella zoster (chickenpox), neonatal herpes simplex virus, hand, foot, mouth disease, and Kaposi varicelliform eruption
- *Pustular*: Sepsis (staphylococcal endocarditis) and disseminated candidiasis
- *Maculopapular*: Viral infections, pityriasis rosea, scabies, hepatitis B, and rickettsial infections
- *Diffusely erythematous*: Staphylococcal scalded skin syndrome and toxic shock syndrome
- *Violaceous skin discoloration*: Necrotizing fasciitis and infectious gangrene
- *Annular erythema*: Lyme disease
- *Hansen's disease*: Usually mycobacterial infections do not constitute emergencies. But in few cases patients may

TABLE 4: Differentiation between EM, SJS/TEN, and bullous fixed drug eruption.

	EM major	***SJS/TEN***	***Generalized bullous fixed drug eruption***
Lesion pattern	Typical target lesion present	Flat/atypical target lesion present	Absence of target lesions/bullous lesions with surrounding rim of erythema
Mucosal involvement	Yes	Yes	Yes/no
Distribution	Mainly acral involvement/limbs	Widespread	Widespread
Blister/erosions	Yes at the center of target lesions	Yes <10%: SJS 10–30%: SJS/TEN overlap >30%: TEN	Yes
Recurrence history	Occasional	Rare	Common
Prognosis	Excellent	Mortality depends on risk factors (SCORTEN)	Generally favorable if <20% body surface area is involved

(EM: erythema multiforme; SCORTEN: SCORe of Toxic Epidermal Necrolysis; SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis)

TABLE 5: Differentiation between pemphigus vulgaris and bullous pemphigoid.

	Pemphigus vulgaris	*Bullous pemphigoid*
Age	Middle aged	Elderly
Clinical features	Monomorphic lesions	Polymorphic lesions
Blisters	Flaccid blisters and ruptures easily	Tense blisters
Content of blisters	Fluid filled	Often hemorrhagic
Mucosal involvement	Common	Rare
Nikolsky sign	Positive	Negative
Tzanck smear	Acantholysis	No acantholysis

undergo "reversal reaction" after starting the treatment. This may produce erythema of skin along with swelling of subcutaneous tissues and nerve involvement.

NONINFECTIOUS CAUSES OF HEMORRHAGIC LESIONS

- *Coagulation abnormalities*: Idiopathic thrombocytopenia, DIC, and clotting factor deficiencies
- *TEN*: Initial lesion presents as petechial lesions
- *Vasculitides*: Leukocytoclastic vasculitis
- Raynaud's syndrome or disease

Usually it is difficult to differentiate maculopapular eruption caused due to drug and viral infection. **Table 6** demonstrates maculopapular drug rash and maculopapular viral exanthema.

TABLE 6: Maculopapular drug rash and maculopapular viral exanthema.

	Maculopapular drug rash	*Maculopapular viral exanthema*
History of drug rash	Present	Absent
Onset or rash	7–10 days after drug intake	Prodromal symptoms such as fever, conjunctivitis, headache, rhinorrhea, cough, sore throat, and myalgia present before onset of the rash
Temperature	Low to moderate	Low grade to high grade
Type of rash	Erythematous maculopapular rash on trunk, extremities, and folds. Progresses cephalocaudally. It is symmetrical.	Cephalocaudal distribution of maculopapular eruption and usually associated with lymphadenopathy
Pruritus	Mostly pruritic	Usually nonpruritic
Palms and soles involvement	Present	Spared
Laboratory investigations	Occasionally derangement of liver function test and raised eosinophil count	Usually shows elevated blood counts and lymphocytosis/ lymphocytopenia/ thrombocytopenia

NECROTIZING FASCIITIS

It is a bacterial infection that is rapidly progressive, often over hours, destroying muscle, and subcutaneous tissues. It is commonly associated with beta-hemolytic streptococci. The bacteria usually enter through surgical or traumatic wound and move quickly along facial planes destroying vessels and tissues.

URTICARIA AND ANGIOEDEMA

Urticaria is characterized by appearance of pruritic, evanescent, erythematous, and edematous lesions on skin called as wheals. Approximately 40% of patients with urticaria also experience angioedema. Acute urticaria (disease duration of <6 weeks) occurs usually from secondary causes such as allergic reaction to food, drugs, infections, or insect stings. Chronic urticaria is characterized by symptoms >6 weeks.

Urticarial lesions can sometimes be difficult to differentiate from urticarial vasculitis. However urticarial vasculitic lesions generally last longer than 24 hours and leave some hyperpigmentation as they resolve. Also urticarial vasculitic lesions tend to be painful and to burn rather than itch. When there is difficulty in differentiating urticaria from vasculitis, a skin biopsy may give a definite answer.

Angioedema manifests as sudden localized, nonpitting swelling of certain body parts including skin and mucous membranes. Acute episodes of angioedema can be life-threatening if it involves the larynx leading to the obstruction of upper airways and it is a major cause of death. Angioedema involving the lips, cheek, and tongue are common with bizarre presentations. Angioedema of the gastrointestinal tract frequently mimic an acute abdomen resulting in unnecessary surgical intervention and increased morbidity. Drug-induced angioedema, like other cutaneous drug reactions, is most frequently elicited by beta-lactam antibiotics and nonsteroidal anti-inflammatory drugs.

ERYTHRODERMA

It is also known as generalized exfoliative dermatitis. There is generalized skin redness and scaling. It is a potential presentation of a variety of diseases. It is an emergency in certain due to the fluid and electrolyte imbalances, tachycardia, disturbances in thermoregulation, and risk of cardiac failure. It can be due to underlying skin conditions such as staphylococcal scalded skin syndrome, contact or allergic dermatitis, atopic dermatitis, leukemia/lymphoma/ paraneoplastic, drug induced (includes DRESS), psoriasis, idiopathic, mycosis fungoides (cutaneous T-cell lymphoma/ Sézary syndrome), and pityriasis rubra pilaris.

INFLAMMATORY CUTANEOUS DISORDERS

- *Pyoderma gangrenosum*: It is one of a neutrophilic dermatoses. It is a dermatologic emergency because it is rapidly progressive, causing severe local tissue destruction. It is frequently misdiagnosed as an infectious process or a brown recluse spider bite and is treated by debridement.
- *Childhood vascular anomalies*: The most common vascular anomalies (about 3% of birth) that have potential to become dermatologic emergencies are infantile capillary hemangioma. When they occur around eye and oral cavity can cause significant morbidity and mortality. Some ophthalmologists suggest that even few days of obstructed vision in newborn can inhibit normal visual development so treated aggressively. Likewise enlarging infantile hemangioma of upper respiratory tract and oral cavity can result in acute emergent situation.
- *Acne fulminant*: Although acne is not usually considered an emergency condition, if not treated acutely, can lead to severe cutaneous scarring and psychological problem. The eruption is characterized by rapid suppuration of large, highly inflamed nodules and plaque resulting in ragged ulceration and scarring of chest, back and less commonly face. Often attendant with the cutaneous symptoms are fever, leukocytosis, arthralgia, and myalgia suggesting a systemic upregulation of the immune system.
- *Drug eruption*: On occasion, drug eruption can present as diffuse exfoliative erythroderma or red man syndrome. In addition to drugs, other causes of exfoliative erythroderma that must be ruled out include psoriasis, lymphoma, and flare of seborrheic or atopic dermatitis. Other that can cause dermatologic emergencies include toxic epidermal necrolysis, leukocytoclastic vasculitis, and severe urticarial or angioedema.
- *Kawasaki disease*: The mucocutaneous findings include conjunctival congestion, oropharyngeal lesion (mucosal inflammation), strawberry tongue, fissure lips, hand and foot erythema, and exanthema (generalized macular erythema). These findings along with lymphadenopathy, constitute the minor criteria for Kawasaki disease. Four of five minor plus one major criterion fever >38.3°C.

ENVIRONMENTAL DISORDERS

- *Heat stroke*: It is not a typical skin problem but in heat stroke patient's skin is erythematous, hot, and dry. These findings in association with unconsciousness should alert one to diagnosis.
- *Cutaneous sign of child abuse*: e.g., bruising and abrasion, burn with unusual pattern, e.g., cigarette burn that appears randomly over body, dunking scald injury which have distinct border or sometimes have doughnut pattern.
  - Generalized wastage and dermatitis
  - Traumatic alopecia
  - Bite mark of adult usually >4 cm
- *Lightning strike*: These patients have characteristic skin finding in addition to entry and exit wound skin can often exhibit whirled or fern-like erythema.
- *Scleroderma neonatorum*: It is typically seen in newborns but may occur up to 3 months of age. Clinically, it presents as a hardening of skin with decreased temperature, vascular mottling, and yellow white discoloration in a symmetric distribution usually over thigh and trunk.
- *Cholesterol emboli*: They can be present anywhere in body but cutaneous manifestation commonly occurs in lower extremities. This condition commonly occurs after angiography when trauma to aortic plaque dislodges cholesterol into circulation. Clinically patient presents acutely with fairly well demarcated areas of cyanosis or livedo reticularis on feet and lower leg, these areas can undergo necrosis or ulceration.

ACUTE SKIN FAILURE

It is a dermatological emergency where total dysfunction of the skin occurs due to different dermatological conditions. Acute skin failure is associated with hemodynamic changes, impaired thermoregulatory control, and metabolic complications. In addition, fluid and electrolyte imbalance and loss of essential nutrients affecting patient's survival. It requires multidisciplinary and intensive care approach. Adequate knowledge about monitoring these patients and hospitalization in specialized units can reduce the high morbidity and mortality associated with this condition.

Disposition of the Patient

- Patient requiring aggressive resuscitation should be treated in intensive care unit (ICU).
- *Admission for further assessment and treatment*: For patients who are ill but not toxic necessitate in patient care.
- *Observation in ED*: For patients such as anaphylaxis, angioedema, or urticaria, who respond to treatment quickly.
- Can be treated at home, after patients in ED have been thoroughly evaluated and are stable to be managed at home with proper instructions.
- *Referral to the dermatologist*: In patients when diagnosis is unknown or unclear.

SUMMARY

Skin diseases are one of the most common types of health issue faced by all age groups. The diagnosis of skin disease mostly depends on the expertise of the physician and result of skin biopsy, which is a time-consuming process. Skin disease identification and classification through automated computer-based system images identification is needed to improve for diagnostic accuracy as well as to handle the scarcity of skin specialist. Diagnosis and classification of skin disease from an image is challenging because many skin diseases have highly similar visual characteristics and highly depend on the features of the diseases. Better and cost-effective treatment can be delivered to the patient with accurate analysis of any skin diseases and improvement of the diagnosis techniques.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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149 CHAPTER

Generalized Dermatologic Emergencies

Tejas D Patel

INTRODUCTION

An emergency physician may be the first to see a patient with life-threatening dermatologic conditions. Early recognition and treatment of the conditions help in reducing the mortality and mortality. Interruption of the normal anatomy and physiology of skin is caused by varied dermatological emergencies leading to a number of complications collectively known as acute skin failure. Acute skin failure has been defined as loss of normal temperature control and inability to maintain core body temperature; barrier mechanism against foreign material is also compromised. Fluid, electrolyte, and protein loss along with other serious complications such as sepsis, multiorgan failure, and pulmonary embolism can also happen. Understanding the pathogenesis and systemic complications of acute skin failure and aggressive management in intensive care unit significantly reduces the fatality rate due to dermatologic emergencies. For better understanding of the chapter dermatological emergencies are classified as shown in **Table 1**.

STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Synonyms: Lyell syndrome

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are blistering diseases of the skin. In 1922, Steven and Johnson described a condition which was characterized by disseminated cutaneous eruption with central necrosis, febrile erosive stomatitis, and severe purulent conjunctivitis. Adverse reactions of drugs are the common cause of these complex conditions (SJS and TEN). Adverse drug reaction is the cause in about >80% of the TEN and 50% cases in SJS. Condition is associated with widespread erythema, necrosis, and bullous detachment of extensive areas of epidermis. SJS is considered as erythema multiform major. Epidermal detachment in SJS is <10% while epidermal detachment in TEN is >30%. 10–30% cases overlap between SJS and TEN. Diagnosis is mostly clinical (**Figs. 1A** to **C**).

Clinical Presentation

The patient with SJS/TEN presents with fever, malaise, muscle and joint pain with purpuric lesions which occur on the face, upper torso, and proximal limbs. Lesions gradually involve other body parts eventually turning into fluid-filled blisters. Hemorrhagic crust on lips is characteristic. Ocular manifestations include conjunctivitis, clouding, symblepharon, corneal erosions, and photophobia. Erosion can spread to gastrointestinal (GI) tract and respiratory tract giving rise to symptoms such as dysphagia, diarrhea, pulmonary edema, and bronchopneumonia. Glomerulonephritis represents renal involvement. Evaluation of patient needs medication history and management of complications (**Table 2**).

TABLE 1: Etiologic classification of dermatologic emergencies.

Noninfectious	*Infectious*	*Autoimmune causes*	*Others*
• Stevens–Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • Pyoderma gangrenosum	• Staphylococcal scalded skin syndrome • Necrotizing fasciitis • Fournier's gangrene • Herpes zoster • Meningococcemia • Rocky mountain spotted fever • Febrile viral exanthems	• Type I (immunoglobulin E dependent) • Anaphylaxis and urticaria angioedema • Type II (cytotoxic) • Pemphigus group of diseases • Type III (immune complex) • Vasculitis • Lepra reaction type 2 • Type IV (delayed) • Lepra reaction type 1 • Graft-versus-host disease	• Psoriasis • Dermatitis (atopic, contact, and seborrheic) • Disorders of keratinization (lamellar ichthyosis, bullous, and nonbullous ichthyosiform erythroderma) • Cutaneous T-cell lymphoma

FIGS. 1A TO C: (A and B) Epidermal involvement in Stevens–Johnson syndrome (SJS); (C) Toxic epidermal necrolysis (TEN). ***(For color version, see plate 26)***

TABLE 2: Complications of SJS and TEN.

Acute complications	*Long-term complications*
• Thermoregulatory dysfunction • Fluid and electrolytes dysfunction (if >50% BSA involvement) • Anemia and leukopenia • Hypalbuminemia • Hyperglycemia • Life-threatening complication—septicemia	• Postinflammatory dyspigmentation • Onychomadesis (shedding of nails) • Abnormal photosensitivity and sweating • Ocular: Corneal and conjunctival scarring, dry eye, trichiasis, and entropion • Oral mobility limitation due to gingival synechiae • Lung: Bronchiolitis obliterans • GIT: Esophageal stricture • Urogenital: Vaginal and introital adhesions
Most common drugs associated with SJS and TEN are allopurinol, carbamazepine, lamotrigine, nevirapine, sulfamethoxazole and other sulfa antibiotics, sulfasalazine, nonsteroidal anti-inflammatory drugs, phenobarbital, and phenytoin	

(BSA: body surface area; GIT: gastrointestinal tract; SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis)

Management

Indian Association of Dermatologist, Venereologist, and Leprologist (IADVL) consensus treatment guidelines for SJS/TEN.

Immediate Management

- Stop all drugs
- Fluid replacement
- Nutritional support
- Sterile Vaseline or Paraffin Gauze Dressing
- Temperature regulation
- Antacids and analgesics
- Initiation of disease-specific therapy—corticosteroids, cyclosporine, intravenous (IV) immunoglobulin, and plasmapheresis
- Other drugs—cyclophosphamide, thalidomide, N-acetyl cysteine, and pentoxifylline

Continued Management

- Ophthalmic and oral care
- Pulmonary care
- Antibiotics

Prognosis

Stevens–Johnson syndrome (5% mortality) has better prognosis than TEN (30–40% mortality) SCORe of Toxic Epidermal Necrosis (SCORTEN) score for probability of death (%) (**Table 3**).

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is an uncommon, chronic and recurrent, idiopathic, and ulcerative condition (**Fig. 2**) predominantly involving the skin, with distinctive morphologic characteristics and frequent association with few systemic diseases.

Diagnostic Criteria for Pyoderma Gangrenosum

- *Major*:
  - Rapid progression of painful necrolytic cutaneous ulcer with an irregular, violaceous, and undermined border
  - Exclusion of other causes of ulceration

TABLE 3: SCORTEN score for probability of death (%).	
Parameters	***Points***
Age > 40 years	1
Presence of a malignancy	1
Epidermal detachment >30%	1
Heart rate >120 beats/min	1
Bicarbonate <20 mmol/L	1
Urea >10 mmol/L (28 mg/dL)	1
Glycemia >14 mmol/L (252 mg/dL)	1
Score and % mortality correlation (score 0: 1–3%) (score 2: 12%) (score 3: 35%) (score 4: 58%) (score >5: 90%)	

(SCORTEN: SCORe of Toxic Epidermal Necrosis)

FIG. 2: Pyoderma gangrenosum. ***(For color version, see plate 26)***

- *Minor*:
  - History suggestive of ulcer development at sites of trauma or clinical finding of cribriform scarring
  - Systemic diseases associated with pyoderma gangrenosum
  - Histopathological findings (sterile dermal neutrophilia ± mixed inflammation ± lymphocytic vasculitis)
  - Rapid response to systemic corticosteroid therapy (50% decrease in size within 1 month in response to a dose of 1–2 mg/kg/day)

In adults, the most frequent association is rheumatoid arthritis and in children it is ulcerative colitis.

Topical steroid or tacrolimus 0.1% ointment used for mild cases and severe cases respond to oral corticosteroid (1–2 mg/kg). Cyclosporine acts rapidly in corticosteroid resistant cases.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

It is commonly seen in infants and children due to exotoxin released by *Staphylococcus aureus* group 2 phage 71. Exotoxin is an epidermolytic toxin also called exfoliating toxin or epidermolysin. Clinically, intense erythematous cutaneous eruptions occur following an upper respiratory tract infection or purulent conjunctivitis. Painful erosions appear when

FIGS. 3A AND B: Necrotizing fasciitis. ***(For color version, see plate 26)***

erythematous sheets of skin are shed which is referred to as potato chip desquamation. Patient should be admitted and treated promptly with antibiotics covering *S. aureus*.

NECROTIZING FASCIITIS

Necrotizing soft tissue infections are divided into three categories according to their depth of involvement:

1. Necrotizing cellulitis
2. Necrotizing fasciitis (NF)
3. Myonecrosis (MN)

Necrotizing cellulitis progressing to involve fascia is considered to be NF (**Figs. 3A** and **B**); further extension of NF to muscle is MN.

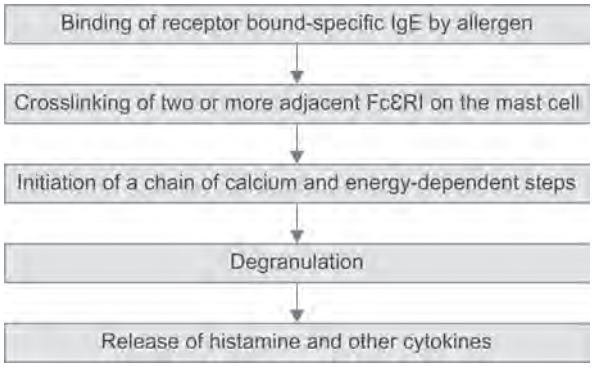
Predisposing factors include trauma, diabetes, drug injection, and burns. The most common sites of involvement are the extremities, trunk, perineum, head, and neck.

Necrotizing fasciitis of perineum and genitals is known as *Fournier gangrene*. Patient of NF usually have history of surgery wound and trauma. Type 1 NF is due to polymicrobial involvement and associated pathogens are streptococci, *Bacteroides,* or Enterobacteriaceae. Type 2 NF is caused by single pathogens such as beta-hemolytic streptococci and *S. aureus*. Fever, chills, erythema, edema, and pain over involved skin are common features. Erythematous skin gets a blue discoloration and vesicular and bullous lesions develop over erythematous skin with serosanguinous discharge. After that gangrene develops in next 4–5 days and black eschar by 10 days.

There is no specific diagnostic test for NF. Routine blood tests should be done. Radiology is used to detect gas within soft tissue and muscle. Hospitalization, surgical debridement, fluid resuscitation, and broad-spectrum antibiotic therapy are the main steps in the management.

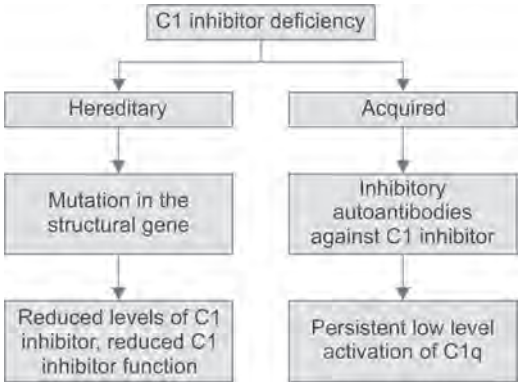
URTICARIA (HIVES), ANGIOEDEMA, AND ANAPHYLAXIS

Urticaria is a common skin reaction that may be transient for 12–24 hours or last long for 6–8 weeks. Urticaria and angioedema have similar mechanism of action; histamine and other mediators (anaphylatoxins, C3a, and C5a) are released from mast cell and basophils (**Flowcharts 1** and **2**).


Binding of receptor bound-specific IgE by allergen
Crosslinking of two or more adjacent FcεRI on the mast cell
Initiation of a chain of calcium and energy-dependent steps
Degranulation
Release of histamine and other cytokines

(IgE: immunoglobulin E)

FLOWCHART 1: Mast cell-dependent urticaria and angioedema.


C1 inhibitor deficiency
Hereditary
Acquired
Mutation in the structural gene
Inhibitory autoantibodies against C1 inhibitor
Reduced levels of C1 inhibitor, reduced C1 inhibitor function
Persistent low level activation of C1q

FLOWCHART 2: Mast cell-independent urticaria.

Mostly these are type I hypersensitivity reaction mediated by immunoglobulin E (IgE) antibodies.

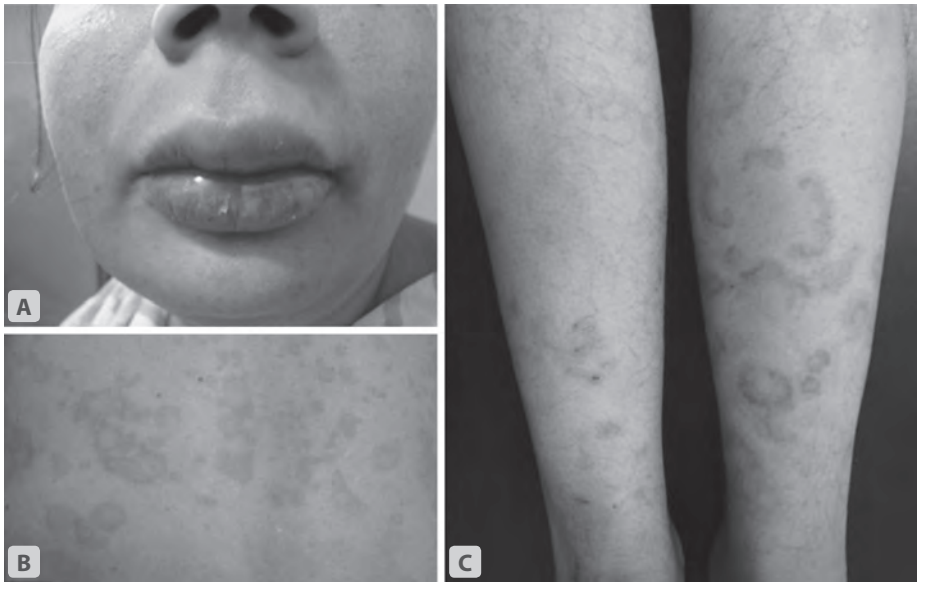
In urticaria, mast cells are present in superficial dermis while in angioedema mast cells are present in dermis and subcutaneous tissues. Both conditions are self-limiting but when respiratory mucus membranes are involved producing laryngeal edema it indicates a medical emergency (**Figs. 4A** to **C**). Differentiating features of urticaria angioedema and anaphylaxis are shown in **Table 4**.

Common trigger factors are allergens, insect envenomation, and physical stimuli such as heat, cold, vibration, or pressure. Patient on angiotensin-converting enzyme (ACE) inhibitors may develop angioedema. Slightly elevated pruritic, erythematous papules, and plaques are the common presenting clinical features. Relevant history taking and physical examination should be performed to determine cause. Laboratory workup is not helpful unless history and examination suggest some specific cause.

Investigations in chronic or recurrent urticaria—complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), rheumatoid factor (RF) testing, examination of stool for ova and parasites, serum complement assays, serum cryoglobulin, thyroid function test, and C1 esterase inhibitor functional assays.

Management

According to the European Academy of Allergy and Clinical Immunology (EAACI)/World Allergy Organization (WAO) guidelines if angioedema persists with urticaria, parenteral



FIGS. 4A TO C: (A) Angioedema; (B and C) Urticaria. ***(For color version, see plate 27)***

TABLE 4: Differentiating features of urticaria, angioedema, and anaphylaxis.

Urticaria	*Angioedema*	*Anaphylaxis*
(Synonyms: Hives and nettle rash)	(Synonyms: Quincke's edema and angioneurotic edema)	
• Itching • Edema in dermis • Well defined • Only skin involved	Painful rather than itchy, edema in deeper dermis, subcutaneous fat, and submucosal tissues. Ill defined, skin, mucous membrane, lips, larynx, gastrointestinal mucosa, causing upper airway obstruction, and angioedema is emergency	• Type I hypersensitivity urticaria and/or angioedema plus hypotension and tachycardia • Treatment: Epinephrine and corticosteroids

corticosteroid and epinephrine 0.3–0.5 mg should be given (**Table 5**).

PEMPHIGUS GROUP OF DISEASES

The word pemphigus is derived from a Greek word "pemphix" meaning blister or bubble. Pemphigus is a group of autoimmune blistering disorders characterized by intraepidermal split. Pemphigus can be classified into pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, immunoglobulin A (IgA) pemphigus, and drug-induced pemphigus. From the above-mentioned diseases pemphigus vulgaris and pemphigus foliaceus are the most common diseases to present to the emergency department in the form of acute skin failure (**Figs. 5A** and **B**).

Pemphigus vulgaris presents with vesicles, bulla, erosions or crusted plaques on skin, and oral erosions and ulcers. Antibodies (IgG class) are directed against desmoglein-1 (Dsg1) and desmoglein-3 (Dsg3). Pemphigus foliaceus presents with small flaccid bullae with crusting and scaling. Here target antigen is Dsg1. Bullae readily rupture, resulting in moist erosions and cornflake-like crusts.

TABLE 5: Stepwise approach for management of urticaria.

Basic treatment	*Step 1*	*Step 2*	*Step 3*	*Step 4*
• Avoidance of triggers and relevant physical factors if physical urticaria/angioedema is present	• Monotherapy with second-generation antihistamine (sgAH) • If inadequate control: After 2–4 weeks or earlier, if symptoms are intolerable	• Increase sgAH dose (up to four times) • If inadequate control: After 2–4 weeks or earlier, if symptoms are intolerable	• Add on to sgAH: Omalizumab [monoclonal antibody against immunoglobulin E (IgE) • If inadequate control: With in 6 months or earlier, if symptoms are intolerable	• Add on to sgAH: Cyclosporin

FIGS. 5A AND B: (A) Pemphigus vulgaris; (B) Pemphigus fallacious. ***(For color version, see plate 27)***

Most common complications are septicemia or secondary bacterial infections, hypoproteinemia resulting from decreased oral intake and iatrogenic side effects of corticosteroids such as hyperglycemia and osteoporosis.

Mainstay of treatment for pemphigus is systemic corticosteroids and prednisolone is the most preferred agent started at a dose of 0.5–1 mg/kg. It is tapered off by 50% every 2 weeks after 80–90% of lesions have healed. In recent times, rituximab (IgG type chimeric monoclonal antibody against CD20) has emerged as a popular therapy due to its advantages of long-term remission and lesser steroid induced side effects.

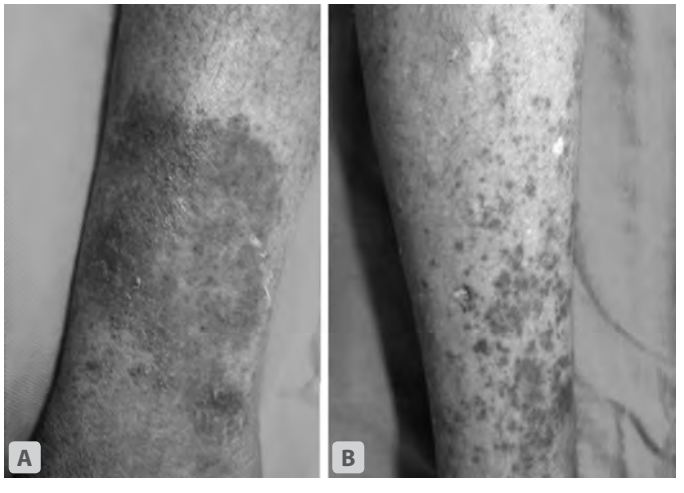
Other treatment modalities include dexamethasone-cyclophosphamide pulse, azathioprine (2–4 mg/kg/day), mycophenolate mofetil (2 g/day), cyclosporine (3–6 mg/kg/day), and IV immunoglobulin (2 g/kg/cycle divided over 3–5 days, minimum of three cycles).

VASCULITIS

Systemic vasculitis primarily classified in to primary vasculitis syndrome and secondary vasculitis syndrome. Primary vasculitis syndrome is a type of vasculitis caused by inflammation of blood vessels while secondary vasculitis syndrome is caused by underlying connective tissue disease, tumor, infections and drug allergies. The etiology of both vasculitis syndrome is not clear. Primary vasculitis syndrome and secondary vasculitis syndrome are included within the systemic autoimmune disease (**Figs. 6A** and **B**).

Conditions where vasculitis should be suspected:
- Fever of unknown origin
- Multisystem disease
- Active glomerulonephritis
- Ischemic symptoms in young patients
- Palpable purpura
- Mononeuritis multiplex

Pathogenetic factors in vasculitis:
- Immune complex deposition
- Complement activation
- Antineutrophilic cytoplasmic antibodies
- Cell-mediated immunity:
  - *Three types*: Small vessel, medium vessel, and large vessel vasculitis
  - *Most common type*: Leukocytoclastic vasculitis
  - *History is important*: Medications [penicillin (PCN), nonsteroidal anti-inflammatory drugs (NSAIDs), sulfas, and cephalosporins]
  - Workup for systemic involvement
  - *Treatment*: Eliminate cause, treat infection, steroids, colchicine, and immunosuppressants



FIGS. 6A AND B: Vasculitis. ***(For color version, see plate 28)***

LEPRA REACTION

Lepra reaction occurs during the treatment course of leprosy. Lepra reactions are treated as emergencies because they may lead to permanent damage to nerves, limbs, or may cause blindness. There are two types of lepra reaction (**Table 6**).

PSORIASIS (ERYTHRODERMIC PSORIASIS)

It is a generalized form of psoriasis involving >90% body surface area (BSA) with erythema, induration, and superficial scaling (**Figs. 7A** to **D**).

Precipitants are infections, alcohol, drugs, and sudden withdrawal of corticosteroids. It is diagnosed by histopathological and clinical features. Erythrodermic psoriasis is a kind of acute skin failure so main focus of management is directed to skin barrier repair, fluid and electrolyte balance, cyclosporine for short period to manage acute flare up, and then addition of methotrexate for maintenance, if not contraindicated.

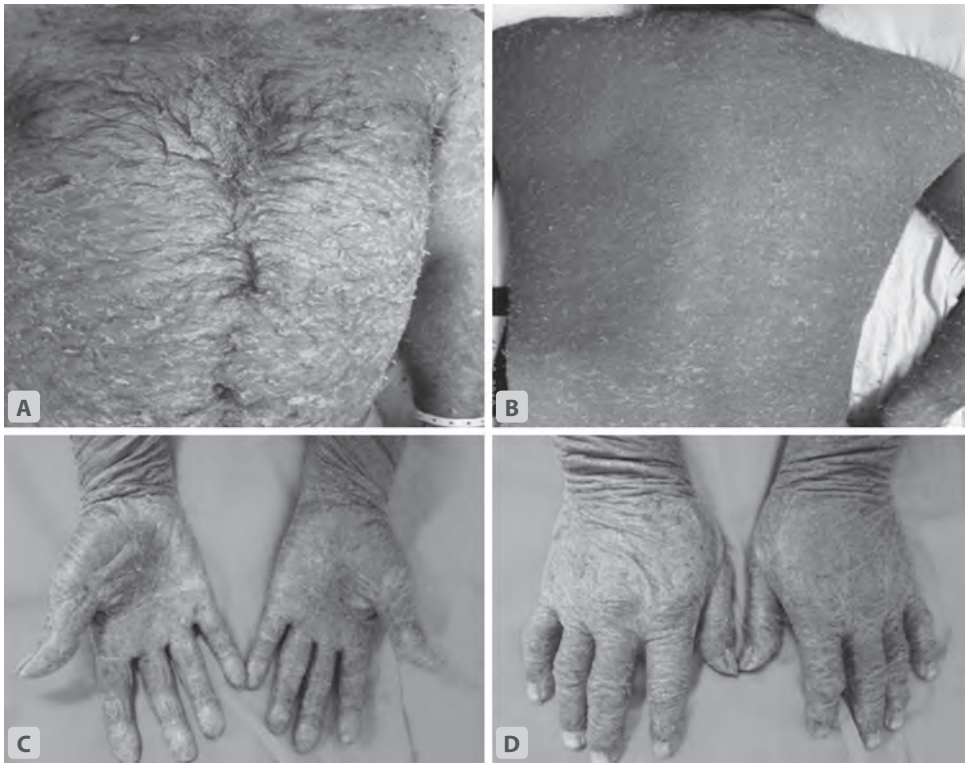
ACUTE SKIN FAILURE

Acute skin failure is a state of total failure of skin functions due to various dermatological conditions requiring a multidisciplinary and intensive care approach for management. The major consequences of acute skin failure are:
- *Fluid and electrolyte imbalance*: In normal circumstances, water loss through the skin is 1 mL/cm^2/h. In patients with acute skin failure, the daily water loss through skin increases to 40 times more than the normal range. This is due to the destruction of skin layer stratum corneum responsible for the barrier function of the skin. If about 50% BSA is affected, estimated daily fluid loss is up to 4–5 L, loss of protein (40 g/L), Na (120–150 mmol/L), Cl (10–90 mmol/L), and K (5–10 mmol/L). The manifestations are dehydration and decreased urinary output, electrolyte imbalance (low Na^+ and high K^+) and raised serum levels of urea and creatinine.
- *Infection*: Damaged barrier function of the skin supports growth of endogenous and exogenous organisms resulting in systemic infection and increases the incidence of septic complications.
- *Hemodynamic alteration*: Persistent inflammation of the skin leads to marked peripheral vasodilatation and increased cutaneous blood flow nearly doubles the cardiac output resulting in high-output cardiac failure in compromised cardiovascular system (elderly, hypertensive, ischemic, or valvular heart disease).
- *Thermoregulatory dysfunction*: Either hypothermia or hyperthermia can occur depending on surrounding environment.
  - *Hypothermia*: It manifests as sign of septic shock. Compensatory mechanisms against hypothermia are shivering [due to increased interleukin-1 (IL-1)] and raised basal metabolic rate (BMR).

TABLE 6: Differentiating features of lepra reactions.

Features	*Type 1*	*Type 2*
Type of immunological reaction	Delayed type hypersensitivity reaction (type 4)	Antigen antibody immune complex reaction (type 3)
Type of patients affected	Borderline type (BT, BB, and BL)	LL rarely BL
Constitutional signs and symptoms	Rare (fever, malaise, arthralgia, and myalgia)	Common (fever, malaise, arthralgia, and myalgia)
Type of the skin lesions	Existing skin lesions suddenly become reddish, swollen, warm, painful, and tender	• Fresh red, painful, tender, cutaneous nodules, and plaques • The existing lesions remain unchanged
Nerve involvement	Nerves close to skin lesions may be enlarged, painful, and tender due to acute neuritis with loss of nerve functions (loss of sensation and muscle weakness). Neuritis may also appear suddenly	Nerves may be affected but not as common or as severe as in type 1 reaction
Eye involvement	Corneal anesthesia and lagophthalmos may occur due to nerve involvement (5th and 7th CN)	Internal eye disease such as iritis, iridocyclitis, glaucoma, and cataract are common
Other organs	Not affected	May be affected: Lymphadenitis, epididymo-orchitis, painful dactylitis, periosteal pain, myositis, arthritis, and glomerulonephritis are common
Treatment	NSAIDs and corticosteroids	NSAIDs, corticosteroids, clofazimine, thalidomide, and Biologics

(BB: midborderline; BL: borderline lepromatous; BT: borderline tuberculoid; CN: cranial nerve; LL: lepromatous leprosy; NSAIDs: nonsteroidal anti-inflammatory drugs)



FIGS. 7A TO D: Psoriasis. ***(For color version, see plate 28)***

  - *Hyperthermia*: It is seen in conditions like erythroderma due to psoriasis as skin is already hypohidrotic or anhidrotic as a result of intraepidermal occlusion of the sweat duct.
- *Metabolic abnormalities*: Hypercatabolic state leads to increased energy expenditure. Further worsening of hypercatabolic state is caused by amino acid breakdown from hyperglycemia and glycosuria which results from relative insulin resistance and decreased insulin secretion.

Management

The management of patients with acute skin failure requires well-coordinated teamwork. Care should focus on double

barrier nursing care; monitoring hemodynamic changes; fluid, electrolyte balance, and nutrition; prevention of complications (e.g., sepsis); prompt identification of risk factors; and topical therapy.

Monitoring Hemodynamic Changes

Due to disruption of barrier mechanism of the skin, continuous loss of water occurs through the body surface and it is thus important to monitor hourly hemodynamic status via pulse rate, heart rate, urine output (50–100 mL/h). Temperature, blood glucose, and gastric content to be monitored every 3 hourly.

Fluid, Electrolyte, and Nutrition

Fluid and electrolyte administration to correct and maintain hemodynamic and electrolyte equlibrium is a necessity. In the initial 24 hours, the IV fluid administered contains human albumin 1 mL/kg/%BSA and isotonic saline 0.7 mL/kg/BSA. Though TEN is often compared with burn injury, the fluid requirement is three-fourths of that of patients with burns covering the same area. This is because the depth of tissue destruction and underlying vascular injury is less in case of TEN. 1,500–2,000 mL of nasogastric feed is required. Start with total 1,500–2,000 kcal/day then daily increment of 500 kcal up to 3,500–4,000 kcal/day and 2–3 g/kg/day protein intake in adults can be added (3–4 g/kg/day in children).

Nursing Care and General Measures

The environmental temperature should be maintained at 30–32°C. Use of air fluidized beds and burn cage ensures patient comfort and easy handling. Regular cleaning and removal of crusts from the oral and nasal cavities and care of the eyes, genitalia, and perianal region is essential to prevent infections.

Topical Management

Various topical agents such as silver sulfadiazine, nonphysiologic lipids (petrolatum jelly and lanolin), and physiologic lipids (component mixture of cholesterol, ceramide, and free fatty acids in an optimized ratio of 3:1:1) should be used as barrier repair agents and to accelerate the barrier repair after cleaning.

Antibiotics

Prophylactic antibiotic use in absence of strong evidence of infection is not recommended by many authors. Indications of antibiotic use are as follows:

- Culture from skin and urine shows high bacteria count
- Sudden hypothermia in a relatively stabilized patient
- An altered sensorium (first sign of sepsis)
- Signs and symptoms of infection related to particular system, e.g., increased respiratory rate due to hypoxia resulting from pneumonia

SUMMARY

Sudden alteration in the anatomy and physiology of skin results from certain generalized dermatoses can lead to life-threatening syndrome of acute skin failure. Understanding of etiopathogenesis and their prompt and early management in emergency department itself can salvage many lives.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Approach to Joint Pain

Sourabh Malviya

INTRODUCTION

Joint pain is one of the most common presentations in emergency ward. Thorough initial assessment always helps to differentiate and characterize joint pain. All emergency practitioners should be well versed in the evaluation of the "red hot joint". Rarely it can be life-threatening and may be sole manifestation of serious systemic diseases and infections. So "red flags" of joints should be in the mind of every emergency department (ED) clinician if he/she encounters any patient of acute joint pain. These "red flags" are septic arthritis, acute gout, and fracture. On the other hand, inflammatory arthritis can present with acute joint pain and swelling and if not diagnosed and treated on time can lead to long-term deformity and disability. So through clinical examination and then evaluation should be done for any joint pain.

EVALUATION OF JOINT PAIN

Clinical History

Detail clinical history and physical examination (**Table 1**) may help in evaluation whether patient has articular or periarticular disease. If articular, then type, number, and areas of joints involved can give information of probable disease.

Location of Pain

Articular pain may be described as generalized sensation of joint pain. On the other hand, periarticular pain is localized to a specific site of inflammation.

Acute or Chronic

Injury, infection or inflammatory process, or acute exacerbation of a chronic arthritis can give rise to acute joint pain. History of recurrent acute pain could be due to chronic arthritis.

Worsening Factor

Joint pain is often exacerbated by both active and passive motion of the join, can also occur at rest, as seen in acute inflamed joint (inflammatory or infective arthritis). If muscles or tendons are actively or passively moved then periarticular pain can be exacerbated, commonly seen with overuse conditions.

TABLE 1: Evaluation (history and physical examination) of joint pain.

History	***Probable diagnosis***
Fever and history of infection recently	Septic arthritis
History of immunosuppression	Septic arthritis
Elderly and diabetic	Septic arthritis
IV drug abuser	Septic arthritis
History of hyperuricemia	Gout
History of trauma	Fracture
Cancer	Pathologic fracture
History of inflammatory back pain	Spondyloarthritis
History of uveitis/psoriasis/IBD	Spondyloarthritis
Physical examination	
Examination clues	***Probable diagnosis***
Sick look or toxic	Septic arthritis
Limited range of motion	Fracture or septic arthritis
Single red hot swollen joint	Septic arthritis
Pustular skin lesion	Gonococcal arthritis
Heart murmur	Endocarditis
Urethritis/cervicitis/conjunctivitis	Reiter's syndrome
Firm hepatosplenomegaly	Malignancy
Multiple joints involved	Inflammatory arthritis
Malar rash and Raynaud's phenomenon	SLE
Psoriasiform rash	Psoriatic arthritis
Tophi	Gouty arthritis

(IBD: inflammatory bowel disease; IV: intravenous; SLE: systemic lupus erythematosus)

Number of Joints Involved

Bursitis/tendinitis or any periarticular problem usually involve single joint. Arthritis should be differentiated into monoarticular (septic and gouty arthritis), oligoarticular [juvenile idiopathic arthritis (JIA), sarcoidosis, and

seronegative spondyloarthritis (SpA)] or polyarticular [Acute: Viral arthritis or gonococcemia; Chronic: Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis, or dermatomyositis] (**Table 2**).

Symmetric or Asymmetric

If it is polyarthritis then it should be looked whether it is symmetric (e.g., drug-induced arthritis, RA, and SLE) or asymmetric (e.g., psoriatic arthritis, gonococcal arthritis, and acute rheumatic fever).

Distribution of Joints

Location of joint pain may be characteristic of some arthritis. Proximal interphalangeal (PIP) commonly involved in RA, SLE, osteoarthritis (OA), and distal interphalangeal (DIP) joints of the hand in psoriatic arthritis, OA, or sarcoidosis. Metacarpophalangeal (MCP) commonly affected in RA. Gout commonly affects the great toe metatarsophalangeal (MTP) joint (known as podagra). Ankle and knee commonly affects in OA or seronegative SpA. Hip joint is usually involved in JIA, OA, or SpA.

Associated Clinical Findings

Extra-articular signs and symptoms should be elicited in a patient of joint pain to reach proper diagnosis. High-grade fever can be a symptom of septic arthritis whilst low-grade of inflammatory arthritis or connective tissue diseases (CTDs). Other constitutional features such as Raynaud's phenomenon, malar rash, erythematous skin rash, recurrent hair fall, and recurrent oral ulcer may suggest SLE while dryness of mouth or eyes more likely of Sjögren's syndrome. Track marks in skin may be of injection drug users in endocarditis. Ocular findings can also give some clues like episcleritis may points towards RA or anterior uveitis for ankylosing spondylitis. Tophi in the skin or uric acid stones in kidneys may be associated with gouty arthritis. Purulent urethritis suggests infective etiology like gonococcal disease. The combination of palmoplantar skin lesions, conjunctivitis, and urethritis suggests Reiter's syndrome.

Past Medical History

One should always enquire about past history of chronic inflammatory arthritis other autoimmune disease, gout, hemophilia, and malignancy. Drug history should be taken as few drugs do have joint or skin manifestations. Thiazide diuretics increase uric acid levels and may precipitate gout. Isoniazid, procainamide, and hydralazine therapy may lead to a lupus-like syndrome. Family history is important in diagnosing few arthritis, especially seronegative SpA. Inquiries about overuse activities, sports, injection drug use, and sexual history should also be made. History of infections like tuberculosis (TB) or leprosy should be elicited to look for infective arthritis related to said diseases.

Physical Examination

To reach into differential diagnosis of joint pain in ED after history thorough physical examination should be conducted.

General Examination

With mere general appearance sometimes clinician can make out what patient could be having, like if infective or septic arthritis patient will have sick look. Abrasions or contusions may be there in case of traumatic joint.

Infective or traumatic conditions may give rise to tachycardia or hypotension. Inflammatory arthritis or CTD typically present with a normal temperature or low-grade fever, and possibly mild tachycardia or tachypnea due to pain.

Examination of Joints

Joint swelling may be secondary to hemorrhagic fluid from an injury, infection (purulent fluid), or due to synovitis, excessive amounts of synovial fluid. Initial look to be given to number of joints involved. If monoarticular, predominantly large joints of the the lower limb, then it could be be crystal arthritis. If nearby skin is indurated and some signs of cellulitis is there along with red swollen joint then infection will be more likely. In case of knee pain if both joints are involved, looks swollen, may be one more than other then one should think of OA. OA of hands commonly involves first carpometacarpal (CMC) and DIP joints. While in inflammatory arthritis like RA mainly small joints of hands (PIP/MCP) are affected. Joints will be swollen in RA and are mostly symmetrical. In RA there can be deformities of hands involved, but in CTD like lupus there may not be the same. Tophi anywhere in the skin or joint line can suggest gouty arthritis.

Typical signs of inflammation would be there in case of inflammatory arthritis or infective arthritis or crystal arthritis such as redness, warmth, tenderness, and range of motion will be reduced. These findings should always be compared to opposite joint. These palpatory examination findings can also take examiner towards diagnosis, can delineate if its particular joint structure (ligament or tendon), or whole joint. Swelling,

TABLE 2: Differential diagnosis as per number of joint involved.

Monoarticular	*Oligoarticular*	*Polyarticular*	*Periarticular*
Septic arthritis	Reiter's syndrome	Acute rheumatic fever	Bursitis
Hemarthrosis	Sarcoidosis	Drug-induced arthritis	Cellulitis
Osteoarthritis	Juvenile idiopathic arthritis	Gonococcal arthritis	Tendonitis
Gout/pseudogout	Lymphoreticular malignancy	Systemic lupus erythematosus (SLE)	
Trauma	Oligoarticular onset polyarthritis	Rheumatoid arthritis	
Monoarticular onset polyarthritis	Seronegative spondyloarthropathies	Seronegative spondyloarthropathies	
	Reiter's syndrome	Viral arthritis	

particularly due to a joint effusion, may be palpable if not easily visualized on inspection.

Range of motion may be decreased secondary to pain from degenerative joint disease, inflammation, infection, or injury or with increasing age. Hypermobile joints may occur with joints that are unstable from ligamentous injury, or in association with joint hypermobility syndrome such as benign hypermobile joint syndrome and Ehlers–Danlos syndrome. Few tests can help examiner to look for subtle effusion in joint such as patellar tap test or wave test in the knee joint.

Patellar Tap Test

The patient is lying in supine with the leg extended. Examiner puts pressure on the proximal side of the knee in an effort to squeeze the fluid out of the suprapatellar pouch. The fluid can be moved under the patella while maintaining the pressure on the suprapatellar pouch; the examiner uses his/her other hand to press up on the medial and lateral recesses forcing the fluid under the patella. Tapping down the patella with the index to create an upward and downward movement and a palpable "click" as the patella hits the underlying femur. If the test is negative, the femur and the patella are already in contact. A positive test is when the patella can be felt to move down through the fluid and rebounds on the patella. The test can be false positive, therefore we must always test both sides to compare.

Fluid Wave Test

It is used when the effusion is <30–50 cc. The patient lies supine and examiner presses his/her fingers in both parapatellar gutters. Because there is a pressure from below upward, the gutters are emptied. The patient is asked to stand while the examiner keeps his/her fingers in the parapatellar gutters. If examiner releases his/her fingers and the fluid comes back in the parapatellar gutters, it is a positive sign. Pain in weight bearing joint suggest arthritis. Periarticular structural problem commonly results in pain during active range of motion.

Detail General and Systemic Examination

Detail general and systemic examination should be done in presence of other patient complaints, signs, or symptoms (**Table 3**). A detailed examination will be helpful in identifying an underlying systemic disease, like skin tightening in scleroderma, heart murmur of endocarditis, pharyngitis or eye findings of associated arthritides, or skin rashes of SLE or of dermatomyositis. Reduced salivary pool in oral cavity or reduced tear secretion points towards Sjögren's syndrome. Hypoesthetic patch with dactylitis may suggest leprosy. Chronic cough with chest findings like localized crepitations with history of TB can guide to us diagnosing Poncet's arthritis.

LABORATORY TESTS

Evaluation through blood tests is not of very much significance in reaching diagnosis, but clinical examination. Leukocytosis may suggest infective etiology of joint pain, while anemia may point towards chronic arthritis like RA. Inflammatory markers [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)] may be elevated in infection or inflammatory arthritis but may be nonspecific sometimes. Hyperuricemia can be there in up to 5% patient in normal individual but in case of acute gout, serum uric acid levels are often normal. Any patient presented to ED if has polyarthritis, few tests to be done, routine tests such as complete blood count (CBC), liver function tests (LFTs), kidney function tests, and also subjected to rheumatoid factor (RF) if symptoms are >6 weeks duration. In RA, RF has sensitivity of around 80–95% but specificity 55–60%. Anti-cyclic citrullinated peptide (CCP) antibody can also be done if RF is negative or for prognostication and in some cases of diagnostic dilemma if clinical profile suggests RA. Anti-CCP has 50–60% sensitivity and 95–98% specificity in RA. If some other features are there apart from joint pain which are mentioned for CTD then antinuclear antibody (ANA) can be ordered. Gold standard method of ANA is by indirect immunofluorescence rather than enzyme-linked immunosorbent assay (ELISA). For further characterization of CTD, extractable nuclear antigen (ENA) profile may help in further delineating diagnosis. In case of acute onset polyarthritis associated with fever, viral etiology like chikungunya fever should be suspected, especially if it is of short duration of <6 weeks. Routine blood tests should be done such as CBC, LFT, and parvovirus and so few viral markers such as human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and anti-hepatitis C virus (HCV). If clinical possibility of infection is there than blood culture do guide us if there is hematogenous spread. In case of trauma hemarthrosis can be suspected but if not, then coagulation disorders should be ruled out with routine coagulation profile such as prothrombin time (PT), partial thromboplastin time (PTT), bleeding time, and platelet count.

SYNOVIAL FLUID ANALYSIS

Synovial fluid analysis (**Table 4**) is a very useful tests to march towards diagnosis, especially in case of septic arthritis, crystal arthritis, or to differentiate between inflammatory versus infective arthritis and also in a case of joint effusion if diagnostic dilemma. These can be done through arthrocentesis. Synovial fluid analysis includes routine such as cell count and differential, sugars, or glucose and microscopy such as Gram stain and culture. Also crystal analysis should be done. Gram stain and cultures should send to microbiology laboratory once aspirated. Crystal analysis is performed using polarizing microscopy, with monosodium urate crystals in gout appearing as, needle-shaped crystals that are negatively birefringent. In contrast, calcium pyrophosphate crystals in pseudogout appear as polymorphic (often rhomboid) positively birefringent crystals.

IMAGING

In ED setting, X-rays are indicated for patients with a history of significant trauma looking for fractures, deformities, neoplasm, osteomyelitis, avascular necrosis, or other bone disease or foreign bodies. Radiographs may show loss of joint space, periarticular osteopenia, or erosions. In infective or septic arthritis, one may find subchondral bone destruction, erosions, or periosteal new bone formation. Ultrasonography may be useful in confirming a joint effusion, tendinitis, or tenosynovitis and can also be used to guide joint aspiration. For further confirmation of findings, computed tomography can be done for better bony anatomy, whereas magnetic resonance imaging (MRI) is extremely useful for defining soft tissue pathology.

TABLE 3: Causes of joint pain and characteristic features.

Diagnosis	*Symptoms*	*Signs*	*Evaluation*
Osteoarthritis	Monoarticular acute flares with chronic arthritis without any systemic findings. First CMC, DIP, PIP, joint and knees and first MTP joints are most commonly affected	Generally elderly age groups are affected. Joint examinations have crepitus and swelling in the affected joints. Bouchard's nodes (PIP) and Heberden's nodes (DIP) often present in the hands	CBC and biochemistry is often normal; inflammatory markers (ESR/CRP) typically normal. Plain radiographs demonstrate formation of osteophytes and joint space narrowing
Gout	Monoarticular symptoms, with MTP joint of the great toe. At onset pain may be severe. Systemic symptoms are uncommon. Tophi can be there on examination in few cases, mostly in polyarticular involvement	Patients are generally afebrile. Affected joints are erythematous, warm, and painful on movement	• Serum uric acid may be normal in acute attacks. Synovial fluid analysis demonstrates negatively birefringent, needle-shaped crystals and high WBC counts in the fluid • If turbid or purulent fluid then associated septic arthritis must be ruled out by joint fluid Gram stain and culture
Pseudogout	Can be seen in osteoarthritic joint. Monoarticular arthritis usually occurring in the knee, wrist, ankle, and elbow. More than one joint maybe involved. Typically less acute and less severe than gout	Affected joints are erythematous, warm and painful to touch, or movement. Systemic systems typically absent	CBC and biochemistry is often normal; inflammatory markers (ESR/CRP) typically normal. Radiographs sometimes show calcifications (chondrocalcinosis) in joints, tendon insertions, ligaments, and bursae. Synovial fluid examination under polarized microscopy will reveal rhomboidal, weakly positive birefringent crystals of calcium pyrophosphate dehydrate
Septic arthritis	Mostly monoarthritis, erythema, warmth, and swelling. More than 70% of cases involve large joints. Associated symptoms may be fever with chills, loss of appetite, and malaise	Affected joints are erythematous, warm, and exquisitely sensitive to touch or movement. Fever may be present	Leukocytosis may be there. ESR is commonly elevated. CRP may be disproportionately higher than ESR. Blood cultures may grow etiologic agents (about half). Synovial fluid analysis shows marked polymorphonuclear leukocytosis. Gram stain may demonstrate organisms (50–70%), although synovial culture is the gold standard. Plain radiographs could suggest soft tissue swelling only
Rheumatoid arthritis	Polyarticular, usually symmetric, arthritis with acute flare-ups occurring in the context of chronic disease. The hands (MCP and PIP joints), wrists, elbows, and feet (MTP joints) are most often affected. Constitutional/extra-articular symptoms may be there with joint pain lasting months	Joints are warm, tender, and swollen. Deformities such as *swan neck and boutonniere* deformities in the hand, and muscle atrophy and subcutaneous nodules maybe present	• Synovial fluid is typically inflammatory. ESR/CRP is often elevated • Hemoglobin may be low due to anemia of chronic disease. Rheumatoid factor, an antibody against IgG, is positive in 70–80% of patients but is nonspecific. Radiographs demonstrate soft tissue swelling, periarticular osteopenia, erosions in joints or joint space narrowing
Seronegative spondyloarthropathies	Polyarticular and symmetric arthritis often associated with other symptoms such as psoriatic rash, low back pain from sacroiliitis, urethritis, or uveitis. Family history of similar illnesses (ankylosing spondylitis, psoriatic arthritis, arthropathy of IBD, Reiter's syndrome, and other reactive arthritides) often present. Onset is subacute (may occur over several months). Morning stiffness may be a component of all of these	In addition to polyarticular and symmetric arthritis, a variety of clinical signs related to the underlying condition (psoriatic rash or uveitis) may be present	Laboratory analysis shows a negative rheumatoid factor, although CBC may show mild anemia with elevated WBC. ESR is often elevated. Up to 80% of patients have HLA-B27 marker. Radiographs may demonstrate sacroiliitis and "bamboo spine" in ankylosing spondylitis. Synovial fluid is typically inflammatory

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Diagnosis	*Symptoms*	*Signs*	*Evaluation*
Trauma/ hemarthrosis	Monoarticular joint pain and swelling, with history of known trauma. In the case of coagulopathy, a history of trauma may be absent. Systemic symptoms are absent, although a personal or family history of bleeding diatheses may be present in patients with coagulopathy	Pain and swelling in the affected joint. Signs of inflammation are minimal acutely. Systemic signs, such as fever are typically absent	Laboratory testing (PT, PTT, bleeding time, and platelet count) may demonstrate evidence of coagulopathy if the hemarthrosis is atraumatic. Radiographs may demonstrate fracture if traumatic etiology. The synovial fluid is bloody, with <10,000 WBC presence of marrow elements possible in trauma
Viral arthritis (immune complex disease)	• Polyarticular (symmetric or asymmetric) concomitantly or following viral syndrome, typically rubella, hepatitis B, parvovirus, mumps, or adenovirus. Typically, the PIP, knee, ankle, and MCP joints are most commonly affected • Other symptoms dependent on the temporal relationship of the arthritis to the primary viral infection; fever with swollen lymph nodes may be the only other symptoms	Fever may be present, and signs of hepatitis or other specific viral illness may be noted. The arthritis is typically severe	Elevated WBC count may be noted. Liver function tests may be abnormal in hepatitis, and should be followed with serologies for specific viral etiologies. The synovial fluid is typically noninflammatory, with cell counts—2,000 cells/mm^3. May develop inflammatory characteristics as the disease progresses

(CBC: complete blood count; CMC: carpometacarpal; CRP: C-reactive protein; DIP: distal interphalangeal; ESR: erythrocyte sedimentation rate; HLA-B27: human leukocyte antigen B27; IBD: inflammatory bowel disease; IgG: immunoglobulin G; MCP: metacarpophalangeal; MTP: metatarsophalangeal; PIP: proximal interphalangeal; PT: prothrombin time; PTT: partial thromboplastin time; WBC: white blood cell)

TABLE 4: Synovial fluid analysis.

Characteristics	*Normal*	*Noninflammatory*	*Inflammatory*	*Septic*	*Traumatic*
Color	Colorless	Yellow	Yellow	Yellow	Red
Appearance	Clear	Clear	Cloudy	Cloudy	Cloudy
WBC/mL	<200	<2,000	2,000–100,000	>100,000	
% PMNs	<25	<25	>50	>95	
Crystals	None	None	May be present	None	None
Cultures	Negative	Negative	Negative	Positive	Negative
Conditions		Trauma, osteoarthritis, and viral infections	Inflammatory arthritis such as, RA, spondyloarthritis, SLE, acute rheumatic fever, reactive arthritis, and crystal-induced arthritis	Bacterial arthritis and tubercular arthritis	Fractures and coagulopathies

(PMNs: polymorphonuclear leukocytes; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; WBC: white blood cell)

TREATMENT

Treatment should be based on differential diagnosis of any patient presenting with joint pain. But few general principles should be followed immediate immobilization of joint, adequate analgesia, joint aspiration in case of septic arthritis, appropriate antibiotics as per suspected antibiotics, and proper referral to concerned specialty as per differential diagnosis.

When to give analgesia?

Step ladder approach should be followed for analgesia like if suspected of degenerative arthritis then begin with paracetamol first, maximum 1 g 6 hourly can be given. If no response than opioid analgesia might help like codeine, tramadol, or morphine in severe cases if no contraindication.

In cases of inflammatory arthritis paracetamol or opioids may give mild relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often helpful in relieving pain in inflamed joint. Steroids can be added judiciously if pain does not get relieved with NSAIDs as former can reduce synovitis and thereby pain.

In cases of crystal arthropathies like gouty arthritis, first line of treatment is NSAIDS in adequate dosages. Secondly colchicine (a microtubular inhibitor to reduce inflammation) may be added to reduce synovitis. In resistant cases or in patients where NSAIDS are contraindicated, steroids can be given in tapering schedule. Sometimes intra-articular steroids can also be given if there is large synovitis which reduces joint inflammation significantly. There is no role of urate-lowering therapy (ULT) (uric acid lowering agent) in acute setting. If patient is already on ULT then it should be continued.

Is there any role of immobilization?

Immobilization of affected joint might help in reducing pain by not stimulating stretch receptors in synovium. Measures like

rest, ice fomentation, compression, and elevation of affected joint can reduce pain. Patients should be encouraged to begin range-of-motion exercises to avoid the loss of function, stiffness, and muscle atrophy once pain relief with all measures (both pharmacologic and nonpharmacologic).

Arthrocentesis: Is it important?
In case of acute onset arthritis, especially monoarthritis, joint aspiration and drainage with lavage help for diagnostic and therapeutic purposes. In cases of septic or infective arthritis, this is most important if large joint like knee or hip is involved. If large joint even have moderate effusion than aspiration and drainage is always better than medical management.

Do antibiotics have any role?
In case of septic arthritis, antibiotic should be started as soon as diagnosis is being made. It could be life-threatening if not treated on time and patient improves with administration of appropriate intravenous (IV) antibiotics and should be broad-spectrum covering major organism such as *Staphylococcus aureus*, *Streptococcus*, and *Escherichia coli*. If organism is methicillin-resistant *Staphylococcus aureus* (MRSA) then IV vancomycin is the drug of choice. In case of gonococcal infection, IV ceftriaxone could be ideal. Acute rheumatic fever is best treated with injectable benzathine penicillin G or oral penicillin V for 10 days. In case if suspicion is of TB, then joint fluid should be sent for demonstration of acid-fast bacillus (AFB) and culture, appropriate drugs should be started as soon as diagnosis is made.

Steroids: Where does it stand in ED for a patient with Joint Pain?
It is very tricky situation regarding usage of corticosteroids in ED. On one hand it can worsen septic arthritis but on the other hand it helps in improving patients of inflammatory or crystal arthritis. It should be used if one has ruled out infective cause. Because of its beautiful anti-inflammatory action steroids does improves synovitis although temporarily. It can be given either intramuscular, IV, or even high-dose pulse therapy in very severe cases. In cases of diabetes mellitus, it should be used with caution or with strict glucose monitoring or control.

When to start disease modifying antirheumatic drugs?
Disease modifying antirheumatic drugs (DMARDs) are the main stay and anchor-sheet drugs in case of inflammatory arthritis like RA. But it may take few weeks to show its action so sometimes steroids can be used as a bridging therapy. Different DMARDs are methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine, cyclosporine, etc. These drugs should be used for long-term but needs frequent monitoring of laboratory tests such as complete blood count, LFTs, and renal function tests for its side effects. If a patient of inflammatory arthritis is already on this drug then it should be continued in ED. DMARDs are true disease modifiers, control long-term disease activity, and complications of primary disease.

What is the role of surgery?
In cases of traumatic or fracture in the joint or joint line or septic arthritis then urgent orthopedic consultation should be sought. Septic arthritis may need lavage of joint or debridement and fracture may need corrective surgery.

SUMMARY

Joint pain is one of the most common presentations in ED. Thorough initial assessment always helps to differentiate and characterize joint pain. All emergency physicians should be well versed in the evaluation of the joint pain. Rarely it can be life-threatening and may be sole manifestation of serious systemic diseases and infections. So "red flags" of joints should be in the mind of every ED clinician if he/she encounters any patient of acute joint pain. These "red flags" are septic arthritis, acute gout, and fracture. On the other hand, inflammatory arthritis can present with acute joint pain and swelling and if not diagnosed and treated on time can lead to long-term deformity and disability. So through clinical examination and then evaluation should be done for any joint pain.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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Overview of Rheumatological Disorders

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CHAPTER

Neeraj Jain, Amit Dua

INTRODUCTION

Rheumatic disorders are a heterogeneous class of chronic autoimmune disorders. They are among the most common chronic diseases. They can affect a wide range of age groups. The spectrum of rheumatic diseases is showed in **Table 1**. About 5% of the population suffer from a chronic inflammatory rheumatic disease. In recent studies it was reported that, in America, a higher number of disabilities are due to inflammatory rheumatic diseases with arthritis than by heart disease, cancer, or diabetes. The Chopra et al. rural community survey in India reported 746 (18.5%) out of 4,092 adults were identified with rheumatological complaints.

CLASSIFICATION AND DEFINITION

Most of the rheumatic diseases can be grouped into 10 major categories. More than 150 rheumatic diseases were classified with specific pathogenesis, clinical features, therapy, and prognosis (**Table 2**).

1. Systemic connective tissue diseases
2. Vasculitides and related disorders
3. Seronegative spondyloarthropathies
4. Arthritis associated with infectious agents
5. Rheumatic disorders associated with metabolic, endocrine, and hematologic disease
6. Bone and cartilage disorders
7. Hereditary, congenital, and inborn errors of metabolism associated with rheumatic syndromes
8. Nonarticular and regional musculoskeletal disorders
9. Neoplasms and tumor-like lesions
10. Miscellaneous rheumatic disorders

ETIOLOGY

Rheumatic diseases are caused by a combination of genes and environmental factors. In general, having certain gene variants can increase a person's susceptibility to rheumatic diseases, and factors in the environment may trigger the onset of the disease. A single gene mutation or a single environmental trigger, most occur as a consequence of a complex interaction of genetic factors and environmental triggers. Some of the environmental predictive and protective factors for rheumatic diseases are depicted in the **Table 3**. Given an overwhelming genetic influence by the human leukocyte antigen (HLA) locus, which include major histocompatibility complex (MHC) and complement genes, individualized recognition and processing of antigens remain a leading pathway to pathogenesis of autoimmunity. Rheumatic disease associations with the MHC are shown in **Table 4**.

EVALUATION

The cardinal manifestations in rheumatology are joint pain and swelling. It is important to recognize the most appropriate cause of joint pain to make proper diagnosis. Detailed history and examination is the cornerstone in diagnosing rheumatic diseases. Rheumatic diseases are multisystem disorders so looking beyond the joints is important to clinch the diagnosis. One must look for rashes, oral and genital ulcers, Reynaud's

TABLE 1: Spectrum of various rheumatic diseases.

Disease	*Type of organ involvement*	*Autoimmune features*	*Examples*
Inflammatory joint diseases	Musculoskeletal	Few	Spondyloarthropathies and reactive arthritis
Inflammation of joints + systemic disease	Musculoskeletal and internal organs	Several	Rheumatoid arthritis
Systemic rheumatic diseases	Multi-organ disease	Many	Systemic lupus erythematosus, scleroderma, and antiphospholipid syndrome

TABLE 2: Definition of common rheumatic disorders.

Disease	*Definition*
Osteoarthritis	Osteoarthritis is the most common form of arthritis which primarily affects and destroys cartilage, the soft tissue that cushions the ends of bones within joints.
Rheumatoid arthritis	Rheumatoid arthritis is known to be one of the most severe and common chronic inflammatory disease with progressive course affecting articular and extra-articular structure resulting in pain, disability, and mortality.
Psoriatic arthritis	Psoriatic arthritis is a complicated disease, characterized by pain, swelling, stiffness, and joints tenderness as well as the surrounding ligaments and tendons.
Juvenile idiopathic arthritis	Juvenile idiopathic arthritis is the most common chronic rheumatic disease in childhood and which may be accompanied by fevers and rashes.
Ankylosing spondylitis	Ankylosing spondylitis is the most common of seronegative spondyloarthropathies and is a chronic progressive inflammatory disease, which primarily affects sacroiliac joints and axial skeleton.
Gout	Gout is the most common inflammatory arthritis caused by deposition of monosodium urate (MSU) crystals formation, which forms due to the presence of increased urate concentration.
Systemic lupus erythematosus	Systemic lupus erythematosus is a systemic autoimmune disease, with multisystemic involvement.
Vasculitis	Vasculitis is a broad term encompassing a group of disorders characterized by blood vessel inflammation and necrosis.
Fibromyalgia	Fibromyalgia a chronic condition marked by tender points and localized pain throughout the musculoskeletal system.
Reactive arthritis	Reactive arthritis, or Reiter's syndrome, a spondyloarthropathy that develops after an infection of the urinary tract, bowels, or other organs.
Polymyalgia rheumatic	Polymyalgia rheumatica which causes pain and stiffness in tendons, muscles, ligaments, and tissues around joints.
Scleroderma	Scleroderma or systemic sclerosis, an autoimmune rheumatic disease that leads to a thickening and tightening of the skin and inflammation and scarring in various other parts of the body, including the blood vessels, joints, and certain organs.
Polymyositis	Polymyositis which affects the muscles and can affect the entire body.

TABLE 3: Some of the environmental predictive and protective factors for rheumatic diseases.

Musculoskeletal condition	*Environmental risk factor*	*Protective factor*	*Risk factors for a poor*
Rheumatoid arthritis	• Female gender • Smoking • Obesity • Silica exposure • Nulliparity	Oral contraceptive use, high fruit intake, and moderate alcohol intake	Rheumatoid factor and anti-citrullinated peptide antibodies
Ankylosing spondylitis	• Male gender • Certain infections	Smoking	
Psoriatic arthritis	• Psoriasis • Trauma		
Gout	• Alcohol (especially beer and spirits) • Dietary factors (e.g., meat, seafood, sugary drinks, and fructose) • Early menopause • Thiazide and loop diuretics • Chemotherapy for cancer • Components of the metabolic syndrome	Dietary factors (e.g., dairy produce, cherries, and coffee)	

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Musculoskeletal condition	*Environmental risk factor*	*Protective factor*	*Risk factors for a poor*
Systemic lupus erythematosus	• Female gender • Ethnicity • Current smoking • Silica exposure • Female hormones • Some drugs	Moderate alcohol intake	• Ethnicity • Lower socioeconomic status
Scleroderma	• Female gender • Ethnicity • Silica exposure • Organic solvents • Some drugs (e.g., bleomycin)		
Polymyalgia rheumatica	• Female gender • Age >50 • Northern latitude		
Osteoarthritis of the hip	• Obesity (bilateral disease) • Childhood hip disease (e.g., Perthes) • Hip dysplasia • High bone mass • Certain occupations (e.g., farming)	Frequent squatting	
Osteoarthritis of the knee	• Obesity • High bone mass • Joint laxity • Certain sports (e.g., football) and occupations	Smoking	• Obesity • Quadriceps muscle weakness • Low vitamin C or D intake

TABLE 4: Rheumatic disease associations with the major histocompatibility complex.

Gene	*Disease*
HLA	Systemic sclerosis
HLA-B	Ankylosing spondylitis
HLA-B	Behçet's disease
HLA-B	Sarcoidosis
MICA	Behçet's disease
MICA	Rheumatoid arthritis
TNF	Ankylosing spondylitis
TNF	Rheumatoid arthritis
NFKBIL1	Rheumatoid arthritis
BTNL2	Sarcoidosis
HLA class II	Juvenile ankylosing spondylitis
HLA class II	Systemic lupus erythematosus
HLA class II	Systemic sclerosis
HLA-DRB1	Rheumatoid arthritis
HLA-DRB1	Sarcoidosis
HLA-DRB1	Sjögren's syndrome
HLA-DRB1	Takayasu arteritis
TAP2	Rheumatoid arthritis
TAP2	Sjögren's syndrome
TAP2	Systemic lupus erythematosus

phenomenon, digital ulcers, thickening of skin, and eye involvement.

Stepwise Approach to the Patient with Musculoskeletal Pain

There are numerous causes of arthritis or musculoskeletal complaints. This stepwise approach to arthritis is important to narrow down the diagnostic possibilities to only few conditions.

The *first step in the approach* is to identify whether the pain is arising from the joints, i.e., from joint capsule, synovium, synovial fluid (SF), cartilage intra-articular ligaments and adjacent bones (articular origin) or from the periarticular structures (bursa, tendon, muscle, bone, and ligaments). Rheumatoid arthritis (RA) is a disease of synovium and osteoarthritis involves cartilage. These are the examples of true arthritis. Achilles tendonitis causing ankle pain, carpal tunnel syndrome causing wrist pain, frozen shoulder, etc., are all not true arthritis but are examples of periarticular pain. In arthritis, pain emerges with virtually all movements of the joints but periarticular pain is selective and localized to the structure affected. **Table 5** enumerates the difference between articular and periarticular pain. *As a second step*, we should look for the number of joints involved (**Table 6**). *Third step* is to identify the duration of joint pain. Conventionally arthritis duration of <6 weeks is acute arthritis, and ≥6 weeks is chronic arthritis. *Fourth step* is to differentiate whether the arthritis is inflammatory or noninflammatory in nature. This is the most important step as it determines the management and prognosis of the patient. This is because if the inflammatory arthritis is not diagnosed

TABLE 5: Difference between articular and periarticular pain.

Articular	*Periarticular*
Pain is deep and diffuse	Pain is localized
Painful and limited range of movement in both active and passive movement of the involved joints	Pain is more in active movement
Swelling and tenderness over joints	Local tenderness and swelling in region away from joint line
Deformity, crepitus, instability, and contractures are seen	Rare

TABLE 6: Number of joints involved.

Number of joints	*Types of arthritis*
1	Monoarthritis
2–4	Oligoarthritis
>4	Polyarthritis

and treated timely can cause deformities, e.g., as in RA and psoriasis, and even can cause life-threatening complications if major organs are involved as in systemic lupus erythematosus (SLE), vasculitis, etc. The classical sign of inflammation (namely red, hot, tender, swallow, and nonfunctional) may not always be used to classify arthritis as inflammatory and noninflammatory, as these signs may not be easily recognizable in all cases of inflammatory arthritis, moreover, noninflammatory conditions like traumatic arthritis may have some inflammatory signs. Therefore, rheumatologists have identified some sets of clinical features that can differentiate between inflammatory and noninflammatory arthritis with good sensitivity and specificity (**Table 7**). *Morning stiffness* is defined as the time to maximal improvement after prolonged period of inactivity. Inflammatory arthritis is characterized by the presence of prolonged early morning stiffness (after waking up in the morning) and is present at least for 30 minutes, sometimes may be for hours. Activity (gentle use of the joints) improves the symptoms but inactivity increases the stiffness. **Flowcharts 1** and **2** summarize the approach to a patient with musculoskeletal pain.

DIAGNOSIS

Acute polyarthritis is a diagnostic challenge as this category of arthritis has much differential diagnosis and many a times it is not possible to diagnose the exact cause at the onset of disease. Acute inflammatory polyarthritis could either be a self-limiting viral arthritis or it could be life-threatening and can cause high mortality. It could be the onset of a chronic illness such as RA. The causes may be RA, lupus, vasculitis, hematological malignancies, septic arthritis, reactive arthritis, crystal arthropathies, etc.

For diagnosing patients with chronic oligoarthritis or polyarthritis, we need to identify the pattern of evolution of joint involvement. There are three patterns of joint involvement. They are additive, migratory, and recurrent (intermittent). In additive pattern, the affected joints are added progressively,

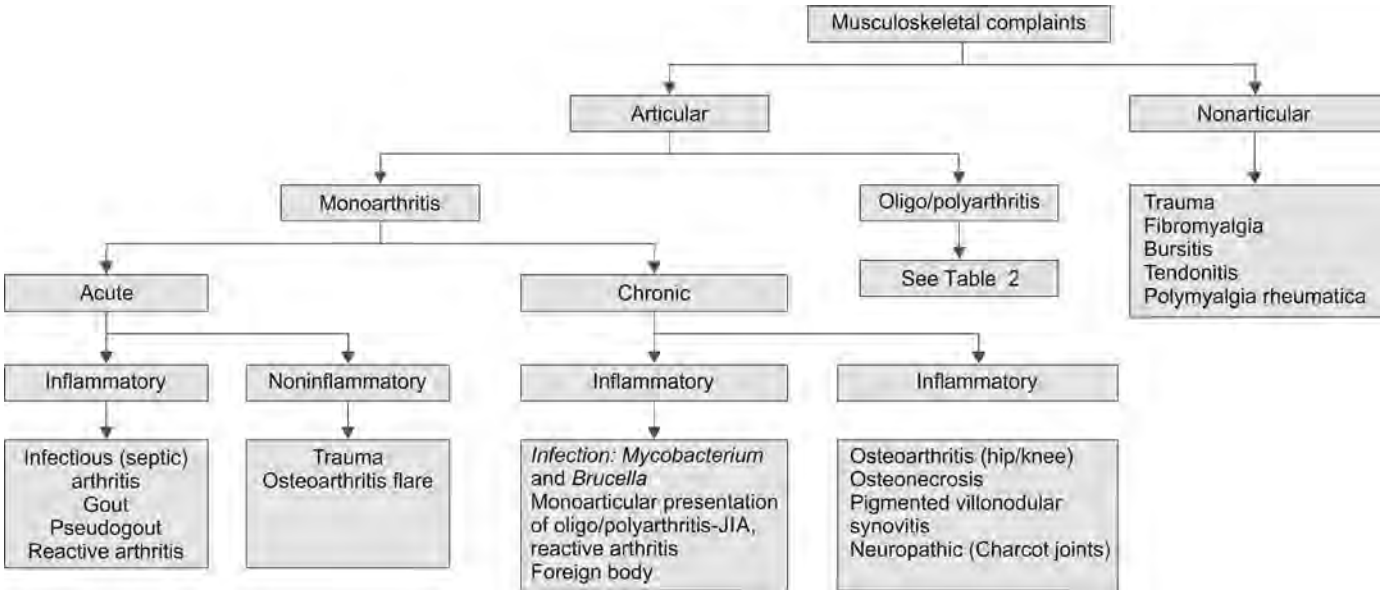
TABLE 7: Clinical features distinguishing inflammatory and noninflammatory arthritis.

	Inflammatory	*Noninflammatory arthritis*
Early morning stiffness (EMS)	>30 minutes, may last for hours	Brief
Inactivity stiffness	Prolonged, precipitated with prolonged inactivity	Brief, precipitated with brief periods of rests (gel phenomenon)
Pain increase	Prolonged inactivity	On repeated use of joints
Pain decrease	With exercise and gentle use of joints	On taking rest
Constitutional symptoms—fatigue, low grade fever, and weight loss	+	–
Effusion	+++	+/–
Erythema	+/–	–
Crepitus	–	+++
Malalignment/deformity	–	+
Instability	–	+/–

i.e., many joints are getting involved over time, e.g., RA. In migratory pattern, the inflammatory process flits from one joint to another as seen in rheumatic fever and gonococcal arthritis. In intermittent or recurrent pattern there are episodes or crises of arthritis separated by symptom-free "intercritical" intervals, e.g., palindromic rheumatism and acute gout.

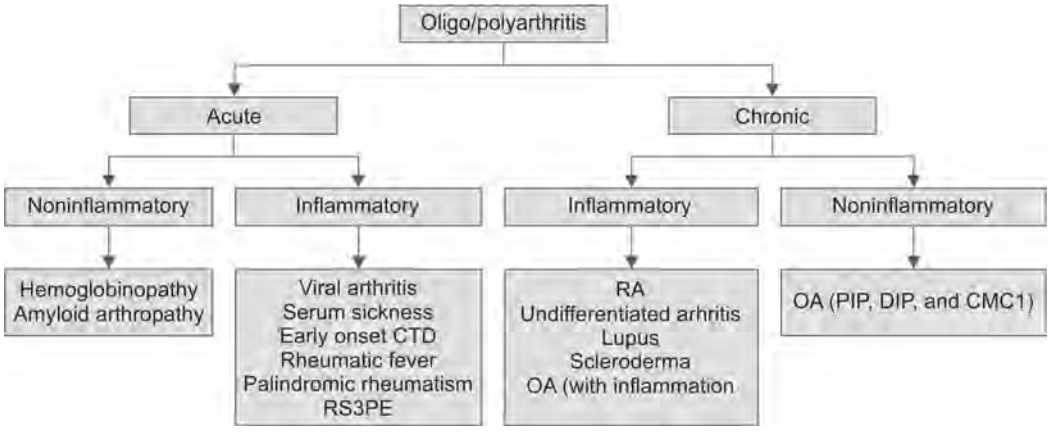
Apart from pattern, distribution of joint involvement (topography) also helps in further narrowing down the diagnostic possibilities. Before describing the topography, one should be aware of the following anatomical regions and pattern of joints involvement. Peripheral joints are the joints of extremities, axial joints mean the spine and sacroiliac joints, root joints mean which connects axial with peripheral joints, i.e., shoulder and hip joints. Proximal arthritis mainly affects the large joints, i.e., proximal to wrist or ankle and spine, e.g., spondyloarthropathy (SpA), Behçet's, and juvenile idiopathic arthritis (JIA). Distal arthritis mainly affects small joints of hands and feet with or without involvement of ankle and wrist, e.g., SLE and RA. Arthritis can be predominantly proximal or predominantly distal or it can be a mixture of both involving small and large joints. For peripheral arthritis, it is important to note the symmetry or asymmetry of joint involvement. Symmetrical involvement means arthritis affects the same joint groups on each side of the body and asymmetrical involvement means that there is no correlation between the joints affected on either side. Topography of joints and their differential diagnosis are shown in **Flowchart 3**.

Although most rheumatic disease diagnosis is made through detailed history and physical examination but investigations are also helpful in some cases, if used judiciously. Investigations are important guides not only for screening and confirming diagnosis but they also help in following disease



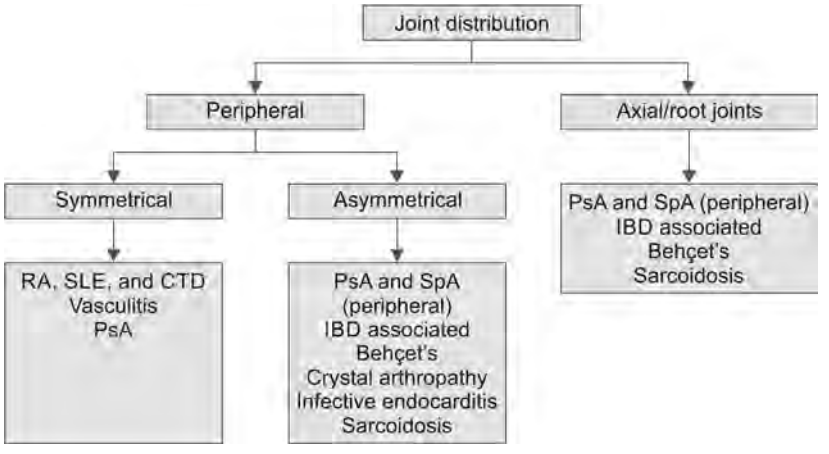
(JIA: juvenile idiopathic arthritis)

FLOWCHART 1: Algorithm showing approach to musculoskeletal complaints with differential diagnosis of monoarthritis.



(CMC: carpometacarpal joint; CTD: connective tissue disease; DIP: distal interphalangeal; OA: osteoarthritis; PIP: proximal interphalangeal; RS3PE: remitting seronegative symmetrical synovitis with pitting edema)

FLOWCHART 2: Differential diagnosis of oligo/polyarthritis.



(CTD: connective tissue disease; IBD: inflammatory bowel disease; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SpA: spondyloarthropathy)

FLOWCHART 3: Topography of joint involvement and their differential diagnosis.

activity and response to treatment. Investigations may also determine the prognosis of the disease.

As the understanding of rheumatic disease progresses, new biomarkers are developed and the utility of existing ones is refined. Laboratory tests can be valuable guides for screening, confirming diagnosis, establishing disease stage, and prognosis, as well as for following disease activity and response to treatment.

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) frequently correlate well with disease activity in inflammatory disorders. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies are helpful in diagnosing RA. The specificity of RF for RA is poor. Antinuclear antibodies (ANAs) are found in many patients with rheumatic diseases and in essentially all patients with SLE and systemic sclerosis (SSc). Under the proper clinical conditions, the finding of a positive ANA assay is an indication for additional investigations directed at identifying the precise autoantibody leading to the ANA pattern. Autoantibodies directed against individual antigens have increased specificity for particular diseases. These autoantibodies are associated with a range of different rheumatic diseases (**Table 8**). Some investigators believe anti-CCP antibodies have a role in the pathogenesis of RA. Despite the development of increasingly sophisticated serologic tests and imaging techniques, SF analysis remains one of the most important diagnostic tools in rheumatology. Imaging modalities that are important in rheumatology include conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, radionuclide imaging, arthrography, bone densitometry, and angiography.

TREATMENT

For successful treatment, identifying each condition and its variations is essential. Various types of medication are prescribed to treat rheumatic diseases (**Table 9**). Some drugs only treat symptoms such as pain and inflammation, while others can alter the course of the disease. Disease-modifying antirheumatic drugs (DMARDs) are a class of drugs indicated for the treatment of inflammatory arthritides including RA, psoriatic arthritis (PsA), and ankylosing spondylitis (AS). They can also be used in the treatment of other disorders including connective tissue disease such as SSc, SLE, and Sjögren's syndrome (SS), as well as in treatment of inflammatory myositis, vasculitis, uveitis, inflammatory bowel disease, and some types of cancers. DMARDs are classified as either conventional DMARDs or biologic DMARDs. Biologic DMARDs are highly specific and target a specific pathway of the immune system in rheumatic disease (**Table 10**).

TABLE 8: Rheumatic diseases and autoantibodies.

Pattern	*Nuclear antigen*	*Clinical associations*
Anti-dsDNA	Antibodies to dsDNA	• High specificity for SLE • Often correlates with more active, more severe disease • ELISA test is very sensitive and can be positive in other diseases, normal people
Anti-histone	Five major types exist	• SLE, drug-induced SLE, and other autoimmune disease • SLE patients will likely be positive for other autoantibodies as well
Anti-ENA	• Sm (Smith) • RNP (ribonucleoprotein) • RNA–protein complexes	• High specificity for SLE • Mixed connective tissue disease • Higher prevalence in African American and Asian patients
Anti-SSA (Ro)	Ribonucleoproteins	SLE (especially subacute cutaneous lupus), neonatal lupus, and Sjögren's syndrome
Anti-SSB (La)	Ribonucleoproteins	Sjögren's syndrome, SLE, and neonatal SLE
Anti-centromere	Antibody to centromere/kinetochore region of chromosome	• Limited scleroderma • High rate of pulmonary hypertension • Primary biliary sclerosis
Anti-Scl-70	Antibodies to DNA topoisomerase 1	• Diffuse scleroderma • Risk of pulmonary fibrosis
Anti-Jo-1	Antibody to histidyl-tRNA synthetase	• Poly/dermatomyositis • Patients tend to have interstitial lung disease, Raynaud's phenomenon, mechanic's hands, and arthritis • Typically resistant to treatment
Anti-SRP	Antibody to signal recognition protein	• Cardiomyopathy • Poor prognosis
Anti-PM-Scl	Antibody to nucleolar granular component	Polymyositis/scleroderma overlap syndrome
Anti-Mi-2	Antibodies to a nucleolar antigen of unknown function	• Dermatomyositis • Favorable prognosis

(dsDNA: double stranded deoxyribonucleic acid; ELISA: enzyme-linked immunosorbent assay; SLE: systemic lupus erythematosus)

TABLE 9: Drug treatment of inflammatory rheumatic diseases.

Drugs	*Rheumatoid arthritis*	*Connective tissue diseases**	*Spondyloarthropathies*
NSAID	+	+	+
Glucocorticosteroids	+	+	+
Immunosuppressive			
Gold	+		
D-penicillamine	+	+	
Antimalarials	+	+	
Sulfasalazine	+		+
Azathioprine	+	+	+
Cyclosporine	+	+	
Leflunomide	+		
TNF-antagonists	+		+
Mycophenolate	+	+	
Cytotoxic			
Methotrexate	+	+	+
Cyclophosphamide	+	+	
Anticoagulants		+	

*Systemic lupus erythematosus, antiphospholipid syndrome, polymyositis, dermatomyositis, scleroderma, and mixed connective tissue disease.

TABLE 10: Biologic DMARDs for rheumatic diseases.

Target	*Drug*	*Disease*
TNF-α inhibitor	Adalimumab	• Ankylosing spondylitis • Psoriasis/psoriatic arthritis • Rheumatoid arthritis • Crohn's disease
	Etanercept	• Ankylosing spondylitis • Psoriasis/psoriatic arthritis • Graft-versus-host disease
	Golimumab	• Ankylosing spondylitis • Psoriatic arthritis • Rheumatoid arthritis • Ulcerative colitis
IL-17 inhibitor	Secukinumab	• Ankylosing spondylitis • Psoriasis/psoriatic arthritis
IL-17A inhibitor	Ixekizumab	• Psoriasis/psoriatic arthritis
IL-6 inhibitor	Tocilizumab	• Giant cell arteritis • Rheumatoid arthritis
IL-12/23 inhibitor	Ustekinumab	• Psoriasis/psoriatic arthritis • Crohn's disease
mAb directed against CD20 antigen on B-cells depletes and inhibits B-cells	Rituximab	• Granulomatosis polyangiitis • Rheumatoid arthritis • Pemphigus vulgaris • Microscopic polyangiitis
• Anti-CD257 (BAFF) mAb • Inhibits B-cell survival	Belimumab	Systemic lupus erythematosus
Small molecule (JAK Inhibitors)	Tofacitinib Baricitinib	Rheumatoid arthritis

(BAFF: B-cell activating factor; DMARDs: disease-modifying antirheumatic drugs; IL: interleukin; JAK: Janus kinase; mAb: monoclonal antibody; TNF-α: tumor necrosis factor α)

SUMMARY

Rheumatic disorders are among the most prevalent chronic diseases of the musculoskeletal system and connective tissue, and they can affect a wide range of age groups. Their etiology is still not completely clear, and they cannot be effectively prevented. Identifying each condition and its variations is essential for effective treatment.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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152 CHAPTER

Evaluation of Mental Health and Common Psychiatric Emergencies

Mohammad Anzal Rehman, Mansoor Masarrat Husain

INTRODUCTION

Mental and behavioral health disorders constitute a significant portion of all emergency department (ED) visits. A systematic review in 2016 concluded 4% of ED visits to be attributable to psychiatric causes. However, prevalence has been shown to have a significant degree of variability between institutions. Commonly encountered acute presentations involve self-harm, substance abuse, suicidality, agitation, and/or exacerbations of underlying mood, anxiety, and thought disorders. The prevalence of psychiatric disease presentation to the ED has seen a significant rise over the years. Despite the relative frequency of presentation, Emergency physicians still face considerable challenges when encountering these patients. This is owed in no small part to the fact that psychiatric emergencies are vastly underrepresented in most emergency medicine academic curriculums. Reduced exposure to psychiatric disease during clinical training, along with the inherently confounding nature of acute mental illness often contribute to emergency physician hesitance when faced with these patients in the ED. Nevertheless, the ED continues to grow increasingly responsible for providing care to patients presenting with mental and behavioral health issues, making it crucial for emergency physicians to practice and develop skills in acute psychiatric care. This chapter will attempt to highlight techniques in recognition, assessment, management, and disposition of commonly encountered psychiatric emergencies.

EVALUATION OF MENTAL HEALTH

Assessment at Triage

The psychiatric patient may present to the ED in a variety of ways. These patients are often either referred by existing psychiatric and primary care providers, or they are brought in by police or emergency medical services due to acutely agitated, self-harming, disruptive, or intoxicated states. Occasionally, patients with psychiatric complaints will refer themselves to the ED, and there are even instances where psychiatric disease is newly uncovered by the emergency physician while evaluating the patient for a separate medical condition. Recognition of psychiatric disease therefore forms an integral component of appropriate care for these individuals. Most emergency triage systems are ill-equipped to adequately recognize patients with mental or behavioral health issues, as they are generally tailored toward assessment for medical complaints. However, specialized triage assessment systems, termed as *Mental Health Triage Scales (MHTS)* (**Table 1**), may provide more reliable means of gauging severity in psychiatric illness for patients presenting to the ED. Understandably, severity is usually estimated by assessment of risk of harm to self and/or others.

Evaluation

The initial ED assessment for a psychiatric patient frequently aims to identify the presence of a medical condition that may be causing or worsening the patient's mental health before addressing the psychiatric issue. The American College of Emergency Physicians (ACEP) recommends a focused medical assessment in the ED whereby any organic causes of disease can be identified through relevant diagnostic evaluation as needed based on the patient's presenting signs and symptoms.

Routine laboratory testing and diagnostics are not recommended to exclude medical causes for the patient's condition. Investigations may be useful, however, in those patients over 45 years of age with new onset of psychiatric symptoms, those with cognitive impairment, delirium, substance abuse or withdrawal, decreased levels of consciousness, abnormal vital signs, or advanced age (≥65 years).

History

Patients with mental and behavioral disorders present a unique challenge to the interviewing physician. An altered mental status may predispose to inaccurate, unreliable, and incomplete histories when taken from the patient themselves. Where patients can adequately articulate their problems, fear of repercussions or ulterior patient motives may confound the reported history. When conducted amidst the commotion of the ED, history taking can turn into quite an unsettling experience for the patient.

TABLE 1: Example of a commonly used Australian Mental Health Triage Scale (MHTS).

Triage code	*Description*	*Treatment acuity*	*Typical presentation*
1	Definite danger to life (to self and others)	Immediate	• Violent behavior • Possession of weapons • Self-destructive behavior in emergency department (ED)
2	Probable risk of danger to self and others (severe behavioral disturbance)	Emergency (within 10 minutes)	• Extreme agitation/restlessness • Physically/verbally aggressive • Require restrain • Attempt to self-harm and others also
3	Possible risk of danger to self and others (moderate behavioral disturbance and severe distress)	Urgent (within 30 minutes)	• Agitation/restlessness • Intrusive/bizarre/disorganized behaviors • Confusion withdrawn and uncommunicative • Suicidal ideation, hallucination, delusion paranoid ideas, severe symptoms of depression, and anxiety. Elated and irritable mood
4	Moderate distress	Semiurgent (within 60 minutes)	• No agitation restlessness • Irritability without aggression • Cooperative • Gives coherent history • Symptoms of anxiety depression without suicidal ideation
5	No harm to self and others (no acute distress and no behavioral disturbance)	Nonurgent (within 120 minutes)	• Cooperative • Communicative • Known patient of psychotic symptoms • Financial/social/relationship problem • Minor adverse effect of medication

Source: Broadbent M, Moxham L, Dwyer T. The development and use of mental health triage scales in Australia. Int J Ment Health Nurs. 2007;16(6):413-21.

Good interview technique involves the use of calm, open-ended questions, with emphasis and further elaboration on concerning signs of illness. Besides discussion of recent symptoms and the current condition, it is vital to also obtain information about past medical, surgical, and family history, known medication or substance use, lifestyle, allergies, and previous hospital visits or admissions. When possible, utilize accompanying or known friends, family, caretakers or even law enforcement, and emergency medical services personnel as sources of information. History taking questions should attempt to explore and identify changes in mood, affect, thought, speech, judgment, altered perceptions, and substance abuse, with particular emphasis on suicidal or homicidal ideation.

Physical Examination

Unfortunately, due to the complexity and unconventional presentations of psychiatric disease in the ED, physicians often overlook performing a complete physical examination and thorough review of systems. Since medical disease can cause or even worsen psychiatric complaints, the importance of an initial medical assessment for the patient cannot be understated.

When examining the patient who displays signs of altered mental status, considered exclude nonpsychiatric causes, an organized approach is useful to ascertain the specific type of alteration and its degree. Begin by evaluating the patient's level of consciousness, which will vary based on their alertness, awareness, and attention. A commonly used tool to assess for this is the Glasgow Coma Scale (GCS), which looks at motor, verbal, and eye-opening responses to estimate the patient's consciousness level. Any alteration in consciousness will undoubtedly also impact cognition and behavior.

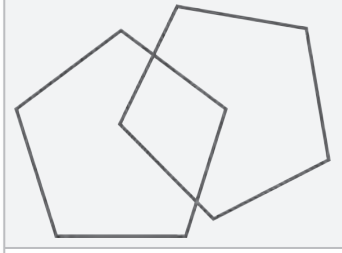
Cognitive assessment should start by assessing the patient's orientation, which indicates awareness of their situation and surroundings. Orientation assessment involves asking the patient to identify themselves, usually with a request to verbalize their full name, and then mention where they are and what time (or time of day) it is to establish orientation to person, place, and time. You may proceed further with a focused *Mini-mental State Examination (MMSE)* to review the patient's attention, memory, and executive function (**Table 2**). The ease of incorporation and relatively short amount of time needed to complete assessment makes the MMSE one of the more relevant tools to integrate into ED examinations for altered mental status.

An impaired cognitive ability may signify dysfunction secondary to dementia or delirium. The unpredictable and changeable pattern of delirium may be better identified using the *Confusion Assessment Method (CAM)*. The CAM diagnostic algorithm looks at four features:

1. Acute onset and fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

The diagnosis of delirium is then made when both features 1 and 2 are present along with either one of 3 or 4.

TABLE 2: Example of a standard Mini-mental State Examination form.

Mini-mental State Examination (MMSE)	Patient name: _____ Date: _____ Medical Record Number: _____	
One point for each correct answer	Patient score	Maximum score
Orientation		
What is the (year) (season) (date) (day) (month)?	__	5
Where are we: (state) (county) (town or city) (hospital) (floor)?	__	5
Registration		
Name three common objects (e.g., apple, table, and penny)	__	3
Note: Take 1 second to say each. Then ask the patient to repeat all three after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all three. Count trials and record. Trials:		
Attention and calculation		
Spell "world" backwards. The score is the number of letters in correct order. (D___L___R___O___W___).	__	5
Recall		
Ask for the three objects repeated above. Give 1 point for each correct answer.	__	3
Note: Recall cannot be tested if all three objects were not remembered during registration		
Language		
Name a "pencil" and "watch"	__	2
Repeat the following: "No ifs, ands, or buts"	__	1
Follow a three-stage command: "Take a paper in your right hand, fold it in half and put it on the floor"	__	3
Read and obey the written statement: "close your eyes"	__	1
Write a sentence (with subject and verb)	__	1
Copying		
Copy the following: 	__	1
Total Score	___	30
Key: **24–30: No cognitive impairment** **18–23: Mild cognitive impairment** **0–17: Severe cognitive impairment**		

Source: Adapted from Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.

INVESTIGATIONS

As mentioned earlier, laboratory testing is guided by focused medical assessment for each patient and routine investigations may not be necessary for the evaluation of patients without high risk of disease, despite the common practice of being requested from the emergency physician by psychiatric facilities and colleagues. When incorporated, the most essential test to include is blood glucose at triage or initial presentation, along with a full set of vital signs, oxygenation, and electrocardiogram (ECG) where feasible.

Other valuable laboratory investigations that may be useful include a complete blood count (CBC), electrolytes, comprehensive metabolic panel, urinalysis, pregnancy testing, and blood levels of known psychiatric medication (e.g., lithium, valproate, etc.) as appropriate for the patient. Suspicion of drug or alcohol intoxication should be established by clinical assessment of level of consciousness, cognition, coordination, gait, and/or nystagmus. Current ACEP guidelines advise against routine urine toxicological screens in awake, alert, and cooperative ED patients as these will not affect acute care management. Blood alcohol concentrations also correlate

poorly with level of intoxication, which should be a clinical diagnosis rather than a laboratory one. These are usually only utilized where altered mental status has no other known or explained etiology.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain are often debated for their use in exclusion of organic causes in the psychiatric patient. However, there are very few instances where neuroimaging will result in actionable findings in acute psychiatric complaints, leading to recommendations against using them routinely for these patients. In the ED, a noncontrast CT may be of some benefit in those patients with acute psychiatric presentations that have focal neurologic deficit, head trauma, new-onset seizures, new-onset psychosis in older patients (psychotic disorders unlikely to manifest for the first time in those older than 40 years), immunosuppression, excessive cognitive decline, or altered level of consciousness not otherwise explained by other etiologies.

HIGH-RISK PSYCHIATRIC PRESENTATIONS IN THE EMERGENCY DEPARTMENT

Agitation

A US study in 2018 revealed that, though the prevalence of agitation among patients presenting to the ED is approximately 2.6%, an overwhelming majority of agitated patients require restraint, with many patients experiencing subsequent clinical events. Despite the fact that agitated patients present unique challenges that include violence toward healthcare professionals, most physicians tend not to receive formalized training in managing these high-risk individuals.

Causes of agitation may be metabolic, ranging from electrolyte abnormalities, abnormal glucose levels, and hypoxia to disorders of thyroid hormones and nutritional deficiencies (e.g., Wernicke's encephalopathy). Infectious causes, shock, thermal dysregulation, intracranial injury or abnormality, and toxins can all manifest as agitation. Psychiatric causes of agitation can include psychosis, schizophrenia, delusions, and personality disorders. It is therefore essential to keep broad a differential diagnosis in mind when dealing with agitated patients, as most of the conditions above will likely require rapid identification and timely management for reversal of symptoms.

Initial assessment of the agitated patient should prioritize safety, with adequate screening of the patient for weapons, interview conducted in a room that allows privacy without compromising security, easily accessible entry and exit points for the provider and readily available personnel and protocols for appropriate restraint and intervention, as necessary. The ED physician should consider the use of verbal deescalation tactics first when the situation allows, and the patient appears to be receptive and cooperative. These include communicating with the patient in a calm, concise, and respectful manner while avoiding provocative statements, threats, and condescension.

If verbal techniques fail to manage the patient's agitation, the use of restraint should be considered. Typically, chemical restraint is preferable to physical restraint, but these may be used in combination as appropriate for the severely combative patient. Pharmacologic options traditionally incorporate antipsychotic agents and benzodiazepines. Classically, first-generation (typical) antipsychotics such as haloperidol [2.5–5 mg intramuscular/intravenous (IM/IV)] were used. However, second-generation (atypical) antipsychotics, such as olanzapine (10 mg IM or 5–10 mg PO) have been shown in recent studies to perform better with lower rates of adverse events compared to first-generation antipsychotics. Commonly used benzodiazepines include lorazepam (2–4 mg IM/IV) and midazolam (2.5–5 mg IM/IV). All medication used to control agitation should aim to calm, not sedate the patient, and can be titrated up to achieve the desired effect.

Several recent studies have explored the use of IM ketamine at 5 mg/kg (1–2 mg/kg IV) in controlling agitation, revealing that it may be superior in efficacy, safer, with a faster onset when compared to conventionally used medication, such as haloperidol and midazolam. However, the drug may be associated with more complications, loses its effect faster and can even cause acute agitation in patients with schizophrenia.

Physical restraint, when applied, should be done so in a systematic, team-based approach with coverage of five points (four limbs and head) and avoidance of prone positioning. In any form of restraint, postrestraint monitoring and evaluation should be implemented to assess for any adverse effects from the intervention to the patient and progression of patient condition.

Delirium

Delirium has been described as an acute disturbance in attention and awareness that fluctuates in severity and is not otherwise explainable by an existing underlying disease process. It can present as hypoactive, hyperactive, or mixed type, with the sign being highly predictive of worse outcomes, especially in older patients.

Unfortunately, healthcare providers often fail to recognize delirium in the ED, leaving patients vulnerable to clinical deterioration and showcasing a need for a more systematic approach to better identify delirium. Though several tools exist to facilitate recognition of delirium in healthcare settings, the CAM may be preferred for use in the ED, largely due to its superior performance in reliably identifying delirium as well as its feasibility as a bedside assessment method. According to the CAM, criteria for delirium are met if the patient has an acute onset with fluctuating course and inattention with either disorganized thinking or an altered level of consciousness.

Several variables can serve as triggers for delirium. These include drugs (e.g., anticholinergics, alcohol, medication interactions or changes, sedative, or anesthetic medication), electrolyte disturbances, infection, cerebral abnormalities (e.g., stroke, encephalopathy, and space-occupying lesions), uremia, shock, hypoxia, and cardiac injury (e.g., heart failure, arrhythmia, or arrest). Management of delirium therefore revolves primarily around identification and treatment of the underlying cause. Ongoing delirium with no identifiable cause or no significant improvement with intervention may be managed pharmacologically with antipsychotic medication, such as haloperidol.

Catatonia

Catatonia is a neuropsychiatric phenomenon that can be observed in various neurologic, medical, and psychiatric disorders. While it was initially perceived to be associated with

schizophrenia, over the past few decades it has been shown not to be uniquely linked to any one disease and is slowly being recognized as its own distinct entity.

Catatonia can present as a wide variety of symptoms, such as stupor, negativism, posturing, echolalia, echopraxia, rigidity, waxy flexibility, agitation, mutism, and catalepsy. Immobility and mutism have been shown to be the most common signs of catatonia, but three or more of the signs above are considered diagnostic. Catatonia is generally classified into two subtypes: excited (e.g., agitation, impulsivity, and excitement) and retarded-stuporous (e.g., rigidity, immobility, stupor, mutism, and echophenomena) and catatonia. Malignant catatonia is a rare, severe form that presents with hyperthermia, tachypnea, hypotension, tachycardia, labile blood pressure, and excitement alternating with stupor.

It is important to note that catatonia may be associated with an underlying medical cause and management should focus on investigation for and reversal of these where appropriate. Catatonia also lends itself to various medical complications, such as pulmonary embolism, rhabdomyolysis, urinary tract infection, dehydration, aspiration, and electrolyte abnormalities.

Patients are primarily treated with benzodiazepines, such as lorazepam and diazepam, which have shown to be particularly effective in retarded-stuporous types of catatonia. Typical antipsychotics, antidopaminergics, and neuroleptics are generally avoided as they may worsen disease symptoms. Symptoms refractory to benzodiazepines may be candidates for electroconvulsive therapy (ECT).

Self-harm

Self-harm is described as an intentional injury or poisoning of oneself, which may or may not include suicidal ideation or attempt. It is usually a manifestation of a maladjusted emotional response to distressing stimuli or triggers. Patients of self-harm are often particularly vulnerable and distraught, with the extreme nature of the phenomenon making them more likely to present to EDs. Therefore, it is vital for healthcare providers assigned to these patients to understand the fragile nature of presentation and their roles in providing compassionate care without the influence of commonly encountered negative attitudes surrounding the concepts of self-harm.

Current standards of assessment for self-harm in the ED are highly variable and risk assessment tools for suicide are underdeveloped and often not properly utilized, increasing the likelihood that many patients with substantial risks are missed or undetected. Improved awareness about self-harm with regular, formalized training, and the potential integration of psychiatric liaison team (PLT) in the ED can all assist in improving care for these patients.

Protect the patient first by placing them in a private room without any dangerous objects, de-escalate any acute agitation as needed and perform a focused medical assessment to search for any underlying organic condition. Patients should undergo risk assessment for suicide and safety for discharge. Consideration of risk should combine clinical judgement as well as factors for family and community, with a low threshold for consultation with the psychiatry team. Specific risk factors to identify would include prior attempts, history of psychiatric illness, presence of triggering events (e.g., abuse), signs of impulsiveness, anhedonia, or psychosis as well as access to firearms.

Communication plays a vital role in exploring the frequency and intensity of suicidal ideation, and the physician should attempt to ascertain the presence of a prepared plan, history of previous attempts, and patient's beliefs on self-harm to thoroughly comprehend the risk of suicide. Presence of social, religious, or personal coping mechanisms may be protective for some patients. Most patients with considerable risk of suicide will typically be admitted to the hospital. However, any patients discharged after being deemed to be low risk should cautiously and comprehensively document their decision-making, risk assessment, findings, rationale, and any consultations as appropriate.

OVERVIEW OF PSYCHIATRIC ILLNESS

Mood Disorders

Mood can be defined as a state of mind or an emotion that one is feeling. A mood disorder occurs when this state of mind lasts for a significant length of time and significantly impairs function. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) broadly separates mood disorders into two groups—depressive disorders and bipolar disorders.

The etiology of mood disorders is not fully understood as there are many complex factors at play including neuroanatomy, neurochemistry, drug and alcohol use, and complex environmental, social, and cultural factors that can vary significantly in different patient populations.

Depressive Disorders

The most common feature of depressive disorders is a feeling of anhedonia, which is defined by a loss of interest or feeling of pleasure in activities and situations that would bring joy to most people.

Up to one in five Americans will meet the DSM-5 criteria for a depressive disorder at some point in their life. Mood disorders are very common in patients who present to the ED. One study showed that 76% of patients with depressed mood visited an ED one or more times in the last 6 months. Another study showed that on screening patients who visited an ED using the Beck Depression Inventory-II (a widely used test for measuring the severity of depression), 15% had mild depression, 20% had moderate depression, and 8% had severe depression.

Life events such as being the subject of abuse (physical, sexual, emotional, financial, domestic, and neglect), bereavement, chronic illness, and catastrophe can all trigger or worsen symptoms of a depressive disorder. These psychosocial factors are often complex and not easily defined.

There is a link between low levels of norepinephrine, serotonin, glutamate, and γ-aminobutyric acid in the brain and the likelihood of suffering a depressive episode. Antidepressant medications target these neurochemicals (and others) and aim to increase their levels. Other physiological factors that have been implicated in depressive disorders include cortisol levels and neuroanatomical variations. Additionally, there is some evidence towards familial concordance in severe mood disorders pointing towards a genetic link.

The *DSM-5* criteria for diagnosing depression are as follows:

- Depressed mood (also irritable mood in children and adolescents)
- Loss of pleasure or diminished interest in almost all activities (anhedonia)

- Significant weight change or appetite disturbance (failure to achieve expected weight gain in children)
- Sleep disturbance (too little or too much sleep)
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Feelings of worthlessness
- Decreased ability to think or concentrate or indecisiveness
- Recurrent thoughts of death, recurrent suicidal ideation (with or without a plan), and a plan for committing suicide or a suicide attempt.

At least one of the first two symptoms and five of above list in total must be present together over a 2-week period. These feelings must cause significant impairment socially to the patient. They must not be the direct result of a medical condition or due to substance misuse. There must also not be another mental health diagnosis that better explains the symptoms and the patient must not have a diagnosis of a bipolar disorder.

There are many useful *mnemonics for depression*. One easy way to remember the diagnostic criteria is to use the word "depression" as your guide (**Table 3**).

There are certain special considerations in depressive disorders. Patients can present with somatic symptoms including sleep disturbance, appetite, and weight loss and amenorrhea. Careful screening of patients may reveal a depressive disorder as a cause for their symptoms. Also, one should be mindful of postnatal depression in postpartum women as up to 10% of women can be diagnosed with a major depressive episode. This is especially important when considering the health of the family unit and potential for abuse of the newborn.

Bipolar Disorder

Bipolar disorders are characterized by episodes of extreme mood changes from severe depression to abnormally elevated mood that last from days to weeks. If there are features of psychosis, then that period can be described as "mania" but if the symptoms are less severe, then it is described as "hypomania". While bipolar disorders are rare in the ED, there is a higher rate of hospitalization and potential for harm and thus must be approached with careful consideration.

During a manic episode there must be significant impairment to the patient's life, need for hospitalization, or psychotic symptoms. Common features of mania include over-cheerfulness, over-talkativeness, and over-activity. These can also frequently be associated with episodes of irritability and distractibility. There can be thought disorders including flight of ideas and delusions of grandeur or a feeling of grandiosity. These are often associated with impairment in judgement and irresponsible behavior and impetuousness in activities such as gambling and sexual relations.

The *DSM-5* criteria for diagnosing a manic episode are as follows:

- Distinct period of abnormally, persistently elevated mood or irritability, and persistent goal-directed activity or energy lasting at least 1 week (or if hospitalization is needed)
- During the period of mood disturbance, three or more (four if the mood is irritability) of the following:
  - Inflated self-esteem or grandiose thoughts
  - Decreased need for sleep
  - Increased talkativeness
  - Racing thoughts or flight of ideas
  - Distractibility
  - Increase in goal directed activity or psychomotor agitation
  - Excessive involvement in pleasurable activities that have potential for harm (sexual/financial/behavioral)
- The mood disturbance is sufficiently severe enough to impact patient's occupation/social functioning; requires hospitalization to prevent harm to patient or those around them; and features of psychosis are present.
- The symptoms are not caused by the effects of a medical condition or drugs/alcohol.

Differential Diagnosis of Mood Disorders

Many medical conditions including hypothyroidism, Parkinson's disease, dementia, and long-term, serious medical conditions including cancer and ischemic heart disease (IHD) can cause the patient to have major depressive symptoms. These symptoms may be treated similarly to a formal depressive disorder but are often linked to the underlying condition and either the physiological or psychosocial impact on the patient's life.

Substance abuse including drugs and alcohol can often cause symptoms like a mood disorder and have significant negative impact on the life and functioning of the patient. Help must be sought to engage the patient in lifestyle modification and rehabilitation and referral to the appropriate services in your area should be explored.

Many prescription medications can also have mood-related side effects—antipsychotic and antiepileptic medications are linked to depressive features and steroids have been known to cause manic symptoms.

Grief and bereavement and experiencing significant stressors are linked to mood disorders but it should be noted that feelings of guilt, loss of self-esteem, or significant impact on a patient's occupation or social activity may indicate an underlying depressive disorder. Normal grief and adjustment reactions vary among individuals and in different cultures, but rarely last longer than a few months.

Treatment of Mood Disorders

Patients are often in crisis and steps should be taken to place them in a quiet, private environment, engage with the patient, and try and reduce their agitation. If verbal and environmental

TABLE 3: Mnemonic for DEPRESSION.

D	Depressed mood
E	Energy loss/fatigue
P	Pleasure lost
R	Retardation or excitation
E	Eating (change in appetite/weight)
S	Sleep changed
S	Suicidal thoughts
I	I'm a failure (loss of confidence)
O	Only me to blame (guilt)
N	No concentration

Source: Davies AC, Birley H, Chiganze A. Chlamydia is being managed in primary care. BMJ. 2006;332(7540):551.

strategies to calm the patient fail, then one can consider giving medications to reduce anxiety and calm the patient.

Oral medications such as lorazepam (1–2 mg), haloperidol (2–10 mg), or promethazine (25–50 mg) are preferred. IM medications can be considered if the patient is not compliant with oral medications. If it is deemed by the attending physician that the patient is at significant risk of immediate harm to themselves or to others then physical restraint and IV sedation using benzodiazepines or haloperidol can be used.

Whenever chemical or physical restraint is used, it must be justifiable, reasonable, proportional to the situation, and used for the minimal length of time needed. As ever, one must be ready to deal with any adverse outcomes.

Specialist drugs including antidepressants and antipsychotic medications must be prescribed by those experienced in their use and as such, most patients who at high risk of harm from their depressive disorder, suffering major depression, or experiencing bipolar symptoms should be referred to psychiatric services for further care.

All patients with depressive symptoms require an assessment of suicide risk. If there is risk of self-harm/suicide or risk of the patient harming others, then inpatient care must be arranged. Otherwise, it is possible to discharge patients home with close outpatient follow-up with psychiatric services or a suitable family medicine doctor.

Anxiety Disorders

Anxiety is a normal emotion that healthy people feel at times. If a person feels a disproportionate amount of anxiety or for prolonged periods of time, then there may be an underlying anxiety disorder. Anxiety disorders can affect to 20% of adults at some point in their lives and can vary from specific phobias (7–9%), social anxiety (7%), panic disorder (3%), and generalized anxiety disorder (3%).

Panic Disorders

A panic attack is an abrupt period of fear and discomfort associated with physical and cognitive symptoms.

The *DSM-5* criteria for diagnosing panic disorder are as follows—four or more of the following symptoms:

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling/shaking
- Shortness of breath/feeling of smothering
- Feelings of choking
- Chest pain or discomfort
- Nausea/abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Chills/heat sensations
- Paresthesia (numbness or tingling sensations)
- Derealization (feeling of unreality) or depersonalization (being detached from oneself)
- Fear of losing control/going crazy
- Fear of dying

A patient who experiences multiple panic attacks may have an underlying panic disorder or another mental health disorder and often this requires specialist consultation before a diagnosis can be made. Panic disorder is often accompanied with specific behavioral changes in the patient leading them to avoid situations and locations and can lead to significant changes in the patient's personality leading them to become withdrawn, passive, or dependent on others.

Generalized Anxiety Disorder

In some people, the excessive worry and anxiety about different events, topics, and activities can be very difficult to control. In generalized anxiety disorder, the symptoms occur on most days for at least 6 months. This excessive anxiety is associated with three of the following six symptoms:

1. Restlessness or feeling "on edge"
2. Irritability
3. Feeling easily fatigued
4. Difficulty in concentrating or going blank
5. Muscle tension
6. Sleep Disturbance

Post-traumatic Stress Disorder

Post-traumatic stress disorder is caused by witnessing or experiencing a highly traumatic event and manifesting symptoms of re-experiencing the events months or years later. The symptoms can range from mild anxiety symptoms to more severe symptoms that lead the patient to avoid triggers and can lead to changes in personality like those in anxiety disorders.

General Approach to Panic Disorders

Take a thorough history about the precipitants and situation leading to the symptoms. Pay special consideration to alcohol and drug use (both prescribed and illicit). Take a full social and past social history to help determine if there are any elements in the patient's life that may have led to their current state of mind.

It is also important to pay attention to stimulant use including caffeine and nicotine (tea, coffee, and tobacco usage) as excessive use of these can exacerbate anxiety states.

There are many significant medical conditions that can present with anxiety symptoms and one must try and exclude these as the cause of symptoms (**Table 4**).

TABLE 4: Common medical conditions that can present with anxiety or present as an anxiety disorder.

Cardiac	• Acute coronary syndromes (MI and angina) • Cardiac dysrhythmias • Congestive cardiac failure
Respiratory	• Pulmonary embolus • Asthma and COPD exacerbations • Hypoxia/hypercapnia
Endocrine	• Hyperthyroidism • Hypoglycemia • Pheochromocytoma • Hypoparathyroidism
Neurological	• TIAs and stroke • Seizure disorders/postictal state • Head injury/intracranial bleeding
Environmental	• Alcohol intoxication and withdrawal • Drug abuse/intoxication and acute withdrawal carbon monoxide poisoning

(COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; TIAs: transient ischemic attacks)

Treatment for Anxiety Disorders

Significant anxiety can sometimes manifest as acute agitation. In these patients, proceed with cautious verbal and environmental de-escalation strategies as described earlier, with use of medical or physical restraint as appropriate to the circumstance.

Specialist treatment with selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors SNRIs should be initiated by doctors experienced in their use and hence the patients should be referred to psychiatric services. Benzodiazepines must be prescribed with caution due to risks of addiction and dependence. It may be appropriate to use them in short, minimal dosed prescriptions from the ED to allow patients to bridge the gap till they can be seen and assessed by psychiatric services.

Other treatment modalities including counselling, psychotherapy, and cognitive behavioral therapy (CBT) have been shown to improve symptoms. Often a combination of medication, counselling and CBT, is needed for long-term treatment success.

Most patients with anxiety disorder can be discharged from the ED with arrangements for outpatient follow-up. However, patients with suicidal or homicidal ideation, severe depressive symptoms, or psychosis require inpatient care.

THOUGHT DISORDERS, PSYCHOSIS, AND SCHIZOPHRENIA

Thought Disorders

Formal thought disorders (FTDs) are disorders of organized thinking that manifest as disorganized language (speech and writing). There are >25 forms of thought disorder that have been described and these are often features of schizophrenia. FTDs can also be present in neurological and neurodegenerative conditions, manic disorders, and mood disorders.

Common types of thought disorders include (but are not limited to):

- Alogia (poverty of speech) where there is lack of speech or content
- Thought blocking where there is an abrupt break in a train of thought
- Derailment (knight's move thinking) where speech or writing moves from one idea to another that is either unrelated or very loosely related to the last idea
- Flight of ideas where thoughts move rapidly from one topic to another
- Neologisms where the person makes up new words that may be used to describe an item or idea
- Illogicality where the person reaches a conclusion which does not follow a logical chain of ideas
- Echolalia where a question or statement is repeated multiple times

Formal thought disorder can be present in >90% of psychosis.

Psychosis

Psychosis is a condition where the mind has difficulty in determining what is real and what is not. It is a combination of delusions (beliefs that contradict rational argument) and hallucinations (experiences where one hears, sees, or feels something that are not real) and can be caused by drugs, alcohol, sleep deprivation, postpartum illness, and also schizophrenia and mood disorders (**Table 5**).

Workup of psychotic symptoms should be focused on excluding medical causes before a diagnosis of a mental health condition can be made. A thorough history and examination including collateral history (if possible) should be taken. CBC, kidney function test, Electrolytes, Liver function test, and a venous blood gas should all be performed as well as syphilis serology, if indicated. An electroencephalogram (EEG) should be considered if epilepsy is a possibility. Neuroimaging in the form of CT and/or MRI should also be performed.

TABLE 5: Causes of psychosis.

Primary psychiatric conditions	• Schizophrenia • Mood disorders • Schizoaffective disorder • Delusional disorder • Personality disorders • PTSD
Neurodegenerative	• Alzheimer's • Parkinson's • Lewy body dementia
Neurological	• Space-occupying lesions/tumors • Stroke • MS • Epilepsy
Infection	• Encephalitis • HIV/AIDS • Malaria • Syphilis
Autoimmune	• SLE • Sarcoidosis
Endocrine	• Hypothyroidism and hyperthyroidism • Hypoglycemia • Hypoparathyroidism and hyperparathyroidism • Cushing's
Metabolic	• Electrolyte derangement • Liver failure • Renal failure • B12 deficiency
Environmental and social	• Alcohol excess and withdrawal syndrome • Toxins including heavy metals • Poisoning • Recreational drugs • Medications (sympathomimetics, dopamine agonists, steroids, and stimulants)

(AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; MS: multiple sclerosis; PTSD: post-traumatic stress disorder; SLE: systemic lupus erythematosus)

Schizophrenia

Schizophrenia is a mental health disorder that is characterized by multiple or continuous episodes of psychosis and thought disorder in the absence of an obvious organic cause (although there are known genetic and environmental factors including heavy cannabis use). Males are more commonly affected than females and lifetime incidence is around 1 in 200. There is significant impact on patient's lives as around half of people with schizophrenia suffer lifelong symptoms and life expectancy may be reduced by 20 years due to an increase in suicides and physical health conditions.

The *DSM-5* criteria for schizophrenia are as follows:

- The presence of two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated), with at least 1 of them being (1), (2), or (3): (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, and (5) negative symptoms.
- For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas (e.g., work, interpersonal relations, or self-care) is markedly below the level achieved before onset; when the onset is in childhood or adolescence, the expected level of interpersonal, academic, or occupational functioning is not achieved.
- Continuous signs of the disturbance persist for a period of at least 6 months, which must include at least 1 month of symptoms (or less if successfully treated); prodromal symptoms often precede the active phase, and residual symptoms may follow it, characterized by mild or subthreshold forms of hallucinations or delusions.

Negative symptoms are a lack of normal emotional responses or thought processes and include blunted affect (flat expression or little emotion); alogia (poverty of speech); anhedonia (inability to feel pleasure); lack of desire/ability to form relationships; and apathy.

A note should be made of schizoaffective disorder which is considered a separate mental health illness to schizophrenia and includes features of both schizophrenia and a mood disorder (manic and depressive types).

Treatment of schizophrenia and schizoaffective disorder should be instigated by experienced mental health physicians. In the ED, patients who are at risk to themselves or others may require sedation (using haloperidol or benzodiazepines) and/or restraint (using the least invasive and risky method possible). Treatment may include antipsychotic medications, psychotherapy, and counselling. These therapies may be performed as inpatient care or in the community, but the ultimate decision should be left to the psychiatric team and early referral from the ED is advised.

SUMMARY

Significant portion of all ED patient constitute mental and behavioral health disorders. Commonly psychiatric acute presentations involve self-harm, substance abuse, suicidality, agitation, and/or exacerbations of underlying mood, anxiety, and thought disorders. Over the years prevalence of psychiatric disease presentation to the ED has seen a significant rise. Emergency physicians still face considerable challenges when encountering these patients despite the relative frequency of presentation, psychiatric emergencies are vastly underrepresented in most emergency medicine academic curriculums. Emergency physician hesitant to face the psychiatric emergency due to reduced exposure to psychiatric disease during clinical training, along with the inherently confounding nature of acute mental illness often contribute to with these patients in the ED. Nevertheless, the ED continues to grow increasingly responsible for providing care to patients presenting with mental and behavioral health issues, making it crucial for emergency physicians to practice and develop skills in acute psychiatric care. Emergency physician should be aware of techniques in recognition, assessment, management, and disposition of commonly encountered psychiatric emergencies.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Acute Pelvic Pain

Dolly C Yadav

INTRODUCTION

Acute pelvic pain is commonly defined as acute onset lower abdominal pain of <3 months duration. Globally, about a tenth of the emergency department (ED) visits are attributed to abdominal pain. However, data is unavailable for the prevalence of acute pelvic pain since it is not distinguished from abdominal pain in studies. It is estimated that over a third of women, in the reproductive age group, experience pelvic pain unrelated to menstruation. Moreover, acute pelvic pain possesses a diagnostic challenge as the multisystem etiologies frequently have overlapping and nonspecific pain, symptoms, and physical examination findings. As with any other clinical presentation, causes of acute pelvic pain can be life-threatening and have lasting sequels. Hence, it is imperative that an emergency physician studies management of acute pelvic pain which is illustrated in this chapter.

ANATOMY, PATHOPHYSIOLOGY, AND ETIOLOGY

The female pelvis comprises organs of the reproductive system—vagina, uterus, fallopian tubes, and ovaries; urinary system—ureters and urinary bladder; gastrointestinal system—sigmoid colon and rectum; as well as components of the musculoskeletal system. Acute pelvic pain can originate from the reproductive organs or from any structures that lie next to or pass through the pelvis. The pelvic organ nerve innervation is from T9–L1 and S2–S4 spinal nerves. Pain may be initiated by inflammation, distention, or ischemia of an organ, or by spillage of blood, pus, or other material into the pelvis. The dull aching or the visceral pain is a result of the overlap of afferent innervation supplying the pelvic organs and the appendix, ureters, and colon, making their precise localization difficult. On the other hand, sharp stabbing like results pain when the afferent nerves in the parietal peritoneum adjacent to an affected organ are stimulated. Further characteristics of pelvic pain along with features and differential diagnoses are illustrated in **Table 1**.

EMERGENCY DEPARTMENT EVALUATION

The history and physical examination help in arriving at the definitive diagnosis. However, due to overlap of clinical presentations and frequent atypical presentations, diagnosis is often reached after investigations, especially pregnancy test and radiological imaging.

History

The characteristics of pain must be included in history as these throw light on the possible disease processes, as shown in **Table 1**. Furthermore, detailed social history should include the patient's sexual history, history of sexually transmitted infection (STI), sex partner's symptoms and details on intrauterine device (IUD), induction of ovulation during infertility treatment; besides questions pertaining to gynecologic, obstetric, urologic, gastroenteric histories must also be elicited. It is fairly common to utilize the mnemonic SAMPLE for comprehensive history taking—Signs and symptoms, Allergies, Medical history, Past medical history particularly about abdominopelvic surgery, Last meal timing, and Events leading to this presentation. Although one study concluded that sexual history and self-assessment can be used as a highly effective predictor of a patient not being pregnant, another study found that 7% of women who denied being pregnant and stated normal last menstrual cycle, tested positive for pregnancy test. Nevertheless, it is a safe practice to test every female with abdominopelvic pain, in reproductive age group and intact reproductive organs, for pregnancy.

Physical Examination

In accordance to the initial assessment in the ED, a rapid primary assessment must be undertaken to recognize and manage life-threatening conditions prior to undertaking detailed systemic examination. In addition to the abdominal and pelvic examination, it is advised to assess other systems as the pain in the pelvic region may be referred due to pathology in other organ system. While performing abdominal

TABLE 1: Characteristics of acute pelvic pain with corresponding features and differential diagnoses.

Pain characteristics	*Features*	*Differential diagnoses*
Site of pain	Right lower quadrant of the abdomen	Acute appendicitis, pyelonephritis, ectopic pregnancy, ovarian cyst or torsion, ureteric colic, inguinal hernia, mittelschmerz, and musculoskeletal pain
	Left lower quadrant of the abdomen	Diverticulitis, ectopic pregnancy, ovarian cyst or torsion, pyelonephritis, ureteric colic, perirectal abscess, inguinal hernia, mittelschmerz, and musculoskeletal pain
	Lower abdomen	Cystitis, bowel obstruction, inflammatory bowel disease, dysmenorrhea, ectopic pregnancy, uterine perforation or myomas, abortion, pelvic inflammatory disease (PID), endometritis, ovarian hyperstimulation syndrome, placental abruption, ovarian vein thrombosis, incarcerated/strangulated hernia, displaced intrauterine device, somatization disorder, and musculoskeletal pain
Onset of pain	Acute	Vascular, obstructive, and viscus perforation causes
	Subacute	Inflammatory causes
	Chronic	Malignancy and inflammatory causes
Character of pain	Tearing like	Dissection of aorta or its branches
	Stabbing like	Irritation of parietal peritoneum
	Colicky	Obstruction of tubular organ and smooth muscle spasms, e.g., ureteric colic
	Dull	Visceral pain
Radiation of pain	Loin to groin	Nephrolithiasis
	Migration of pain from umbilicus to right lower abdomen	Acute appendicitis
	Radiation to back	Aortic dissection, PID, and cystitis
Associating factors of pain	Hypotension or signs of shock	Ruptured ectopic pregnancy, leaking aortic aneurysm, and aortic dissection
	Fever	Acute appendicitis, PID, and pyelonephritis
	Diarrhea, nausea, vomiting, and anorexia	Gastrointestinal pathology
	Vaginal bleeding or discharge, dyspareunia, and cervical motion tenderness	Sexually transmitted infection (STI), PID, and tubo-ovarian abscess (TOA)
	Vaginal bleeding	Placental abruption, miscarriage, and mittelschmerz
	Urinary frequency or hesitancy, hematuria	Nephrolithiasis and urinary tract infection (UTI)
	Pressure-like feeling in perineum	Uterine prolapse
Time course or pattern of the pain	Mid-cycle vaginal bleeding	Mittelschmerz
	During and postcoital pain	PID and gynecological malignancy
	Infertility treatment	Ovarian hyperstimulation syndrome (OHSS) and ovarian torsion
	Urogenital procedure or surgery	Wound infection or sepsis, venous thrombosis, venous thrombophlebitis, and thermal injury
	Trauma	Sexual assault, intimate partner violence, and female genital mutilation
Aggravating factors	Change in posture	Musculoskeletal pain
	Menstruation	Endometriosis and adenomyosis
	Dyspareunia	PID and TOA
	Bouncy movements like jumping or travelling over bumpy road	Peritonitis

Continued

Continued

Pain characteristics	*Features*	*Differential diagnoses*
Relieving factors	Laying still	Peritonitis and musculoskeletal pain
	Passage of urine	Acute urinary retention
Severity	Mild discomfort	PID, UTI, mesenteric ischemia, and hernia
	Moderate pain	Peritonitis, aortic aneurysmal leak or dissection, appendicitis, ovarian or adnexal cyst, miscarriage, placental abruption, strangulated or incarcerated hernia, and musculoskeletal pain
	Uncontrollable	Ovarian or adnexal torsion, ureteric colic, and labor pain

examination, note for surgical scars, assess for tenderness, palpating mass, signs of peritonitis, costovertebral angle tenderness, and digital rectal examination for occult blood. Traditionally, pelvic examination in the ED consists of bimanual and speculum examination. For diagnosing pelvic inflammatory disease (PID), cervical motion or uterine or adnexal tenderness is elicited by bimanual examination. Upon speculum examination, anatomy, source of vaginal bleeding or discharge, masses, and status of cervical os, can be evaluated and endocervical swabs collected. However, these days STI are often tested on self-swabbed vaginal samples or by urine antigen tests. There is a lack of accuracy and reproducibility of pelvic examination, even when undertaken by experienced examiners; positive examination findings do not necessarily rule in serious pathology; and a normal examination does not rule out significant disease; rendering pelvic examination undesirable in the ED. On the contrary, in an unstable patient of trauma, hemodynamic instability, suspected organ prolapse causing acute urinary retention, a pelvic examination is advised in order to identify a source and quantify blood loss, manual aspiration of uterine contents (i.e., retained products of conception) and identify the prolapsed organ, which may be easily reduced. To avoid legal consequence, it is highly recommended to take help of a chaperone during physical examination in case the emergency physician is male or if the patient is uncomfortable. Adolescents, pregnant, and postpartum women deserve special attention. Confidentiality, local laws pertaining to consent, and high-risk behavior makes adolescent population uniquely challenging to evaluate. Besides, for completing medical assessment in adolescents, consent from the patient, understanding of the laws pertaining to consent, and building rapport are vital.

Investigation

Although acute pelvic pain may be caused by pathologies from different organ systems, an important determinant of diagnostic approach in a woman with intact reproductive organs, in reproductive age, is the pregnancy test. More than often, this is undertaken as a point of care testing either using urine or blood sample for beta-subunit of human chorionic gonadotropin (beta hCG). These tests are sensitive to 25 IU/L and become positive 3–4 days after implantation. By 7 days after implantation, or the time of the expected menstrual period, 98% of the pregnancy tests will be positive. A pregnancy test is required in almost all the women of reproductive age with intact reproductive organs. A positive test may indicate intra- or extrauterine pregnancy, or molar pregnancy, or cancer. Hence, it is advised that patients with a positive pregnancy test should undergo ultrasound assessment, bedside or formal, to evaluate for ectopic pregnancy.

In the evaluation of STI or PID or tubo-ovarian abscess (TOA), the nucleic acid amplification tests (NAATs) to detect chlamydia and gonorrhea are often used in the ED. These tests amplify and detect deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) sequences and are much more sensitive than previous chlamydia and gonorrhea tests. Urine NAATs have sensitivities and specificities similar to those of cervical samples. Still, cervical wet mount can be useful in detecting bacterial vaginosis and trichomoniasis, especially to identify antibiotic-resistant organisms when lately antibiotic course for gonorrhea or chlamydia has been finished. Additionally, urine analysis may show pyuria suggesting urinary tract infection (UTI) or hematuria suggesting ureteral stone. It is advised to perform urinalysis in all pregnant patients irrespective of absence of UTI symptoms. Although the white cell count is one of the most common tests ordered in the ED, it is not adequate by itself to diagnose or dispose patient with acute pelvic pain.

It is estimated that up to 65% of patients presenting with nontraumatic abdominopelvic pain will receive a radiological imaging study in the ED. However, selecting an initial imaging modality is challenging as the differential diagnosis for abdominopelvic pain in women is so wide-ranging. The goal of imaging is to make the most accurate diagnosis using the least amount of radiation; therefore, transvaginal ultrasonography is the imaging modality of choice. The American College of Radiology Appropriateness Criteria state pelvic sonography as the preferred first-line imaging modality in the evaluation of acute pelvic pain in pregnant and nonpregnant women of reproductive age when an obstetric or gynecologic condition is suspected, and in the initial assessment of a suspected nongynecologic condition in a pregnant patient. This can be attributed to its ready availability, cost-effectiveness, noninvasive nature, and lack of ionizing radiation.

Furthermore, a patient with a positive pregnancy test results in whom a definite intrauterine pregnancy cannot be seen is presumed to have an ectopic pregnancy until proved otherwise. In 5–10% of ectopic pregnancies though, a pseudosac, which mimics intrauterine pregnancy, may be seen on transvaginal ultrasonography. A pseudosac is characterized by only a single echogenic ring in contrast to an intrauterine pregnancy recognized by double echogenic rings (double decidual sac sign). Also, presence of free intra-abdominal fluid on ultrasound images is consistent with hemorrhage from either an ectopic pregnancy or a ruptured ovarian cyst and must be addressed expediently. Although sonography can be useful, CT is typically the preferred first-line imaging modality in the evaluation of nongynecological causes of pelvic pain in a

nonpregnant woman. If a CT is entirely negative, there is little to no utility in obtaining an immediate follow-up ultrasound.

Diagnosis

Upon completion of evaluation, the emergency physician must be able to reach at a diagnosis. **Table 2** summarizes the differential diagnosis in acute pelvic pain with corresponding ED investigations and **Flowchart 1** shows the algorithmic approach to acute pelvic pain in the ED.

TREATMENT

The goal of the emergency management is to rule out acute causes of abdominal pain associated with high morbidity and mortality, such as acute ovarian/adnexal torsion or ectopic pregnancy, TOA, appendicitis, dissection, abdominal aortic aneurysmal rupture, mesenteric ischemia, strangulated or incarcerated hernia; to assess for the possibility of neoplasm or malignancy; and either to refer the patient to the appropriate consultant or to discharge them with a clear plan for follow-up with an obstetrician/gynecologist. Simultaneously, the pain must be managed adequately as a good medical practice. Although nonsteroidal anti-inflammatory drugs (NSAIDs) are preferred medications for pain, narcotic medications can be utilized if the pain score is high. Ondansetron, metoclopramide, or promethazine are commonly used antiemetics, when indicated. Whenever intra-abdominopelvic infection is suspected, antibiotics must be initiated. It is advised to include metronidazole with an aminoglycoside for anaerobic and gram-negative coverage. Alternative to metronidazole, clindamycin may be used. It is also advised to follow national and institutional antibiotic regimen policies. Although for cervicitis, a single dose of intramuscular ceftriaxone and a single dose of oral azithromycin suffice, PID requires prolonged therapy with broad-spectrum antibiotics.

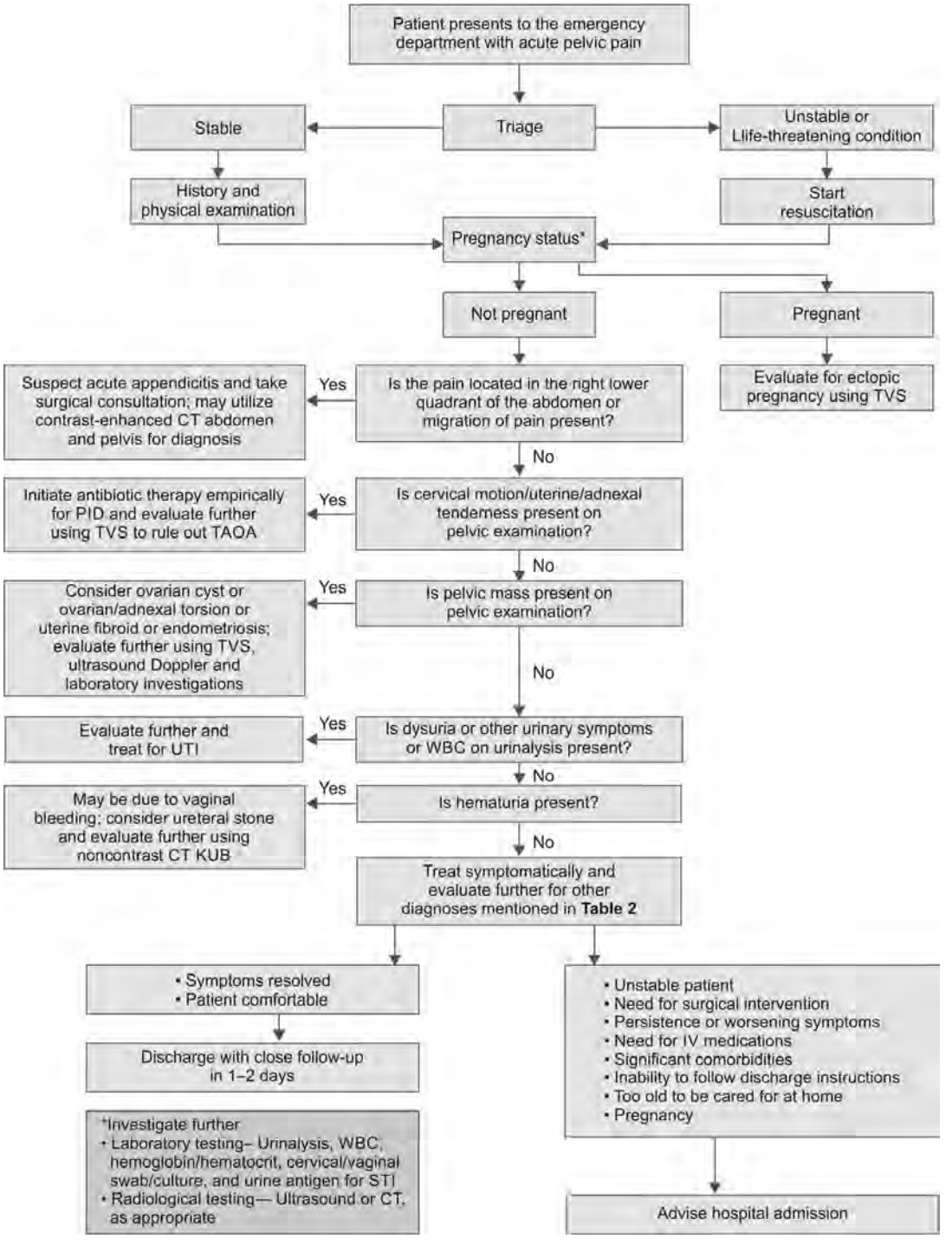
Antibiotic therapy for STI and PID is targeted at the causing organisms. Outpatient therapy with ceftriaxone, azithromycin, or doxycycline is commonly used and is as effective as parenteral treatment in mild-to-moderate disease. Inpatient therapy with cefotetan or cefoxitin intravenously and oral doxycycline is recommended for those with severe infections, including TOA. An alternative regimen is intravenous clindamycin and gentamicin. Delay in diagnosis and treatment of PID probably contributes to inflammatory sequelae in the upper reproductive tract; hence, therapy must be initiated empirically. Additionally, arrangements should be made to link the partners of women who have PID to care.

DISPOSITION AND FOLLOW-UP

First and foremost, patient with a critical etiology of acute pelvic pain must be appropriately resuscitated. Subsequently, the need for admission is decided upon clinical condition of the patient, persistence or worsening of signs and symptoms, need for intravenous medications, significant comorbidities, and vulnerability of the patient which prevents the patient to follow discharge instructions or cared for at home. The rest of the

TABLE 2: Differential diagnosis of acute pelvic pain with corresponding emergency department (ED) investigations.

Women of reproductive age	*Gynecologic diagnoses:* • Endometriosis, adenomyosis, dysmenorrhea, degenerating uterine fibroid, mittelschmerz, ovarian torsion, pelvic inflammatory disease (PID), ruptured ovarian cyst, tubo-ovarian abscess (TOA), ovarian hyperstimulation syndrome, complication of surgery or procedure, and malignancy	• Pregnancy test • White cell count • Hemoglobin and hematocrit • Urinalysis • Transvaginal and/or transabdominal ultrasound
	Gastrointestinal diagnoses: • Appendicitis, bowel obstruction, diverticulitis, hernia, irritable bowel syndrome, mesenteric venous thrombosis, perirectal abscess, volvulus, and bowel obstruction	• Pregnancy test • White cell count • Hemoglobin and hematocrit • Urinalysis • Abdominopelvic CT
	Urologic diagnoses: • Urinary tract infection, stone in bladder or ureter, and acute retention of urine	
	Others: • Dissecting aortic aneurysm, pelvic trauma, sexual assault, lead poisoning, malingering, narcotic seeking, porphyria, sickle cell crisis, and somatization disorder	
Pregnant women	Ectopic pregnancy, corpus luteum hematoma, ovarian vein thrombosis, placental abruption, uterine impaction, postpartum endometritis, and ovarian torsion	• Pregnancy test • White cell count • Hemoglobin and hematocrit • Blood group and Rh factor • Urinalysis • Transvaginal and/or transabdominal ultrasound
Adolescents	Similar to women of reproductive age, with the addition of imperforate hymen and transverse vaginal septum	
Postmenopausal women	Similar to women of reproductive age minus ectopic pregnancy and ovarian torsion	


Patient presents to the emergency department with acute pelvic pain
Triage
Stable
Unstable or Llife-threatening condition
History and physical examination
Start resuscitation
Pregnancy status*
Not pregnant
Pregnant
Is the pain located in the right lower quadrant of the abdomen or migration of pain present?
Yes
Suspect acute appendicitis and take surgical consultation; may utilize contrast-enhanced CT abdomen and pelvis for diagnosis
No
Evaluate for ectopic pregnancy using TVS
Is cervical motion/uterine/adnexal tenderness present on pelvic examination?
Yes
Initiate antibiotic therapy empirically for PID and evaluate further using TVS to rule out TAOA
No
Is pelvic mass present on pelvic examination?
Yes
Consider ovarian cyst or ovarian/adnexal torsion or uterine fibroid or endometriosis; evaluate further using TVS, ultrasound Doppler and laboratory investigations
No
Is dysuria or other urinary symptoms or WBC on urinalysis present?
Yes
Evaluate further and treat for UTI
No
Is hematuria present?
Yes
May be due to vaginal bleeding; consider ureteral stone and evaluate further using noncontrast CT KUB
No
Treat symptomatically and evaluate further for other diagnoses mentioned in Table 2
• Symptoms resolved
• Patient comfortable
Discharge with close follow-up in 1–2 days
*Investigate further
• Laboratory testing– Urinalysis, WBC, hemoglobin/hematocrit, cervical/vaginal swab/culture, and urine antigen for STI
• Radiological testing— Ultrasound or CT, as appropriate
• Unstable patient
• Need for surgical intervention
• Persistence or worsening symptoms
• Need for IV medications
• Significant comorbidities
• Inability to follow discharge instructions
• Too old to be cared for at home
• Pregnancy
Advise hospital admission

(IV: intravenous; KUB: kidney, ureter, and bladder; PID: pelvic inflammatory disease; STI: sexually transmitted infection; TOA: tubo-ovarian Abscess; TVS: transvaginal sonography; UTI: urinary tract infection; WBC: white blood cell)

FLOWCHART 1: Approach to acute pelvic pain in the emergency department.

patients are discharged from the ED after initiating treatment with thorough discharge instructions. The ED discharge instructions must include details of treatment, follow-up plan, and return to the ED instructions; along with information of the potential risks of infertility, disability, and malignancy caused by treatment delays or noncompliance. It is advisable that the discharged patients are reviewed in a day or two in the ED or gynecology clinic. In a STI or PID patient, it is also advised to link, treat, and follow-up patient's sexual partner.

SPECIFIC CONDITIONS IN NONPREGNANT FEMALES

Ovarian Cysts

An ovarian cyst is a sac filled with liquid or semiliquid material that arises in an ovary. The vast majority of these lesions are benign. Most ovarian cysts begin as physiologic follicular or corpus luteal cysts; they become symptomatic by several

mechanisms: rupture of contents with subsequent chemical peritonitis, torsion of enlarged ovaries, and mechanical pressure on adjacent structures due to large size. Functional cysts, formed as part of the normal menstrual cycle, are fluid-filled sacs in the ovary, and are considered cysts once >2 cm in dimension. Most patients with ovarian cysts are asymptomatic, however, some present with sudden-onset, unilateral, dull, or colicky pain, which may begin after sexual intercourse. Besides, pain due to cyst rupture or torsion arises suddenly where as a slowly growing cyst results in pressure effect and chronic dull pain. The risk factors for ovarian cyst formation include infertility treatment, pregnancy, hypothyroidism, tamoxifen, cigarette smoking, and tubal ligation. Risk of cyst rupture increases with ovulation; there is an increased risk with ovulation induction treatments and a decreased risk with use of oral contraceptive pills. **Table 3** describes the characteristic features of different ovarian cysts. In polycystic ovarian syndrome, the ovary often contains multiple cystic follicles (2–5 mm in diameter) as viewed on ultrasound.

Most of the ovarian cysts are discovered incidentally during ultrasonography or routine pelvic examination. As per American College of Obstetrics and Gynecology (ACOG) guidelines, transvaginal ultrasound is the preferred imaging modality for assessment of a suspected pelvic mass. The definitive diagnosis of all ovarian cysts is made based on histologic analysis. Pregnancy test, white cell count, hemoglobin and hematocrit, urinalysis, endocervical swabs, serum biomarkers such as cancer antigen 125 (CA125), hCG, L-lactated dehydrogenase, alpha-fetoprotein, and inhibin may aid in the differential diagnosis of cysts and in the management of cyst-related complications. In most cases, the ovarian cyst is benign and asymptomatic, requires no further management, and will resolve on its own. In other cases, ovarian cyst-related complications, such as rupture and hemorrhage or torsion, occur. In a postmenopausal patient, a persistent cyst <10 cm in dimension in the presence of a normal CA125 value may be monitored with serial ultrasonographic examinations. On the contrary, persistent ovarian cysts >10 cm (especially if symptomatic) and complex ovarian cysts should be considered for surgical removal. Thus, management depends largely on the degree of pain and hemorrhage, and sometimes on the type of cyst. Patients with cysts without concern for torsion and without large hemorrhage can be managed conservatively as outpatients with symptom control and follow-up with a gynecologist for a repeat ultrasound in 4–6 weeks. Rarely, a dermoid cyst or an endometrioma can rupture spilling cysts contents respectively, sebaceous or chocolatey, into the abdominal cavity; leading to chemical peritonitis and shock; almost always requiring an emergent surgical intervention.

Ovarian Torsion or Adnexal Torsion

Ovarian or adnexal torsion is an uncommon but noteworthy cause of acute pelvic pain because it is a surgical emergency, and prompt diagnosis is critical for preserving ovarian function and future fertility. Ovarian torsion can occur at any age, but most frequently occurs in women of reproductive age. Torsion occurs when the adnexa, ovary, or seldomly fallopian tube alone, completes at least one full turn around the long axis of the infundibulopelvic ligament and the tubo-ovarian ligament; initially decreasing the lymphatic draining and venous return from the ovary, followed by hemorrhagic infarction and necrosis of the adnexal structures distal to the point of torsion. It is important to note that, the ovaries have dual blood supply from the ovarian and uterine arteries, and thus, torsion can occur without complete loss of vascularity. Classically, patients present with sudden-onset, severe, and unilateral pelvic pain that may develop after episodes of exertion, frequently associated with nausea and vomiting. Unfortunately, atypical presentations are common and include mild, intermittent, and bilateral pain. History of previous torsion, adnexal masses or cysts, use of assisted reproductive technologies leading to ovarian hyperstimulation, polycystic ovarian syndrome, pregnancy, and previous tubal ligation are the risk factors for torsion of ovary or adnexa. It is thought that mass effect of the sigmoid colon prevents left adnexal twisting. Similarly, endometriosis, PID, and lesions which have a role in affixing the ovary to the pelvic wall may have a role in reducing the likelihood of torsion. Upon pelvic examination, a tender adnexal mass may be palpated. Leukocytosis has been shown to have a modest positive predictive value for adnexal torsion.

TABLE 3: Characteristics of different types of ovarian cysts.

Types of ovarian cyst	*Characteristic features*
Follicular cyst	Follicular cysts occur when the nondominant follicle does not reabsorb and instead grows in size; are thin-walled, avascular, and usually unilocular; and more prevalent
Corpus luteal cysts	Corpus luteal cysts occur when they persist beyond menstruation; are thicker, with irregular and hypervascular walls; more likely to be symptomatic; and more likely to rupture or hemorrhage
Pathologic cysts	• Examples are endometriomas, dermoid cysts, or cystic components of benign or malignant neoplasms; cause pain from growth, rupture, or hemorrhage • *Dermoid cysts* are growths filled with various types of tissue such as fatty material, hair, teeth, bits of bone, and cartilage • *Endometriomas* are collections of endometrium-like material on the outside of the ovary; are filled with a thick chocolate-type material and hence known as "chocolate cysts" • *Cystadenomas* are cysts that develop from cells on the outer surface of the ovary; benign; grow very large; and cause pain • *Neoplastic cysts* arise via the inappropriate overgrowth of cells within the ovary and may be malignant or benign. The most frequent malignant neoplasms arise from the surface epithelium (mesothelium); others may contain granulosa cell tumors from sex cord-stromal cells and germ cell tumors from primordial germ cells. The benign counterparts of these cancers are serous and mucinous cystadenomas

Transvaginal ultrasonography with color Doppler analysis is the method of choice for the evaluation of ovarian/adnexal torsion because it can show morphologic and physiologic changes in the ovary and can help in determining whether blood flow is impaired. Furthermore, in 50–81% of cases of ovarian torsion, an underlying lesion is seen in the ipsilateral ovary. In a premenopausal woman, the ovary is considered enlarged if the greatest ovarian dimension is >4 cm or the volume is >20 cm^3. The presence of the *"whirlpool sign"*, a clockwise or counter-clockwise wrapping of hypoechoic vessels around a central axis, correlates closely with surgically proven torsion. Multiple small, uniform, and peripherally located cysts displaced to the cortex of the engorged ovary are seen in as many as 74% of cases. This finding is sometimes referred to as the "string-of-pearls" sign. The presence of an enlarged ovary with lack of intraovarian arterial or venous flow is highly indicative of torsion, particularly if the typical appearance of an enlarged ovary with small peripheral cysts is depicted. However, the presence of adnexal flow should not be interpreted as ruling out the diagnosis. The most diagnostically accurate sonographic signs are abnormal ovarian blood flow and the presence of free fluid. Since, the diagnostic accuracy of ultrasound is found to be 74.6%, ovarian torsion should not be ruled out when typical findings are absent, especially when clinical history is suggestive of the condition. Abdominopelvic CT may be useful to diagnose other possible causes of lower abdominal pain. The CT findings in ovarian torsion includes enlarged adnexal structure (>5 cm), thick and straight blood vessels draped around the lesion, complete absence of enhancement, hemorrhage or gas in the torsed lesion, misplacement of the torsed structure (to the midline or contralateral side), deviation of the uterus to the ipsilateral side, infiltration of the periadnexal fat, tubal thickening, thickened vascular pedicle with engorged vessels, and ascites.

Regardless of whether laboratory and radiologic studies yield normal results, a patient with a history and physical examination findings suggestive of ovarian or adnexal torsion should be admitted and either operated on or observed by a gynecologist. If no gynecologist is immediately available, transfer to a tertiary center for higher level of care is warranted. Besides, laparoscopy can be used for both confirmation of the diagnosis and treatment. There is an approximately 80% chance of normal follicular development on follow-up ultrasound upon detorsion of adnexa. During the surgery, cyst drainage or cystectomy, along with fixing the adnexa to reduce the chances of retorsion; salpingo-oophorectomy, if the adnexa remain necrotic after detorsion; may be required. Detorsion of the adnexa during pregnancy has not been found to compromise fetal well-being. However, if the corpus luteum cyst is removed during salpingo-oophorectomy, supplemental progesterone is indicated. An adnexal mass concerning for malignancy, in postmenopausal patients, may need extensive resections with biopsies and so surgical intervention may be delayed.

Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) is an infrequent, iatrogenic complication of ovarian stimulation for infertility treatments. Since the frequency of infertility treatment is increasing and because OHSS can cause multi-organ dysfunction and death, it is vital that the emergency physicians become familiar with OHSS. This syndrome is characterized by ovarian enlargement due to multiple ovarian cysts and an acute fluid shift into the extravascular space. OHSS is classified into mild, moderate, and severe. Mild cases of OHSS present with abdominal distension and discomfort, nausea, and vomiting, and have an ovarian enlargement of 5–12 cm. In addition to features of mild category, once ultrasonographic evidence of ascites is present, patients are classified as moderate OHSS. Consequently, patients are categorized as severe OHSS when in addition to all of the above features, clinical evidence of ascites and/or hydrothorax and breathing difficulties, change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function are present. It is desirable to maintain a high degree of clinical suspicion and a low threshold for admission. The emergency physician must note that aggressive palpation of the abdomen can precipitate follicular rupture and early surgery may cause extensive bleeding from ovarian cysts. Fortunately, OHSS is a self-limiting disease. Therefore, treatment is largely conservative and supportive and includes early surgical intervention in cases of ovarian torsion or hemorrhage; paracentesis to address ascites as this reduces the pressure on the inferior vena cava and diaphragm; placement of a transthoracic tube to manage pleural effusions. Nonetheless, laparotomy during torsion and intraperitoneal hemorrhage is lifesaving and recommended. Significant morbidity and fatalities do occur in cases of severe OHSS. However, the prognosis is excellent in mild or moderate cases of OHSS, and in severe OHSS, if appropriate treatment is given.

Pelvic Inflammatory Disease

Pelvic inflammatory disease encompasses a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, TOA, and pelvic peritonitis. The common organisms causing PID are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, microorganisms that comprise the vaginal flora such as anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric gram-negative rods, *Streptococcus agalactiae, cytomegalovirus (CMV)*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium*. Furthermore, women <25 years, multiple sexual partners, not using condom, recent treatment for STI, or human immunodeficiency virus (HIV)-positive status are the risk factors for PID. Many episodes of PID go unrecognized. While some cases are asymptomatic, others get misdiagnosed due to mild or nonspecific symptoms or signs such as abnormal bleeding, dyspareunia, and vaginal discharge. The treatment should be initiated as soon as the presumptive diagnosis of PID is made to prevent long-term sequelae such as increased risk for ectopic pregnancy, infertility, recurrent infection, and chronic pelvic pain. Likewise, the Centers for Disease Control and Prevention (CDC) recommends that a sexually active women with unexplained pelvic pain and one or more of the following—cervical motion or uterine or adnexal tenderness has a high suspicion for PID and empiric treatment must be initiated in these patients. These criteria have a sensitivity of >95%. **Table 4** explains CDC's diagnostic criteria for PID. The evaluation of PID includes pregnancy test; bimanual examination to elicit cervical motion or uterine or adnexal tenderness; speculum examination for cervical friability; cervical or vaginal swab or culture or first void urine NAAT for *N. gonorrhoeae* and *C. trachomatis;* cervical wet mount test for *Trichomonas*

TABLE 4: The Centers for Disease Control and Prevention's sexually transmitted diseases treatment guidelines, 2015 recommended diagnostic criteria for pelvic inflammatory disease (PID).

A diagnosis of PID is made when patient presents with abdominopelvic pain plus one or more mandatory criteria on examination (to initiate empiric therapy, only one mandatory criterion must be fulfilled)

Mandatory criteria (one or more with pelvic pain):	Additional criteria:
1. Cervical motion tenderness 2. Uterine tenderness 3. Adnexal tenderness	1. Oral temperature >101°F (38.3°C) 2. Abnormal cervical discharge or cervical friability 3. Presence of white blood cells on microscopy of vaginal fluid 4. Elevated erythrocyte sedimentation rate 5. Elevated C-reactive protein 6. Laboratory documentation of cervical infection with *Neisseria gonorrhoeae or Chlamydia trachomatis*

The diagnostic approach for PID includes:

- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal ultrasonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
- Laparoscopic abnormalities consistent with PID

vaginalis and bacterial vaginosis; white cell count; transvaginal sonography (TVS); and/or transabdominal ultrasonography. TVS may be normal or show thickened fallopian tubes (>5 mm), and/or cogwheel sign in PID. Pelvic or TOAs may be seen as complex adnexal masses with multiple internal echoes. Pelvic ultrasound is also useful in evaluating the possibility of ectopic pregnancy, ovarian torsion, hemorrhagic ovarian cyst, appendicitis, or endometriosis. Abdominopelvic CT and MRI may also be employed in the diagnosis of PID. Also, endometrial biopsy can be used for the histopathologic diagnosis of endometritis; however, the procedure requires operating room setting. Furthermore, laparoscopy is used to obtain a more accurate diagnosis of salpingitis and a more complete bacteriologic diagnosis, and is gold standard for diagnosing PID.

Pregnant women suspected to have PID are at high risk for maternal morbidity and preterm delivery. These women should be hospitalized and treated with intravenous antibiotics. Women with HIV infection and PID when compared with HIV-negative women with PID were found to have similar symptoms, microbiologic findings and response to treatment; except higher rates of concomitant *M. hominis* and streptococcal infections and TOA. The treatment and disposition of PID is tabulated in **Table 5**. Since intravenous infusion of doxycycline is painful, it should be administered orally when possible. Noteworthy, bioavailability of oral and intravenous doxycycline is similar. Additionally, men who have had sexual contact with a woman with PID during the 60 days preceding her onset of symptoms should be evaluated, tested, and presumptively treated for chlamydia and gonorrhea, regardless of the etiology of PID or pathogens isolated from the woman. If a woman's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated. Patient should be instructed to abstain from sexual intercourse until they and their sex partners have been adequately treated (i.e., until therapy is completed and symptoms have resolved, if originally present). An uncommon complication of PID is Fitz-Hugh–Curtis syndrome or perihepatitis. Patients present with PID and right upper quadrant pain which responds to antibiotic treatment as mentioned above. Improving patient education; abstinence and reducing the number of sexual partners, consistent use of barrier contraceptives; extensive testing for STIs and pre-exposure vaccination in at risk population; empiric treatment and postexposure prophylaxis for HIV and STI; and treating the sexual partner, can reduce the incidence of PID.

Tubo-ovarian abscess may be suspected in a toxic looking PID patient with a significantly tender adnexal mass on pelvic examination and ultrasound. These patients must be admitted for intravenous antibiotics with anaerobic coverage and close monitoring. In case of no improvement in 2–3 days of initiating treatment, laparoscopic or surgical intervention or alternative diagnosis must be considered. Most TOA resolve; however, some may necessitate drainage. Laparotomy in TOA is reserved for ruptured abscesses or when other treatment modalities fail and may include unilateral salpingo-oophorectomy or hysterectomy and bilateral salpingo-oophorectomy depending on patient's choice of preserving fertility.

Dysmenorrhea

One of the most common causes of lower abdominal pain in women of reproductive age is dysmenorrhea or painful menstruation. Dysmenorrhea associated with absence of pelvic pathology is primary dysmenorrhea, commonly seen in adolescents; whereas in secondary dysmenorrhea a pathological cause of pelvic pain is identifiable, such as endometriosis. Most dysmenorrhic patients can be discharged from the ED after treatment with NSAIDs analgesics. Some may require hormonal contraceptive and these patients will require close follow-up.

Leiomyomas or Uterine Fibroids

Leiomyomas are estrogen-dependent, smooth muscle benign tumors, arising from the uterus or myometrium. Depending on their location in the uterus, these are categorized as submucosal (project into the cavity of the uterus), intramural (contained within the myometrium), or subserosal (project outside the uterus). Furthermore, these can have peduncle and may twist on it obstructing its own blood supply. Most women

TABLE 5: Management of pelvic inflammatory disease (PID)—diagnosis, treatment, and disposition.

PID	*Diagnosis*	*Treatment*	*Disposition*
Mild-to-moderate PID	PID without any mass or tubo-ovarian abscess (TOA)	• Ceftriaxone 250 mg intramuscularly once PLUS • Doxycycline 100 mg twice a day orally for 14 days • WITH or WITHOUT • Metronidazole 500 mg twice a day for 14 days	Outpatient follow-up with instructions to abstain from sexual intercourse until treatment is complete and until their partner or partners have been treated
Severe PID	PID with mass or TOA	• Cefotetan 2 g intravenously twice a day OR • Cefoxitin 2 g intravenously four times a day PLUS • Doxycycline 100 mg twice a day orally or intravenously *For TOA to the above therapy, add the following*: • Clindamycin 900 mg intravenously thrice a day PLUS • Gentamicin loading dose (2 mg/kg), followed by a maintenance dose (1.5 mg/kg) intravenously thrice a day or substituted with a single daily dosing (3–5 mg/kg) OR • Ampicillin/sulbactam 3 g intravenously four times a day PLUS • Doxycycline 100 mg orally or intravenously twice a day	Inpatient treatment to ensure clinical stability and improvement in cases of hemodynamic instability, peritonitis, severe systemic symptoms, concern for treatment failure of oral antibiotics (no clinical improvement after 72 h of initiation of oral therapy), pregnancy, and inability to tolerate oral antibiotics

with leiomyomas are asymptotic while the rest present with heavy menstrual bleeding or menorrhagia. It is noteworthy that acute pelvic pain results only when the fibroid has degenerated or torsed (gynecological emergency) or is associated with adenomyosis or endometriosis. Uterine fibroids are usually diagnosed on ultrasound unless they increase in size and are palpable on pelvic examination. When they enlarge, they lay pressure on adjacent pelvic organs and structures. Management in the ED includes analgesia and outpatient follow-up with gynecology unless torsion or heavy vaginal bleeding or transfusion necessitate inpatient admission.

Malposition Intrauterine Device

Intrauterine devices are one of the most effective contraceptive methods. In patients who have pelvic pain with an IUD, it is of utmost importance to completely evaluate them and exclude other causes of pain, such as PID, with and without abscess formation, and ectopic gestation. One of the most significant factors necessitating IUD removal is pelvic pain, which includes insertional pain, intermenstrual cramps often associated with spotting and bleeding, and increased dysmenorrhea. The larger stiff IUD produces localized endometrial ulceration and inflammation as they do not conform to endometrial cavity shape and cause pain. Additionally, endometrial prostaglandin release secondary to the presence of an intrauterine foreign body may also play an important role. The risk for PID associated with IUD use is primarily confined to the first 3 weeks after insertion. If an IUD user receives a diagnosis of PID, the IUD does not need to be removed. However, the woman should receive antibiotic treatment according to the recommendations and should be closely followed up. If no clinical improvement occurs within 48–72 hours of initiating treatment, IUD removal should be considered. A systematic review of evidence found that treatment outcomes did not generally differ between women with PID who retained the IUD and those who had the IUD removed. Although rare, acute pelvic pain may be caused by IUD malposition due to uterine perforation. Lactation and recent delivery are found to be independent cofactors for increased risk of uterine perforation following IUD insertion. Management in such cases begins with analgesia and a pelvic examination to check for the string of the IUD at cervical os. If present, perform an ultrasound to confirm appropriately located IUD and search for alternative diagnosis of pain. However, if the IUD string is not present at the os or is too short or not visualized in the uterus on ultrasound, it either has been expelled out or has perforated the uterus. Subsequently, an X-ray kidney, ureter, and bladder (KUB) should be ordered to visualize the IUD in the abdomen. If the IUD is seen in the abdominal area, immediate expert consultation should be taken to retrieve it surgically. If the KUB X-ray does not locate the IUD, chances are that it has been expelled out.

Endometriosis/Adenomyosis

Endometriosis is presence of endometrial-like tissue outside the uterus whereas when the endometrial-like tissue is present within the uterine muscle, the condition is known as adenomyosis. Both of these ailments result in recurrent inflammation and are seen in women of reproductive age who present with dysmenorrhea, pelvic pain, and subfertility. Dysuria and hematuria can be presenting features in cases where there is bladder involvement; painful defecation and blood in stools sometimes occur in cases where there is bowel involvement. Pelvic examination is notoriously inaccurate in estimating the volume of endometriosis, and X-rays or ultrasound or magnetic resonance imaging techniques do not improve the diagnostic accuracy. Laparoscopy remains the cornerstone of accurate diagnosis of endometriosis. ED management includes pain control using NSAIDs and gynecology outpatient follow-up.

SUMMARY

- Acute pelvic pain possesses a diagnostic challenge due to overlapping multisystem etiologies and nonspecific evaluation findings.
- Determining the pregnancy status is the critical first step in the management algorithm.
- The pelvic examination, due to lack of accuracy and reproducibility, is no longer desirable in the emergency department.
- The goal of ED management is to differentiate life or fertility-threatening emergencies from conservatively treatable pathologies.
- Pelvic ultrasonography is the first choice of imaging investigation for the gynecological causes of acute pelvic pain in all patients and for the nongynecological causes in a pregnant patient.
- A contrast-enhanced CT plays a central role in the nongynecological causes of acute pelvic pain or if the symptoms cannot be clearly localized or the ultrasound findings are unclear.
- Ovarian torsion can occur without complete loss of vascularity due to dual blood supply.
- It is desirable to maintain a high degree of clinical suspicion and a low threshold for admission for OHSS characterized by ovarian enlargement and an acute fluid shift into the extravascular space.
- Upon suspicion of pelvic inflammatory disease, empiric antibiotic therapy must be initiated for the patient and sexual partner.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Abnormal Uterine Bleeding

Sanjukta Dutta, Mainak Majumdar

INTRODUCTION

Abnormal uterine bleeding (AUB) can be broadly defined as bleeding from uterine corpus which is abnormal in volume, duration, regularity, or frequency. It can be acute or chronic and occurs in absence of pregnancy. It may lead to loss of fertility and may end up in poor quality of life even leading to destructive surgeries such as hysterectomy in extreme cases.

Normal average blood loss is 30–35 mL per menstrual cycle. More than 80 mL blood loss per cycle is considered abnormal. Acute AUB is an episode of heavy bleeding which warrants immediate intervention to prevent exsanguination. Chronic AUB refers to bleeding that is persisting for >6 months. Various type of vaginal bleeding has been defined by *International Federation of Gynaecology and Obstetrics (FIGO)* (**Table 1**).

Globally around 9–14% women experience AUB during the childbearing years of life. In India, the prevalence is around 18%.

TABLE 1: Definition of various types of vaginal bleeding: FIGO classification of bleeding.

Type	*Definition*
Abnormal uterine bleeding	• Bleeding which is abnormal with respect to regularity, volume, frequency, or duration • May be acute or chronic (>6 months)
Heavy menstrual bleeding	Excessive menstrual bleeding which hampers physical, social, and emotional quality of life
Amenorrhea	Bleeding absent >6 months
Prolonged menstrual bleeding	Menstrual bleeding continuing for >8 days in each cycle
Intermenstrual bleeding	Episodes of bleeding interspaced between otherwise normally timed cycle
Irregular menstrual bleeding	Unpredictable onset of menstrual period, with cycle >20 days for more than a year
Postmenopausal bleeding	Bleeding occurring >12 months after menstruation has seized

(FIGO: International Federation of Gynaecology and Obstetrics)

BASIC PHYSIOLOGY

Normal menstrual cycle depends upon complex feedback mechanisms involving the hypothalamus, pituitary gland, and the ovaries. During the first half of the menstrual cycle, i.e., the follicular (proliferative) phase, estrogen level rises causing thickening of endometrium while follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secreted from the anterior pituitary stimulates the ovaries to release the oocyte.

During the second half of the cycle, i.e., the luteal (secretary) phase, the corpus luteum (formed from the residual follicular capsule after ovulation) secretes progesterone and estrogen to maintain the structural integrity of the endometrium to facilitate implantation. Involution of corpus luteum occurs in absence of human chorionic gonadotropin (hCG) (if implantation does not take place) with fall in serum concentration of progesterone and estrogen which in turn leads to vasoconstriction of spiral arterioles of endometrium resulting in sloughing of endometrial lining thus causing menstrual bleeding.

ETIOLOGY

Female of different age group with vaginal bleeding present to emergency department and emergency physician should aware of causes related to their age (**Box 1**). A large number of females who present with bleeding in emergency are in the reproductive age group. Pregnancy must always be ruled out for these women. Menopausal women who have per vaginum (PV) bleeding may be have genital tract malignancies, the most common being cancer endometrium. Cancer endometrium is also prevalent in women above age 35 years with history of heavy menstrual bleeding. Endometrial biopsy with or without hysteroscopy must be performed in all these women before initiating therapy. Other differential diagnoses to be kept in mind for menopausal causes of bleeding are atrophic endometritis, urinary infection, or bleeding per rectum.

Points to Remember

- In first 2–3 weeks of life, infants may present with vaginal bleeding. This is mostly nonpathological caused by sloughing and shedding of endometrium due to waning

BOX 1: Age-related etiology—vaginal bleeding.

Adolescent
- Anovulatory cycle (hypothalamic-pituitary-ovarian axis immaturity), pregnancy, and exogenous hormones/oral contraceptive pill (OCP)
- Coagulopathy and pelvic infections

Reproductive
- Pregnancy, anovulatory cycle [polycystic ovary syndrome (PCOS)], exogenous hormones/OCP, leiomyoma, and cervical/endometrial polyps

Perimenopausal
- Anovulatory cycle
- Leiomyoma
- Cervical/endometrial polyps
- Thyroid dysfunction

Postmenopausal
- Atrophic vaginitis
- Exogenous hormones
- Endometrial cancer
- Other neoplasms: Vulvar, vaginal, and cervical

Life-threatening causes
- Acute heavy menstrual bleeding, genitourinary trauma, and uterine arteriovenous malformation (AVM)
- Acronym for abnormal uterine bleeding: PALM-COEIN
- Polyp, adenomyosis, leiomyoma, malignancy, and hyperplasia (structural causes)
- Coagulopathy, ovulatory dysfunction, endometrial causes, iatrogenic causes not yet classified (nonstructural)

of maternal hormonal levels. The condition is self-limiting and does not require treatment.
- In women >45 years of age or in women with risk factors, malignancy and endometrial hyperplasia must be ruled out as amount of bleeding may not always correlate with the disease.

EVALUATION OF ABNORMAL UTERINE BLEEDING

Before the detailed assessment is carried out, one must check for the five crucial parameters:
1. Age
2. Pregnancy (established/unknown)
3. Volume of blood loss
4. Hemodynamic stability
5. Associated acute abdomen

Based on the above information, various differentials are kept in mind while taking history, performing examination, and ordering investigations.

Age

A large number of females who present with bleeding in emergency are in the reproductive age group. Pregnancy must always be ruled out for these women. Menopausal women who have PV bleeding may be have genital tract malignancies, the most common being cancer endometrium. Cancer endometrium is also prevalent in women above age 35 years with history of heavy menstrual bleeding. Endometrial biopsy with or without hysteroscopy must be performed in all these women before initiating therapy. Other differential diagnoses to be kept in mind for menopausal causes of bleeding are atrophic endometritis, urinary infection, or bleeding per rectum. Prepubertal girls presenting with bleeding PV are less common. Causes in this age group include trauma, endocrine tumors, and rare genital tract tumors.

Pregnancy

Pregnancy could be intrauterine or ectopic. Ectopic pregnancy is associated with small volume of bleeding with or without preceding amenorrhea. Pain abdomen is invariably present and of mild-to-severe intensity. In initial phase of rupture, patient's vital parameters may be well compensated, thus this differential must always be borne in mind even in stable patients who do not give history of amenorrhea. The ectopic pregnancy could be ruptured (requiring immediate surgery) or unruptured (qualifying for expectant/medical/surgical management). Threatened or inevitable abortion presents with small volume bleeding with or without pain. Patients are invariably stable. Ultrasound confirms the diagnosis. Incomplete or complete abortions are associated with heavy bleeding and pain. Sometimes patients may be in stage of early compensated hypovolemic shock due to blood loss. Second and third trimester pregnancy bleeding could be due to placenta previa or abruptio placentae. Bleeding is painless in the former while abruption is associated with painful, slight, brownish or dark, or fresh bleeding. Ultrasound confirms placenta previa but may not be useful to diagnose placental abruption.

Volume of Blood Loss

Common gynecological causes of heavy bleeding are fibroids, adenomyosis, dysfunctional uterine bleeding, polyps, trauma, bleeding disorders, uterine inversion, cancers, and polycystic ovaries. *Common obstetric causes of heavy bleeding are* incomplete or complete abortions, placenta previa-vasa previa, placental abruption, and postpartum hemorrhage. *Common gynecological causes of light or irregular bleeding are* polyps, polycystic ovaries, thyroid dysfunction, cancers, pelvic inflammatory disease, and ruptured ovarian hemorrhagic cyst. *Common obstetric causes of light bleeding are* ectopic pregnancy, threatened abortion, placental abruption, and placenta previa.

Hemodynamic Stability

Patients who present to emergency room with bleeding PV could be in various stages of shock. As in all emergency room protocols, the doctors and nurses must first initiate resuscitation of hemorrhagic shock. Minimum of two wide bore intravenous (IV) access lines must be secured. Blood samples must be drawn for crossmatching packed cells, hematocrit values and prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT). Urine for pregnancy or serum beta-hCG may be ordered if clinically indicated. Bedside ultrasound is the imaging of choice for these patients. While packed red blood cells are being issued by the blood bank, hypovolemia must be corrected with colloids and crystalloids. Foleys catheter may be inserted for intake output monitoring. In case surgical

intervention is anticipated, anesthetists, and operating room staff are informed in advance.

Once detailed history, examination, and necessary investigations confirm the diagnosis, immediate treatment action to eliminate cause of bleeding must be initiated. In case medical therapy is planned, patient could be transferred to either intensive care unit or wards based on the patient's clinical condition and results of investigations in triage.

Associated Acute Abdomen

Questions must be directed to elicit onset, duration, intensity of pain along with aggravating, and relieving factors. When slight vaginal bleeding is associated with severe pain abdomen, most common causes include ectopic pregnancy, torsion, and ruptured hemorrhagic ovarian cyst. Bleeding is invariably an incidental finding and reason for emergency presentation is the pain. Pregnancy related causes are placental abruption. Nongynecological cause can be ureteric colic with hematuria. Heavy bleeding with pain abdomen maybe encountered in adenomyosis, fibroids, and abortions. Pain may be present in cases of acute pelvic inflammatory disease with incidental PV bleeding.

History

Best medical practice always teaches the doctor to always take a complete history of the patient even in emergency setting. Questions must be asked while keeping various causes of the presentation in mind. Vital information to be elicited includes a detailed menstrual history, age, and marital status, history suggestive of bleeding disorders, associated amenorrhea, fever, gastrointestinal symptoms, giddiness, and pain.

Menstrual history must include a complete assessment of duration and volume of blood loss, including number of days of heavy and light bleeding. Volume of loss is assessed by the number of sanitary napkins or tampons used. Bleeding lasting >7 days and more than three to four sanitary napkins a day is abnormal. Passage of large clots indicates heavy bleeding. Clots >1 cm indicate blood loss of >80 mL in a cycle. Past menstrual cycle pattern including duration and length of cycles must be asked for. In cases of suspected pregnancy related cause, scanty flow in last menstrual period must be inquired. The gestation maybe greater than amenorrhea in cases with implantation bleeding.

When the woman gives prolonged history of menorrhagia, questions must be directed to rule out fibroids (heavy flow on day 2 of cycle), adenomyosis (dysmenorrhea), polycystic ovaries (irregular cycles, hirsute features, acne, and weight gain), thyroid disorders (weight changes, cold or heat intolerance, and constipation), and bleeding disorders (easy bruisability).

In cases with history of fever, hemorrhagic cystitis or acute pelvic inflammatory disease may by the etiological factor. Past medical history must be asked along with details of all medications taken including any hormonal intake or history of being on blood thinners.

Suspicion of coagulopathies should be considered if, history of heavy bleeding from menarche, postpartum hemorrhage, surgical bleeding, dental procedural bleeding (any one point), one episode of bruising per month, one episode of epistaxis per month, gum bleeding, and positive family history (any two points). Patients who screen positive for coagulopathy should be evaluated further viz, investigations for von Willebrand factor, ristocetin cofactor, and opinion of hematologist is warranted.

Physical Examination

General Examination

Upon presentation to triage, patient's vital parameters are obtained with a cardiac monitor. Signs of hemodynamic instability include tachycardia, hypotension, cold clammy extremities, pallor, and sweating. Mucosal hemorrhage, purpura, or petechial rashes maybe present in patients with bleeding disorders. Hirsutism, acne, and oily skin are present in poly cystic ovarian syndrome. Virilization may indicate an androgen secreting tumor.

Systemic Examination

Respiratory and cardiovascular systems must be checked. Per abdomen examination must be stepwise including inspection, palpation, and auscultation. On inspection, shape and contour of abdomen gives information about pelvic masses or intra-abdominal bleeding which lead to distension. Large fibroids and uterine size in pregnancy can be detected on palpation of the uterus. Presence and location of tenderness on palpation also helps narrow down the differential diagnosis to suspected causes of painful bleeding. Suprapubic tenderness is present in urinary tract infections and uterine pathology whereas in tubo-ovarian pathology the pain is in the iliac fossa. Hepatosplenomegaly may also be present in cases of chronic anemia and malignancies.

Per Speculum Examination

Per speculum examination must be carried out with all aseptic precautions with a good light source and positioning of the patient. Examination must be gentle. Clots present must be removed gently to assess for cervical lesions like polyps or masses. Care must be taken before dislodging large clots in hemodynamically unstable patients. There can be torrential bleeding once a clot is dislodged, especially in cases of genital trauma and pregnancy. In cases of big vaginal lacerations with heavy bleeding, it is prudent to shift patient to the operating room with adequate blood arranged prior to complete assessment of the laceration. Examination under anesthesia and suturing can be performed simultaneously. In such cases, vaginal packing must be done in triage to reduce blood loss in the duration required to shift the patient to the operating theater.

In cases of incomplete abortions, products of conception are also noticed mixed with the blood clots. Grape-like vesicles are present in cases of complete molar pregnancies. A previous antenatal ultrasound and evaluation in triage can clinch the diagnosis and the patient is immediately taken for suction curettage without further delay. Molar evacuations are associated with increased complications such as bleeding and embolism; hence such cases must be referred to higher centers with cardiopulmonary backup for curettage.

Bimanual Examination

As with speculum examination, bimanual examination must be very gentle. A careless bimanual examination can result intra-abdominal bleeding due to dislodgment of clot and worsening of shock in cases of ruptured or impending rupture ectopic. Uterine size, shape, and contour are felt for and adnexal masses are ruled out. Fullness in pouch of Douglas indicates

presence of fluid. Cervical motion tenderness is present in cases of ectopic pregnancy. Bimanual examination must never be performed in cases of suspected placenta previa.

Points to Remember

In elderly or postmenopausal women, genital examination especially speculum examination can be painful due to dry mucosa or vaginal atrophy. Proper explanation of the examination process with reassurance and gentle maneuver along with generous use of anesthetic jelly is warranted. In suspected sexual assault victim, follow proper administrative and medicolegal protocol. Carefully examine patients to pick up early signs of hemorrhagic shock.

INVESTIGATIONS

Blood Investigations

After securing good IV access, samples are drawn for blood grouping and Rh typing, crossmatching of blood products, complete blood count (CBC) with hematocrit, PT, INR, APTT, serum beta-hCG in indicated cases, thyroid profile in indicated cases, kidney function test (KFT) and liver function test (LFT) in indicated cases, and viral markers if the patient requires surgery.

Imaging Studies

Ultrasound (transvaginal where possible) is the diagnostic modality of choice in emergency setting. Not only is it quick, but also relatively easy and also possible to perform at the bedside, if needed. In pregnant women, transvaginal sonography (TVS) can localize a pregnancy at a minimum beta-hCG value of 1,500 IU/mL. Color Doppler studies are useful in cases of ectopic and torsion. Sometimes, MRI may be required if ultrasound is unable to clinch the diagnosis. Hysteroscopy is required for diagnosis, visualization, and characterization of intrauterine abnormalities.

MANAGEMENT

Initial Treatment

Assessment of airway, breathing and circulation should be carried out first with appropriate interventions. Volume status assessment and its correction should be priority. In case of hemorrhagic shock, urgent blood and blood product transfusion is required.

Immediate resuscitation with IV fluids, IV tranexamic acid and IV pain medication is given. Antacids and antiemetics must be given if patient requires anesthesia. Invariably the patient is not in nil per oral status as required for surgery. Tamponade to the uterus can be given with roller gauze pack, balloon devices as done in postpartum hemorrhage, if needed.

Tranexamic acid (competitive plasminogen activation inhibitor):
Dose: 1–1.3 g IV (10 mg/kg) or 1.3 g oral every 8 hours. Contraindications in thrombotic/thromboembolic disease, thrombophilia, and vascular disease.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Reduces pain and bleeding in AUB secondary to ovarian dysfunction by facilitating vasoconstriction via prostaglandin $F_2\alpha$ and thromboxane A. NSAIDs are contraindicated in bleeding disorder, gastrointestinal bleeding/ulcers, platelet function abnormalities, and renal dysfunction.

Naproxen dose: 500 mg 12 hourly until bleeding diminishes or pain in controlled.

Ibuprofen dose: 400 mg 6 hourly until bleeding diminishes or pain in controlled.

Mefenamic acid dose: 500 mg 8 hourly for 4–5 days or until bleeding ceases.

Treatment of Bleeding Per Vaginum in Hemodynamically Unstable Patients

Immediate Invasive Technique

Intrauterine tamponade with Foley catheter, 26F with 30 mL saline in bulb.

Uterine Curettage

It is the treatment of choice for profuse bleeding in hemodynamically unstable women. Curettage is the best modality of therapy in cases of inevitable abortions and incomplete abortions. Curettage removes all products of conception quickly. Completeness of procedure can be confirmed on ultrasound. In centers where ultrasonography (USG) is not available, the surgeon must look for four signs: (1) grating sensation of all walls, (2) reduction is size of the uterus, (3) bubbles seen at the os, and (4) closing of the os. Misoprostol may be used in conjunction with curettage. Prior usage of misoprostol helps contract the upper cavity and open cervical os. Postprocedure, misoprostol helps to keep the uterus well contracted and also expel any small piece of conception.

Emergency curettage can be used as treatment modality in nonpregnant women with heavy bleeding and hemodynamic instability who do not respond to initial measures like injectable tranexamic acid. Emergency curettage should be performed if radioimaging shows increased endometrial thickness despite prolonged and profuse bleeding. This immediately relieves the symptoms and also provides histopathological correlation so as to chalk out the further treatment plan to prevent future menorrhagia. Disadvantage of curettage is that if further treatment is not initiated, it cannot prevent future episodes of heavy bleeding.

Various studies compare results of uterine curettage to hormone therapy show that time required for bleeding to subside is more with medical management. Anesthesia is avoided in medical therapy. Medical therapy maybe preferred if it yields results without need of more blood transfusion. It can also be given after curettage to stop bleeding after the procedure.

High-dose Intravenous Estrogen

Mechanism of action of estrogen therapy is promotion of regrowth of endometrium over the bleeding denuded epithelial surface. Estrogen stabilizes lysosomal membranes and stimulates promotion of endometrial ground substance. A randomized control trail of 34 cases was carried out where women with heavy bleeding were treated with IV conjugated equine estrogen (CEE), 25 mg Premarin in 5 mL saline was instilled over 2 minutes. The dose was repeated every 3–5 hours, if bleeding persisted. In the placebo arm, 200 mg of lactulose was given. The difference in the two arms was not statistically significant in the first 3 hours. However, after 72 hours, 72% of patients in the CEE arm showed improvement versus 38% in the placebo arm. Bleeding persisted at 8 hours in two women

in the CEE group. There was no correlation between histology on endometrial biopsy and success of therapy. 39% women had nausea and vomiting requiring treatment in the CEE arm versus 13% in the placebo group.

If bleeding persists beyond 8 hours, estrogen therapy must be stopped and other treatment modalities started. Maintenance therapy is started once bleeding decreases with IV Premarin. 2.5 mg Premarin four times a day can be continued for 21 days. A progestin must be given in the next 10 days. Maintenance therapy can also be started with oral contraceptive (OC) pills containing 35 μg estrogen. Initially two tablets are given for 5 days, followed by once a day for 20 days. Potential serious side effects of high-dose estrogen include thrombosis and embolism. Thus, minimum dose to produce desired result must be used. In high-risk category, like women at high risk for thrombosis, estrogen therapy is contraindicated.

Uterine Artery Embolization

Uterine artery embolization (UAE) is the first line of management of bleeding due to uterine arteriovenous (AV) malformations. It should not be used as first choice of therapy over emergency hysterectomy due to technical challenges and length of the procedure. However, in higher institutes with good clinical experience of performing the procedure, it can be performed in women who desire future fertility. Current evidence however does not establish safety in future pregnancies. Adverse outcomes in pregnancy have been reported after embolization procedure.

Surgical Management of Ectopic Pregnancy

Laparoscopic surgery is invariably feasible in higher centers with good emergency, anesthesia, and blood bank facilities. Only in hemodynamically unstable patients where head low position is not possible, laparotomy is considered. Goals of surgery must include correct time management to prevent complications due to the delay. A team approach and good communication with anesthetist is imperative to detect any anticipated complications on time.

Hysterectomy

In obstetric cases, when initial measures such as bimanual compression, oxytocin, uterine tamponade, and repair of lacerations fail, patient is taken up for emergency laparotomy. A gynecologist must be well versed with anatomy of the iliac, uterine artery, and ureter. A broad ligament hematoma can be treated with uterine artery ligation at its origin. Internal iliac ligation is recommended to control atonic or traumatic postpartum hemorrhage when previous measures fail. When internal iliac ligation fails, obstetric hysterectomy is performed to save the life of the woman. In gynecological cases of heavy uncontrolled bleeding with hemodynamic instability, when all measures fail, in rare circumstances, emergency hysterectomy maybe performed to treat uncontrolled bleeding.

Treatment of Bleeding Per Vaginum in Hemodynamically Stable Patients

Estrogen Therapy

High-dose oral estrogen therapy is most effective in controlling menorrhagia. It carries risk of thrombosis and embolism and should not be used in high-risk patients. Estrogen therapy alone is more effective than combined estrogen-progesterone therapy because progestins inhibit synthesis of estrogen receptors and increase estradiol dehydrogenase, thereby impeding the rapid proliferation of endometrium induced by estrogen.

Estrogen-progesterone Therapy

This is also used to control heavy and prolonged bleeding. Initial dose is two tablets a day for 5 days, followed by once a day for 20 days. Withdrawal bleeding maybe slightly heavy but usually stops in 7 days.

Progestin Therapy

Medroxyprogesterone 10 mg, two tablets twice a day are started to treat menorrhagia of anovulatory etiology. Progestins inhibit further endometrial growth in women with thickened endometrium. After 5–7 days, the dose is reduced to once or twice a day for a total duration of 25 days. Progesterone causes thinning of endometrium, thus controlling the bleeding. Only progesterone therapy is less effective than estrogen, especially in cases where bleeding is due to denudation of the endometrium.

Endometrial Ablation

This is the procedure of choice after endometrial biopsy confirms benign nature disease. Relatively simple and noninvasive, ablation can help treat the symptom of heavy bleeding without much long-term or short-term complications.

DISPOSITION

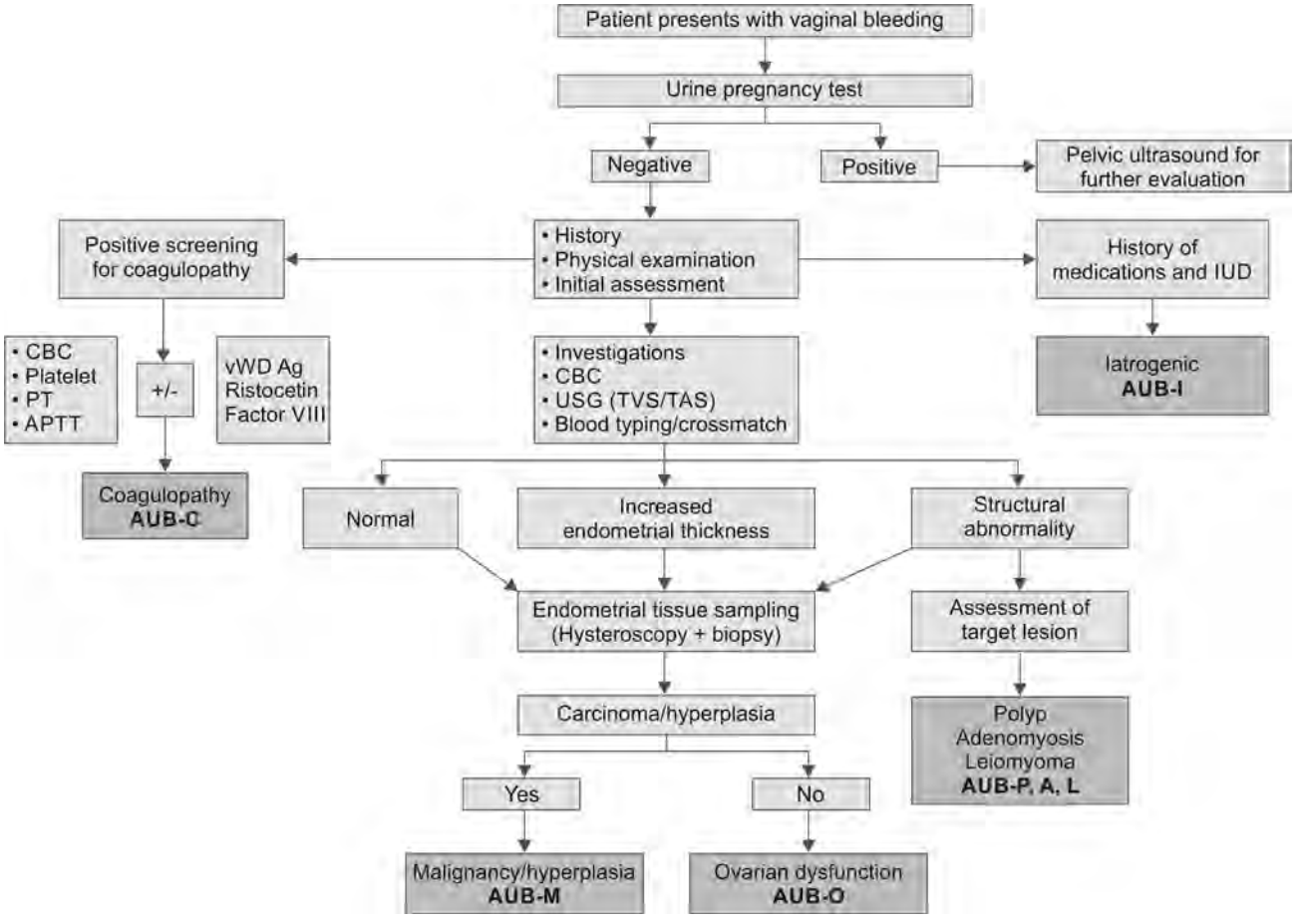
- Hemodynamically stable patients with mild bleeding can be discharged after emergency management with advice to follow-up with gynecologist.
- Unstable patients and patients with significant active bleeding should be admitted for immediate intervention, further evaluation and management.
- Need for surgical intervention depends upon several factors as discussed above.
- Referral for endometrial biopsy or tissue sampling in patients with risk factors and age >40 years.

SUMMARY

Keys to successful outcome in management of emergency vaginal bleeding are thorough knowledge of etiological factors, good time management, and emergency team approach to arrive at the correct diagnosis while resuscitating the patient at the same time, followed by administering the appropriate therapy. Speed, close vigilance, and time-to-time reassessment ensure success of therapy. All patients with AUB will present in emergency as vaginal bleeding. Thus, it is imperative to differentiate the source and the cause.

Thumb Rule 1: All patients in reproductive age group who present with vaginal bleeding to be screened for pregnancy.

Thumb Rule 2: In nongravid patients, careful pelvic examination should be done to rule out sources and causes of bleeding other than the uterus. Approach to vaginal bleeding is summarized in **Flowchart 1**.



(APTT: activated partial thromboplastin time; AUB-A: abnormal uterine bleeding due to adenomyosis; AUC-C: AUB due to coagulopathy; AUB-L: AUB due to leiomyoma; AUB-M: AUB due to malignancy and hyperplasia; AUB-O: AUB due to ovulatory dysfunction; AUB-P: AUB due to polyp; CBC: complete blood count; IUD: intrauterine device; PT: prothrombin time; TAS: transabdominal sonography; TVG: transvaginal sonography; vWD Ag: von Willebrand disease antigen)

FLOWCHART 1: Approach to abnormal uterine bleeding.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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CHAPTER

Ectopic Pregnancy

Sonal Parihar

INTRODUCTION

Ectopic pregnancy (EP) is one of the most dreaded and nightmarish obstetric emergencies. It can lead to massive hemorrhage, infertility, or death. As the name indicates, ectopic means outside. When the conceptus instead of implanting in the uterus, implants outside in the tube (97.7%)/ovary (0.2%)/abdomen (1.4%), or even the cervix (1:1,000 to 1:16,000) its known as EP. In our country, it is one of the most common emergencies in which doctor finds it hard to explain the urgency to the patient, the latter remains unconvinced most of the time unless they present in a state of shock. If left undiagnosed, misdiagnosed or late diagnosed—it can be fatal. Rate of EP is highest among older women and incidence is obviously highest in reproductive age group—25–34 years women. Ruptured EP is the major cause of death in first trimester. Its incidence is 2% of all pregnancies and mortality rate is 4–10%. The incidence of EP has drastically increased over the years because of assisted reproductive technology (ART), delayed conceptions, and better diagnostic tools.

CAUSES

Theoretically anything that hampers or delays the migration of blastocyst to the uterine cavity can be a cause for ectopic. There are various risk factors which can cause an EP (**Table 1**), still many ectopic would occur without any identifiable risk factor.

TABLE 1: Major causes for ectopic pregnancy.

Pelvic causes	*Epidemiological causes*
• Tubal surgery (including sterilization) • Pelvic inflammatory disease (including STDs) • Anatomic abnormality of tubes • Contraceptive failure (both OCPs and IUCD, especially progesterone IUCD) • ARTs (unknown cause), IVF (especially multiple embryo transfer) • History of previous ectopic (22% increase in risk) • Prior spontaneous abortion • History of infertility • Abnormal endometrium factors (e.g., IUCD)	• Maternal age above 35 (age-related tubal changes) • Cigarette smoking—alters tubal motility • History of multiple sexual partners

(ARTs: assisted reproductive technologies; IUCD: intrauterine contraceptive device; IVF: in vitro fertilization; OCPs: oral contraceptive pills; STDs: sexually transmitted diseases)

TYPES OF ECTOPIC PREGNANCY

We all know that fertilization takes place in the ampulla of fallopian tube following which the zygote implants after 7–8 days in the uterus. Only the uterine cavity is designed to expand and accommodate the growing fetus. So, whenever the implantation happens outside uterus it results in ectopic. Various types of EP are shown in **Figure 1**.

Tubal Ectopic

It is the most common site with 80% in ampullary region, 12% in isthmus, 5% in fimbria, 2.3% in interstitium, and 2% in cornua. Generally, it happens because of damage to (1) tubal mucosa which prevents transport of fertilized egg to the uterus, and (2) defects in ovum resulting in premature implantation or elevated estradiol or progesterone levels inhibiting tubal migration.

In 50% cases, it is due to infection in the tube, there is a threefold increase in the risk of ectopic in cases of pelvic inflammatory disease (PID). 25% cases happen due to some kind of tubal surgery. Implantation causes penetration of zygote in muscular wall of tube which surrounds itself with maternal blood vessels as in uterine implantation. There is pain because of intermittent distension of the thin tube and leakage of blood through the fimbrial end. There are three ways it can end: (1) Spontaneous involution, (2) Once the stretching capacity of tube is met, it either bursts (ruptured ectopic), or (3) The abortus is partially or completely extruded out of the fimbrial end into peritoneal cavity or into the vagina (tubal abortion). Most dangerous is cornual pregnancy because firstly

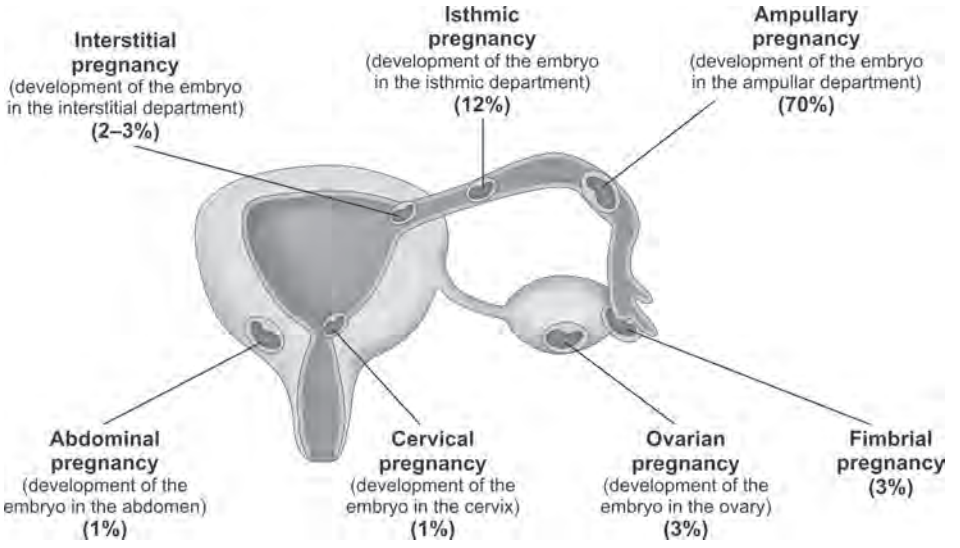


FIG. 1: Types of ectopic pregnancy.

it is close to myometrium and hence can benefit from its blood supply and secondly it has more space to grow and hence can grow larger (10–14 weeks) before rupture.

Cervical ectopic occurs in <1%, generally due to: (1) cervical tissue damage due to dilation and curettage (D&C) endometrial damage, (2) adhesions/fibrosis/previous cesarean/D&C, and (3) in vitro fertilization. It is one of the most dreaded and dangerous sites for EP which can cause profuse vaginal bleeding or uterine rupture and would generally end up in hysterectomy.

Abdominal Ectopic (<1%)

Mostly this develops from early rupture or tubal abortion, when the conceptus reimplants in the peritoneal cavity.

Cesarean Scar Ectopic

With increasing rates of cesarean section, the incidence of scar ectopic is increasing. It is rare, difficult to diagnose, and can cause massive bleeding.

Heterotopic Pregnancy

Simultaneous intrauterine (IU) and extrauterine gestations have been very rare historically (1 in 10,000), but due to ART this rate has increased to 1 in 4,000 now—so not so rare now.

In all cases of ectopic, the implantation is abnormal so the growth of conceptus is abnormal and hence the rise of beta-human chorionic gonadotropin (β-hCG), a hormone produced by the trophoblast is also very slow. There is no doubling after 48 hours as in normal pregnancies. No single value is of any use whether high or low.

CLINICAL PRESENTATION

Most classic presentation would be:

- *Amenorrhea* (of 1.5–2 months), although the presentations are varied and we cannot expect every case to be symptomatic—15–20% cases do not have a history of missed periods.
- *Abdominal pain:* Usually severe, syncopal, peritoneal in nature, and constant. It can be crampy, intermittent, or even absent. Shoulder pain implies free fluid (FF) (significant hemorrhage) in peritoneal cavity causing diaphragmatic irritation and referred shoulder pain.
- *Vaginal bleeding* with or without symptoms of hypotension. Scant bleeding or spotting or even heavy bleeding cannot exclude ectopic. Hypotension without significant vaginal hemorrhage is highly suggestive of EP.

TABLE 2: Differential diagnosis of ectopic pregnancy (EP).

Patients presenting as nonpregnant	*Pregnant patients*
Appendicitis	Normal (intrauterine pregnancy)
Inflammatory bowel disease	Threatened abortion (most common)
Ovarian pathology	Inevitable abortion
Ovarian cyst	Molar pregnancy
Ovarian torsion	Heterotopic pregnancy
Pelvic inflammatory disease	Implantation bleeding
Endometriosis	Corpus luteum cyst (if ruptures)
Sexual assault/trauma	Lateral implanted pregnancy (arcuate uterus) misdiagnosed as interstitial EP
Urinary tract infection	
Ureteral colic	

Features of Concern "Red Flags"

Hypotension because of hemorrhagic shock can be dangerous and is the major cause of death. Undiagnosed ruptured ectopic is main cause. Medical or surgical abortion without confirming intrauterine pregnancy (IUP) can lead to rupture of an EP. Differential diagnosis of ectopic is a big list. Patients not presenting with a classic history can end up getting a wrong diagnosis and wrong line of treatment. **Table 2** shows the differential diagnosis related to and not related to pregnancy. It includes almost all first trimester complications. Beware of heterotrophic pregnancy; it can be dangerous if left undiagnosed.

EVALUATION

History

The classic presentation as mentioned before is highly diagnostic. Any pain in first trimester should be treated as ectopic (pain is seen in 90% ectopic) unless proved otherwise. The idea is to check for all the risk factors with detailed history. Take detailed obstetric history. History of ectopic increases the risk of repeat ectopic to 22%. This rate also depends upon location of implantation and type of management (type of surgery—salpingectomy/salpingostomy; medical management). Discuss about previous medical/surgical history and substance abuse/smoking. Also discuss sexual activity and use of contraception, current medications/over the counter (drugs) (OTCs), etc. If a lady is pregnant postligation (laparoscopic salpingectomy/electrocautery), it should be assumed as ectopic until proved otherwise especially within 15 years.

Examination

Take vital signs. You may or may not find tachycardia, hypotension (shock)/bradycardia (vagal stimulation). Signs and symptoms of shock due to excessive bleeding are sometimes not clear due to compensatory mechanisms in healthy young women. Tenderness and guarding may be there because of adnexal mass (10–20%). Cervical motion tenderness (if blood present in vault). Cervix may show bluish discoloration. Uterus soft and bulky (may be normal size). Bimanual examination is not reliable in case of guarding.

Interpretation of Findings

Any patient with early pregnancy, mild bleeding, uterine/adnexal tenderness, and mild pain abdomen should raise high suspicion for EP. In such presentations, even if the patient does not give a history of amenorrhea, get a urine pregnancy test. If bleeding is heavy with clots and tissue, it generally points towards threatened or incomplete miscarriage, but ectopic cannot be ruled out as endometrial sloughing in failing ectopic may be seen as heavy bleeding.

INVESTIGATIONS

The goal is to make an early diagnosis to reduce morbidity and prevent mortality. Complete blood count (CBC) Blood grouping and typing, coagulation profile and blood sugars are essential investigations in emergency department.

Ultrasonography

Transvaginal scan (sensitivity 90%) is preferred. Demonstration of an echogenic adnexal mass which moves separately from ovary (blob sign) with FF is highly suggestive (almost 100%) of ectopic, large amount of FF alone has 86% risk and if live embryo is demonstrated in adnexa with empty uterus [seen more easily in transvaginal sonography (TVS)], its 100% diagnostic (**Table 3**). TVS can visualize gestational sac (GS), yolk sac (YS), and fetal pole at 4.5, 5.5, and 6.0 weeks, respectively. If an embryo without cardiac activity is visualized within uterus, fetal demise is diagnosed if crown rump length (CRL) ≥5 mm. Otherwise follow-up is required. This is where role of β-hCG starts. See below (discriminatory zone).

TABLE 3: Ancillary ultrasound sonography (USG) findings suggestive of ectopic pregnancy in high-risk patients.

Ancillary findings	*% Risk of ectopic pregnancy*
Any free pelvic fluid (either rupture or leakage from tubal opening)	52%
Complex pelvic mass	72%
Moderate/large amount of free pelvic fluid	86%
Tubal ring	>95%
Mass and free fluid	97%
Hepatorenal free fluid	Almost 100%

TABLE 4: Estimated beta-human chorionic gonadotropin (β-hCG)levels after conception.

Postconception weeks	*B-hCG Level (mIU/mL)*
<1 week	5–50
1–2 weeks	50–500
2–3 weeks	100–5,000
3–4 weeks	500–10,000
4–5 weeks	1,000–50,000
5–6 weeks	10,000–100,000
6–8 weeks	15,000–200,000
8–12 weeks	10,000–100,000

Intermediate ultrasonographic findings: Empty uterus, nonspecific fluid collections, echogenic material, abnormal sac, and single GS.

Diagnostic ultrasonographic features of scar ectopic: Empty uterine and cervical canal, GS seen in the anterior portion of lower uterine segment (LUS), absence of a healthy myometrium between bladder and the GS, and high vascularity at the scar level.

Diagnostic ultrasonographic features of cervical ectopic: Normal size uterus with empty endometrial cavity, embryo in cervical canal, tightly closed internal os, high vascularity in cervical canal, a thin (1–3 mm) or absent myometrial layer between GS and bladder, and presence of prominent subvascular pattern in area of cervix.

Beta-Human Chorionic Gonadotropin

A positive urine test with no IUP on USG is highly suspicious. If the patient is stable, we can opt for serial serum β-hCG measurements. As is clear from the **Table 4**, β-hCG shows a rising trend until 9–10 weeks, then plateaus. No single β-hCG value can be diagnostic. A failed IUP and resolving EP will show a lower than normal hCG value and falling trends. A developing ectopic will show rising titers but it will not double in 48 hours as is commonly seen in normal IUP. Ruptured ectopic will

show very low or absent levels of β-hCG, hence sonography is a must even at very low β-hCG. Serum β-hCG is detected at concentration of ≥10 mIU/mL and urine test at concentration of ≥20 mIU/mL.

Discriminatory Zone

It was developed to establish a relation between β-hCG and USG findings. It is the level of β-hCG at which sonography should detect an IUP. Hence a value below the discriminatory zone (DZ) with empty uterus on USG is intermediate. Levels higher than DZ with empty uterus are highly suggestive of EP. With TVS, the DZ is 1,500 mIU/mL and 6,000 mIU/mL with TAS.

Variations

- Normal pregnancy may show only 53% rise in 48 hours
- Rise of >53% β-hCG does not rule out ectopic
- Ectopic can also show doubling (21% cases)
- hCG is expected to decrease by 21–35% in 2 days in spontaneous miscarriage.

Hence, serial measurements are done to increase or decrease the suspicion rather than diagnosing.

Serum Progesterone

No value is diagnostic. It is the major hormone for pregnancy support. Initial 8–10 weeks, it is produced by ovaries, thereafter placenta takes over and levels keep on rising and then plateaus with levels of >20 ng/mL. In general, 100% pregnancies with value ≤5 ng/mL will be pathologic. There is no use of serial measurements. P levels >25 ng/mL have 97% sensitivity for viable IUP. It is not a recommended standard tool but is of use when USG is negative, β-hCG is very low, and the doctor is contemplating D&C or laparotomy.

Dilation and Curettage

Identification of chorionic villi in endometrial samples diagnoses 70% of normal IUPs, except in patients undergoing ART.

Culdocentesis

Not done these days because of advent of β-hCG. Moreover, it is neither very sensitive, nor very specific.

Laparoscopy

It can be both diagnostic as well as therapeutic.

Magnetic Resonance Imaging

It is useful in diagnosis of scar ectopic.

TREATMENT

Rapid Fluid Resuscitation

Ectopic pregnancy is a time specific gynecolgic emergency. Immidiate assessment of airway breathing circulation should be done and further volume status should be supported by intravenous fluid and blood and blood products. Further management decision should be taken with the help of USG and β-hCG.

Surgical Treatment

Generally laparoscopy/sometimes laparotomy—this decision will depend upon patient's condition, doctor's expertise, availability of team, sonography findings, etc. Sometimes intraoperative bleeding or frozen pelvis during laparoscopy leads to laparotomy.

- *Salpingectomy*: If family is complete or opposite tube is normal, tube is in good condition.
- *Salpingostomy*: If patient is stable, future fertility is required, endometriosis or pelvic adhesions, opposite tube absent/not in good condition, and if technically feasible. But it increases the risk of repeat ectopic because of damaged mucosa of tube. Repeat β-hCG after 7 days, if >1,000 mIU/mL or >15% of original level, persistent EP is diagnosed. This can happen in 10% cases and will need methotrexate (MTX) or reoperation.

Medical Management with Methotrexate

If minimal symptoms, patient is stable, normal baseline liver function test (LFT) and renal function test (RFT), tubal mass <3.5 cm in diameter, no fetal heart, no evidence of rupture, and future fertility is desirable.

Methotrexate act as an antimitotic, folate antagonist, inhibits dihydrofolate reductase (DHFR) enzyme, interferes with fetal deoxyribonucleic acid (DNA) synthesis, destroys rapidly dividing cells, and causes involution of pregnancy. Monitoring of doses is done according to serial hCG levels. *Success rate* is 85–98%, not much difference between single/multiple dose regimen but depends upon pretreatment hCG levels. Prognostic factors which can lead to higher failure rate are: (1) larger tubal diameter, (2) fetal cardiac activity present, (3) higher pretreatment β-hCG, and (4) severe abdominal pain. *Failure rate* is 14.3% (if pretreatment hCG > 5,000 IU) in such cases multiple doses are recommended, 3.7% (if pretreatment hCG < 5,000 IU). Contraindications to MTX administration are presented in **Table 5**.

TABLE 5: Contraindications to MTX administration.

Absolute contraindications	***Relative contraindications***
Intrauterine pregnancy	Embryonic cardiac activity detected by TVS
Evidence of immunodeficiency	hCG > 5,000 mIU/mL
Moderate-to-severe anemia, leucopenia, and thrombocytopenia	Ectopic pregnancy >4 cm in size (TVS)
Insensitivity to MTX	Refusal to accept blood transfusion
Acute pulmonary disease	Inability for patient to return for follow-up
Active peptic ulcer disease	
Hepatic/renal dysfunction	
Breastfeeding	
Hemodynamic instability	

(hCG: human chorionic gonadotropin; MTX: methotrexate; TVS: transvaginal sonography)

Side Effects

Abdominal pain (75%), flatulence, stomatitis, vaginal bleeding, weakness, dizziness, syncope, and hair loss are the common side effects. *"Separation pain"* happens 3–7 days after MTX treatment due to tubal abortion/distension due to hematoma formation. It is a lower abdominal pain, self-limited and responds to nonsteroidal anti-inflammatory drugs (NSAIDs). It is suggested to perform CBC and USG to differentiate such pain from ruptured tube pain. Unwanted outcomes are long resolution period and increased waiting time for future fertility.

Dose

About 50 mg/m^2 single intramuscular (IM) dose. Patient need rescue surgery in 5% cases of MTX failure, if unstable vital signs, decreasing hemoglobin, intolerable pain, and evidence of rupture on USG.

Follow-up is done with β-hCG on (day 4 and 7) initial rise in β-hCG till day 4, then between day 4 and 7, 15% decrease from pretherapy level—if not, repeat MTX dose. After day 7, weekly β-hCG till it comes to zero, this might take 2–3 months. If weekly reports do not show a fall of 15% or more, repeat dose of MTX can be given (maximum three doses). Pelvic examinations should be avoided to minimize the risk of rupture. Patients should avoid sexual intercourse for 14–21 days after treatment or until β-hCG becomes undetectable, avoid pregnancy in next 3 months, take folic acid supplements.

Do not forget to administer anti-D (50 μg), if Rh negative (alloimmunization can occur with even 0.1 mL fetal blood admixing). If β-hCG to start with was very low (<1,000) and shows a falling trend, then just serial assays without any active treatment can be done—till the levels drop to zero. Treatment plan is summarized in **Flowchart 1**.

Special Cases

Cervical Ectopic

Foley catheter is used to give tamponade, placed beyond the internal os and filled with 30 mL saline—mostly after curettage. To reduce blood supply—ligation of uterine artery/internal iliac artery/or angiographic embolization of these arteries is done before curettage along with chemotherapy. Curettage or hysterectomy—former can cause excessive hemorrhage. Latter is lifesaving treatment and is treatment of choice in women diagnosed with cervical ectopic pregnancy (CEP) in second trimester and those who do not desire further pregnancy. Rarely conservative approach by USG-guided instillation of KCl/MTX can be used. Systemic CTH is also an option.

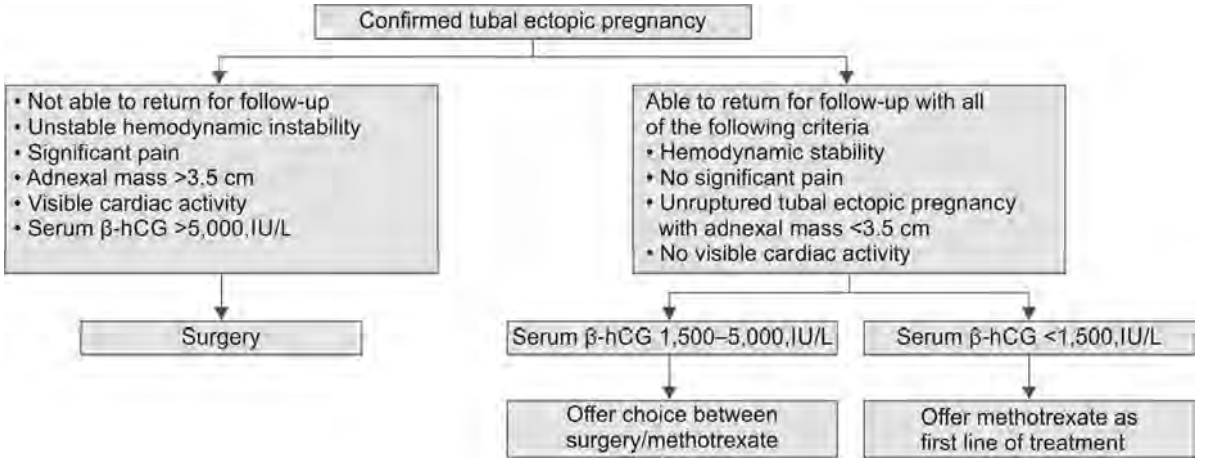
Scar Ectopic

Generally, excision of the scar along with products of conception will be required. Sometimes the pregnancy may expel spontaneously like an abortion (some cases reported).

SUMMARY

Classic presentation of ectopic pregnancy includes mild pain abdomen, positive urine pregnancy test, and mild bleeding with or without signs and symptoms of hemorrhagic shock (only 20%). Most patients would have positive urine pregnancy test, empty uterus on sonography with/without nonspecific fluid collection with ≤5 ng/mL.

With advanced technology and excellent diagnostic modalities, we are at a much better position to diagnose and treat this emergency and avoid laparotomy as well as hysterectomy. Whatever treatment modality is used, it does not affect the fertility (except salpingectomy which will obviously reduce the fertility). Further fertility mainly depends upon patient's age, past history, and state of her pelvis.


Confirmed tubal ectopic pregnancy
• Not able to return for follow-up
• Unstable hemodynamic instability
• Significant pain
• Adnexal mass >3.5 cm
• Visible cardiac activity
• Serum β-hCG >5,000 IU/L
Able to return for follow-up with all of the following criteria
• Hemodynamic stability
• No significant pain
• Unruptured tubal ectopic pregnancy with adnexal mass <3.5 cm
• No visible cardiac activity
Surgery
Serum β-hCG 1,500–5,000 IU/L
Serum β-hCG <1,500 IU/L
Offer choice between surgery/methotrexate
Offer methotrexate as first line of treatment

FLOWCHART 1: Treatment plan for ectopic pregnancy.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Emergencies during Pregnancy

Devyani Misra, Mariyum Faruqi

INTRODUCTION

A healthy mother and healthy baby are the desired outcome of all pregnancies. However, and unfortunately, this normal state of altered body physiology may not always take a favorable course. Maternal morbidity and mortality can result from a complication arising during pregnancy or worsening of a preexisting condition in the woman. Worldwide, an estimated 211 women die from pregnancy and related complications for every 100,000 live births and according to the World Health Organization (WHO), around 295,000 women died during and following pregnancy in 2017. In India, according to the Sample Registration System, a demographic sample survey by the government, the mortality rate for the period 2016–2018 is estimated to be 113/100,000 live births which turns out to be a huge number when considering the actual births. The deadly triad of hemorrhage, preeclampsia, and infection contribute majorly toward mortality accounting for over a third of the causes and the importance of prompt diagnosis and management of these cases cannot be overemphasized. Another significant contributor to maternal mortality is unsafe abortion and complications of abortion which can only be controlled by avoiding unwanted pregnancies.

Obstetric emergencies can arise at any point in time and it is important to diagnose the condition and institute prompt treatment as needed. The early half of pregnancy can have complications related to miscarriages or infection arising as a result of unsafe abortions. Nearly 10 lakh abortions are carried out in India annually and almost 10 women die per day due to related complications. Diagnosis of abortion and treatment of related complications is thus of utmost importance. Since the patient is first attended by the emergency physician, it is imperative that early pregnancy complications be addressed. Pregnancy is often missed or overlooked so it is advisable to ask regarding the last menstrual period in a woman of reproductive age group and carry out a urine pregnancy test whenever in doubt. Liaising with the on-call gynecologist can be helpful. Another important complication in early pregnancy is excessive nausea and vomiting or hyperemesis gravidarum (HG). Though nausea and vomiting complicate most of the pregnancies and can be managed as outpatient, hyperemesis though rare (3%), necessitates prompt inpatient management with intravenous fluid to prevent catastrophic complications.

In the second half of pregnancy, antepartum hemorrhage complicates 3–5% of pregnancies. Of these there are two types, placenta previa where the placenta is implanted partially or completely in the lower uterine segment and abruptio placentae, where there is separation of a normally located placenta. It is one of the most common causes of maternal collapse and the emergency room (ER) physician must institute prompt resuscitation as patient may have collapsed before reaching the hospital due to exsanguination. Another frequently encountered pregnancy complication is hypertensive disorders which have an incidence of 5–10% and are a cause of significant morbidity and mortality. The ER physician has to be acquainted with the antihypertensives that can be used to control high blood pressure in pregnant women and also treatment of eclamptic seizures if the woman has convulsed as a result of hypertensive disorders. As a dictum, all seizures in pregnant women, especially in the second half, should be considered eclampsia unless proved otherwise. Use of the miraculous magnesium sulfate to control seizures should be highlighted and administration should be taught to all ER staff.

Preterm labor with an incidence of 10–15% and prelabor membrane rupture contribute toward neonatal morbidity and mortality and are a common complication in pregnancy. Also, infection as a result of membrane rupture can cause chorio-amnionitis and morbidity in the mother and needs treatment. Correct diagnosis and management are thus important.

In cases pertaining to the obstetric specialty, the primary duty of the ER physician is to diagnose the pregnancy complication and commence initial treatment. Resuscitation may often be required and one must not forget the pressure effects of the gravid uterus which hampers the venous return. Should there arise a need for intubation, it should be carried out by a specialist keeping in mind the difficulties that may be encountered in pregnant women. Promptness of management will decide the outcome in many situations like hemorrhage and thus the effect on morbidity and mortality. Having a sound knowledge of possible obstetric emergencies and anticipating possible complications, the ER physician can contribute significantly toward lowering maternal morbidity and mortality. In the following text, we will discuss a few of the obstetric emergencies mentioned here, how to make a diagnosis, and go about the treatment (**Table 1**).

TABLE 1: Emergencies during pregnancy.	
First 20 weeks of pregnancy	• Nausea, vomiting, hyperemesis, and gravidarum • Spontaneous abortion • Septic abortion
After 20 weeks of pregnancy	• Chronic and gestational hypertension: ○ Preeclampsia ○ HELLP ○ Eclampsia • Placenta previa • Vasa previa • Premature rupture of membrane • Preterm labor

(HELLP: hemolysis, elevated liver enzyme levels, and low platelet count)

NAUSEA AND VOMITING OF PREGNANCY AND HYPEREMESIS GRAVIDARUM

Nausea and vomiting in pregnancy (NVP) is a rather frequent symptom occurring in 70–80% women. NVP is one of the most common reasons for hospitalization in pregnancy and negatively affect the quality of life. In most pregnant women the condition is self-limiting, yet, in a few, symptoms may persist throughout the duration of pregnancy.

Hyperemesis gravidarum is a rare but severe form of NVP reported in 0.3–3.6% pregnancies and an obstetric emergency. Other causes of severe nausea and vomiting should be excluded before coming to the diagnosis of HG.

Etiology/Causes

Exact etiology contributing to symptoms of NVP/HG remains largely eluded. A familial predisposition to NVP exists implicating a genetic cause. Women who have NVP/HG in one pregnancy tend to suffer from the condition in subsequent pregnancies. Various theories have been proposed which include biochemical, immunological, and psychosocial causes. Human chorionic gonadotropin (hCG) hormone released from the placenta during pregnancy is primarily associated with NVP and conditions with higher hCG levels as multiple pregnancy and trophoblastic disease have increased severity. Other common associations are high estradiol and leptin levels, low body mass index (BMI) and female fetus.

Pathophysiology

Excessive vomiting results from emetogenic effects of hCG the pathogenesis of which is largely unknown. There are no marked changes in the organ systems other than features of dehydration and malnutrition in severe cases. Some cases of HG may develop Wernicke's encephalopathy due to vitamin B1 deficiency.

Clinical Presentation and Red Flags

Nausea and vomiting in pregnancy and HG are two ends of a spectrum with NVP presenting as mild form of the disease whereas severe forms present as HG.

In mild cases, nausea and vomiting typically appears by fourth to seventh weeks of pregnancy and resolves completely in 90% women by 20–22 weeks. Around 10% pregnant women may continue to have NVP throughout pregnancy. NVP which has onset after 11 weeks of pregnancy should raise suspicion of some underlying pathology and warrants evaluation. NVP may be associated with retching, hypersalivation, and feeling sick or nauseated.

Hyperemesis gravidarum, the severe form of NVP, is marked by a triad of severe protracted nausea and vomiting associated with weight loss >5% prepregnancy weight, dehydration, and electrolyte imbalances. Severe untreated forms may present with malnutrition, dehydration, neuropathies, Wernicke's encephalopathy, coma, and death. Serious maternal complications may also occur due to Mallory–Weiss tears and esophageal rupture, splenic avulsion, and pneumothorax associated with excessive vomiting.

A Pregnancy Unique Quantification of Emesis (PUQE) score (**Table 2**) has been used to classify the severity of NVP and assessment of improvement of symptoms with treatment. Using PUQE score it is possible to objectively quantify the disease severity and ensure uniformity in treatment to be given. Women with mild NVP can be managed with oral medication. Ambulatory daycare management can be done in cases where vomiting persists despite medication and PUQE score is <13. Those women whose symptoms are not relieved or persist despite treatment with PUQE score >13 need to be admitted (**Box 1**).

Evaluation

History

History of NVP/HG in prior pregnancy must be elicited. Quantification of symptom severity by PUQE score with effects on quality of life should be assessed. Rule out other possible causes of vomiting, history of drug intake, coexisting urinary infection, abdominal pain, and history of chronic *Helicobacter pylori* infection or any other infection. Also, assess family support to elicit psychological/neurological causes for the symptoms.

Physical Examination

This includes assessment of well-being of the woman. Measure the temperature, pulse, blood pressure, respiratory rate, oxygen saturation, and weight. Assess the alertness while looking for signs of dehydration and muscle wasting. An abdominal examination must be done which may indicate alternate causes for the symptoms. Other systems to be examined if history is indicative.

Interpretation of Findings

Altered consciousness, presence of significant weight loss, dehydration, and muscle wasting are indicative of disease severity and warrant immediate treatment.

Investigations

Investigations are done to assess severity and progress of treatment. Some special investigations may be needed to rule out other causes **Table 3**.

TABLE 2: Pregnancy Unique Quantification of Emesis (PUQE) index.					
PUQE-24 scoring system	***1***	***2***	***3***	***4***	***5***
In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all	1 h or less	2–3 h	4–6 h	>6 h
In the last 24 hours have you vomited or thrown up?	Did not throw up	1–2 times	3–4 times	5–6 times	≥7 times
In the last 24 hours, how many times have you had retching or dry heaves without bringing anything up?	No time	1–2 times	3–4 times	5–6 times	≥7 times
PUQE-24 score: Mild ≤6; Moderate 7–12; Severe ≥13					

BOX 1: Indications for inpatient management in NVP/HG (red flags).

- Continued nausea and vomiting and inability to keep down oral antiemetics
- Continued nausea and vomiting associated with ketonuria and/or weight loss >5% of body weight and/or dehydration and electrolyte imbalance
- Coexisting condition requiring treatment

(HG: hyperemesis gravidarum; NVP: nausea and vomiting in pregnancy)

TABLE 3: Investigations to assess severity of NVP/HG.	
Investigation	***Abnormalities***
Urine dipstick	Ketonuria
Urine culture	Urinary tract infection
Complete blood count	Infections, anemia, and hemoconcentration
Blood glucose	Diabetes
Renal function test	Kidney diseases, dehydration, and acute kidney injury
Serum electrolytes/ABG	Hypokalemia/hyperkalemia, hyponatremia, metabolic hyperchloremic alkalosis, and hypocalcemia
Liver function test	Hepatitis and raised transaminases/ bilirubin
Serum amylase	Pancreatitis
Thyroid function test	Hypothyroidism/hyperthyroidism
Ultrasound scan	Multiple pregnancy, molar pregnancy, gallstones, and ovarian/cyst torsion

(ABG: arterial blood gas; HG: hyperemesis gravidarum; NVP: nausea and vomiting in pregnancy)

Treatment

Many oral antiemetics are safe for use in NVP (**Table 4**). Women not responding to single medication may be given combination of different drugs. Parenteral route may be preferable for those with persistent NVP/HG.

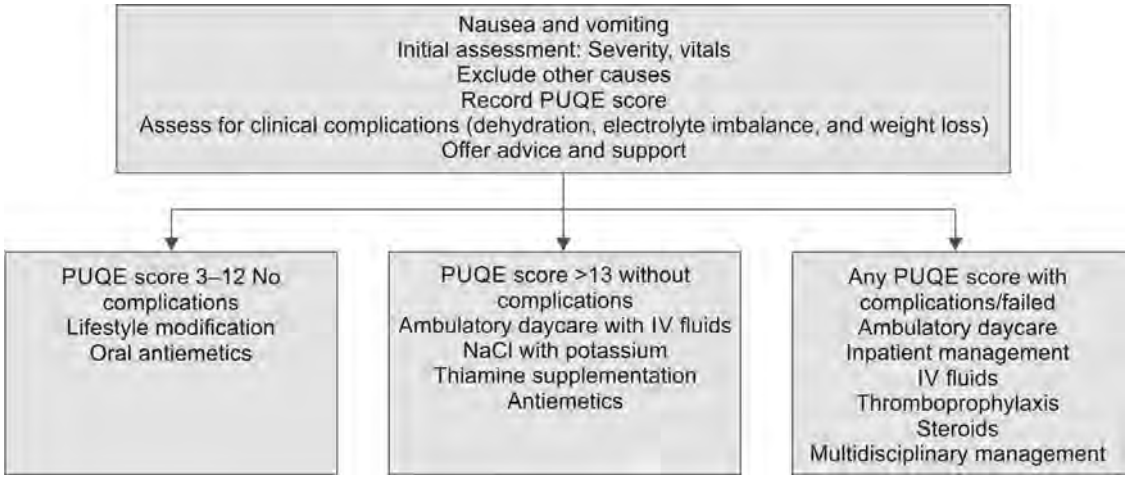
Metoclopramide should be used with caution due to possibility of extrapyramidal symptoms. Ondansetron has limited data on safety but is highly effective and used as second-line management. Corticosteroids are used only in resistant cases.

TABLE 4: Antiemetics recommended for use in pregnancy.	
First line	• Cyclizine 50 mg PO, IM or IV 8 hourly • Prochlorperazine 5–10 mg 6–8 hourly PO; 12.5 mg 8 hourly IM/IV; 25 mg PR daily Promethazine 12.5–25 mg 4–8 hourly PO, IM, IV or PR • Chlorpromazine 10–25 mg 4–6 hourly PO, IV or IM; or 50–100 mg 6–8 hourly PR
Second line	• Metoclopramide 5–10 mg 8 hourly PO, IV or IM (maximum 5 days duration) • Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR • Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV
Third line	Corticosteroids: Hydrocortisone 100 mg twice daily IV; once clinical improvement occurs, convert to prednisolone 40–50 mg daily PO, dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached

(IM: intramuscular; IV: intravenous; PO: by mouth; PR: by rectum)

For the cases needing inpatient management, initial assessment should include airway, breathing, circulation, disability, and exposure (ABCDE) and fluid resuscitation should be guided by degree of shock. Initial resuscitation should be done with crystalloids containing sodium and chloride with supplementation of potassium. Dextrose infusion to be avoided unless sodium has been replenished and thiamine as it can precipitate Wernicke's encephalopathy. Maintenance fluid therapy should be guided by vital monitoring, use of fluid balance charts, daily weight measurement, daily blood counts, urea, creatinine, and electrolytes. Proton pump inhibitors or H_2 antagonists may be added to relieve gastritis or esophagitis. Intravenous antiemetics can be gradually replaced with oral medication once fluid therapy is weaned off. Thromboprophylaxis with low-molecular weight heparin is indicated in admitted patients unless contraindicated. Multidisciplinary team management with nutritionist, endocrinologist, and gastroenterologist should be used when enteral or parenteral treatment is required.

As a last resort, in patients not responding to any treatment modality and with remitting severe symptoms, termination of pregnancy may be considered. Women on discharge from the hospital should have individualized treatment plans. Women who continue to have NVP in second and third trimesters of pregnancy need to be monitored for adequate fetal growth. Iron preparations need to be used cautiously as these can exacerbate symptoms. **Flowchart 1** summarizes the approach to NVP.



(IV: intravenous; PUQE: Pregnancy Unique Quantification of Emesis)

FLOWCHART 1: Approach to nausea and vomiting in pregnancy.

SPONTANEOUS ABORTION

The National Center for Health Statistics, the Centers for Disease Control and Prevention (CDC), and the WHO all define abortion as any termination of pregnancy, spontaneous (which occurs without any means) or induced (termination of pregnancy using medication or surgical procedures), prior to 20 weeks of gestation or with a fetus born weighing <500 g. Nearly 10–20% of all clinical pregnancies end in miscarriages. More than 80% of losses occur before 13 weeks of pregnancy called as early pregnancy loss.

Pathophysiology

In early pregnancy loss, death of the embryo or fetus occurs first along with hemorrhage into the fetal membranes leading to tissue necrosis and subsequent expulsion of the conceptus. Since chromosomal abnormalities are the most common cause, the products of conception may not have any identifiable embryonic elements and termed anembryonic pregnancy, accounting for nearly half of early pregnancy losses. Embryonic pregnancy, on the other hand, may have an abnormality of the embryo or fetus or placenta due to chromosomal anomalies or even be normal. In later losses, the fetus may be expelled live and may die only after birth.

Classification

An abortion is said to be "early" when it occurs prior to 12 weeks and "late" after 12 weeks. Spontaneous abortion may be classified as (1) threatened, (2) inevitable, (3) incomplete, (4) complete, (5) missed, and (6) septic depending on the clinical presentation. These may occur as isolated event or recurrent losses.

Risk Factors

Many risk factors have been identified which can lead to abortions; however, in most cases there may be no definite cause or even a combination of factors (**Table 5**).

Evaluation

Clinical Features

Clinical features differ depending upon the type of abortion. Period of amenorrhea followed by pain abdomen, vaginal bleeding, or passage of product of conceptus are the most common signs and symptoms seen in early pregnancy loss. The various types of abortions may be differentiated on the basis of clinical presentation, examination findings complemented by ultrasonographic findings.

Threatened Abortion

When the process of miscarriage has started but continuation of pregnancy is still possible. Bleeding occurs through a closed cervical os during the first 20 weeks of pregnancy and may persist for days to weeks. There may be accompanying lower abdominal discomfort, cramps, pain, pressure, or lower backache. If the bleeding tends to be heavy, it may eventually progress to pregnancy loss. For those whose bleeding resolves and pregnancy continues, there is persists an increased tendency for development of obstetric complications such as placenta previa, placental abruption, fetal growth restriction, preterm birth, preterm rupture of membranes, and increased operative deliveries.

Inevitable Abortion

It is a clinical type of miscarriage where the abortion process has progressed to a state where from continuation of pregnancy is impossible. In some cases, there is bleeding under the chorion (subchorionic hematoma) with separation of membranes stimulating uterine contractions. In early second trimester, pregnancies are complicated by rupture of membranes prior to achieving the period of viability and tend to progress to expulsion due to onset of uterine contractions. When this process has reached a stage where pregnancy cannot be salvaged, abortion is said to be inevitable. Sometimes products of conception may be seen to come out through the external os. Resuscitation of the patient is to be done and evacuation of the

TABLE 5: Causes of spontaneous abortion.	
Fetal factors	
Genetic causes	• 95% maternal and 5% paternal gametogenesis errors • Aneuploidy—trisomy (trisomy 13, 16, 18, 21, and 22) 64%, monosomy (XO or autosomal monosomy) 7% • Polyploidy (9%)—triploidy, tetraploidy, structural rearrangements (6%)
Maternal factors	
Age	Risk increases with advancing maternal age
Race	More common in Hispanics and Blacks
Habits	Smoking, alcohol consumption, and excessive caffeine uses
Infections	*Chlamydia*, bacterial vaginosis, and genital tuberculosis
Endocrine causes	Uncontrolled thyroid dysfunction (hypo/hyperthyroidism), uncontrolled diabetes mellitus, luteal phase defect, polycystic ovarian syndrome, systemic lupus erythematosus, and obesity
Anatomical causes	• Uterine anomalies: Septum, synechiae, leiomyoma/fibroids • Cervical incompetence
Thrombophilia	Inherited or acquired
Radiation exposure	Therapeutic as in malignancy
Toxins	Antineoplastic drugs, misoprostol, quinine, occupational exposure to sterilizing agents, and nitrous oxide
Idiopathic	

uterus with surgical or medical (oxytocin infusion) methods may be needed for management.

Incomplete Abortion

During abortion, the fetus and placenta may be expelled together in early pregnancy but tend to deliver separately in advanced gestations. The fetus may deliver first and the placental tissue may be retained in the uterus or only partially expelled leading to incomplete abortion. This may present as continued bleeding after passage of products or development of infection. On internal examination the cervical os remains open. It may be diagnosed clinically and ultrasound confirms the diagnosis with retained products in the uterine cavity.

Complete Abortion

There is history of bleeding per vagina, cramps, and passage of tissue followed by closure of the cervical os. This is accompanied by relief of symptoms of pain and bleeding. The entire conceptus may be expelled completely. On ultrasonography, the uterine cavity is empty.

Missed Abortion

The fetus is dead and retained in the uterine cavity and the cervical os is closed in cases of missed abortion. The diagnosis is confirmed by ultrasound or histopathology of products of conception. Those occurring at <10 weeks are termed "embryonic demise" and between 10 and 12 weeks as "early fetal demise". There may be no symptoms at all or slight bleeding/blood stained or brownish discharge per vaginally. When retained for a prolonged period, the size of uterus may be smaller than the period of gestation. Symptoms of pregnancy experienced by the pregnant woman usually subside. The diagnosis is confirmed on ultrasonography.

Septic Abortion

Septic abortion is the entity when any of the abortions, whether spontaneous or induced, are complicated by infection.

Red Flags

Presence of any of the following may warrant further evaluation for an alternate diagnosis like ectopic pregnancy or intensive management for development of sepsis and its complications.

- Giddiness with syncopal attacks
- Severe abdominal pain
- Fever with chills
- Persistent/intermittent heavy bleeding
- Purulent/foul-smelling vaginal discharge

Investigations

Blood investigations for complete blood counts, ABO, and Rh grouping should be done. All routine antenatal investigations should be done. Should ultrasonography be needed, transvaginal scan is preferred (**Box 2**). Serial serum β-hCG should be done where there is a doubt of pregnancy viability or the uterine cavity is empty even with a positive urine pregnancy test, giving rise to pregnancy of unknown location and ruling out ectopic pregnancy.

Treatment

General Measures

A detailed history and physical examination are important to make a diagnosis. Vitals should be monitored and blood loss estimated. Resuscitaion is started with intravenous fluid

BOX 2: Ultrasound features of pregnancy loss.

- Mean sac diameter (MSD) ≥25 mm and no embryo visible
- Crown rump length (CRL) ≥7 mm and no heartbeat visible
- No embryo with heartbeat visible ≥2 weeks after initial scan with gestational sac without a yolk sac
- No embryo with heartbeat visible ≥11 days after initial scan with gestational sac with a yolk sac

as required. Blood transfusion may be needed if the bleeding has been profuse or lead to exsanguination of the woman with fall in blood pressure and tachycardia. For anticipated procedure intravenous antibiotics may be given to reduce the postoperative infections. Informed consent should be taken. Depending upon the state of abortion and type of abortion, various treatment options can be implemented.

Expectant Management

Many women expel the conceptus spontaneously and no further treatment may be required.

Threatened abortion is managed expectantly along with bed rest, progesterone/hCG support, and correction of anemia along with watchful expectancy.

Inevitable abortion may be managed expectantly till some complication like heavy bleeding arises necessitating prompt uterine evacuation.

Some cases of incomplete abortion can also be managed expectantly, however, along with higher failure rates there is also an increased chance of development of sepsis.

In complete abortion, when there is definite history of passage of products of conception, an ultrasound finding of thin endometrial lining with empty uterine cavity confirms the diagnosis when there was a viable pregnancy earlier. The symptoms of pain and bleeding tend to subside.

Missed abortion can be managed expectantly but failure rates may be as high as 50% necessiating uterine evacuation.

Medical Management

Misoprostol (prostaglandin E1) is the drug used commonly to induce expulsion of products of conception.

Some cases of incomplete abortion may be managed with oral misoprostol dose of 600 μg. Alternatively, an 800 μg vaginal or a 400 μg oral or sublingual misoprostol dose may be used.

Missed abortion may be managed medically with a single 800 μg dose vaginally and few may need repeat doses to accomplish the process.

Medical therapy with misoprostol has failure rates of 15–40%.

Surgical Management

It is done in women opting for surgical management or those with failed conservative/medical management. In incomplete abortion, dilatation and curettage may be required to control the bleeding and evacuate the uterine cavity. In case of missed abortion, suction curettage is required. For any procedure, informed consent is must including the possibility of complications. Surgical management results in a quick resolution of symptoms with 95–100% success rate.

Complications of Surgical Management

- *Infection*: If products of conception are retained and the woman presents with symptoms of uterine infection, repeat uterine evacuation may be needed with broad-spectrum antibiotics.
- *Hemorrhage*: Severe bleeding may result from the abortion itself or trauma during the procedure and may require transfusion.
- *Uterine perforation:* Around 1–4 in1,000 cases may be complicated by uterine perforation. Once a perforation is suspected, as a give way feel during procedure, it is wise to abandon the procedure and keep the patient under monitoring. Rarely, laparotomy may be needed to manage hemorrhage in patients with deteriorating condition.
- *Cervical trauma*: Forceful dilatation of the cervix causes damage to the external os in 1 in 100 women leading to cervical incompetence in future pregnancies.
- Menstrual disturbances
- Chronic pelvic inflammation
- *Uterine synechiae* leading to secondary amenorrhea

Women must be informed that any of these complications can occur during surgery. Further treatment in the form of blood transfusion, laparoscopy or laparotomy may be required.

Postabortion Care

Women are counseled regarding pain and bleeding which may persist for a few days. Contraceptive choices are offered. Women are also informed of warning signs and when they need to come back for evaluation.

SEPTIC ABORTION

Septic abortion is any abortion, spontaneous or induced, which is complicated by infection. Unsafe abortions, which usually culminate as septic abortions, are defined by WHO as a procedure for terminating an unintended pregnancy carried out either by persons lacking the necessary skills or in an environment that does not conform to minimal medical standards or both. These include lack of preabortion counseling or advice, involves an unskilled provider, carried out in unhygienic conditions, or by a service provider with inadequate health facilities; abortion is provoked by insertion of objects into the uterus by the woman herself or by unskilled provider, or by other methods. A medical abortion prescribed incorrectly or medication issued by a pharmacist with no or inadequate instructions and no follow-up or an abortion self-induced by ingestion of traditional medication or hazardous substances are also unsafe and can have devastating outcomes. The situation is further worsened by lack of immediate intervention if severe bleeding or other emergency develops during the procedure, failure to provide postabortion checkup and care including no contraceptive counseling to prevent repeat abortions, legal restrictions involved, and sociocultural beliefs linked to abortions. Unsafe abortions contribute significantly to maternal mortality and more than half of abortions in developing countries are unsafe.

Causes

Infections are polymicrobial and the organisms involved in pathogenesis are usually part of the normal vaginal flora. *Peptostreptococcus anaerobius* is the most common blood isolate from cases of septic abortion. Toxin-producing organisms such as *Clostridium perfringens*, group A *Streptococcus* and some strains of *Escherichia coli* proliferate rapidly within dead tissue rendering antibiotic therapy ineffective. *Staphylococcus aureus* is another organism involved in pathogenesis.

Neisseria gonorrhea and *Chlamydia trachomatis* both of which are causative pathogens of pelvic inflammatory disease are also risk factors for septic abortion.

Pathophysiology

Septic abortions, whether induced or spontaneous, occur because of improper, unsafe, or inadequate removal of products of conception. These are usually ascending infections with bacterial infiltration of the uterine contents enabling the infection to invade the myometrium and then cause parametritis, oophoritis and salpingitis, peritonitis, and eventually septicemia. The longer the duration the products are retained, the more chances of developing infections. Duration of pregnancy also correlates with infective morbidity and mortality, both increasing with the gestational age.

Risk Factors

Certain risk factors increase the chances of developing sepsis following an abortion.

- Unsafe abortion
- Sexually transmitted infections such as *Chlamydia*
- Intrauterine device (IUD) insertion
- Tissue from the fetus or placenta retained in the uterus after a miscarriage or elective abortion procedure
- Insertion of foreign body or chemical irritants into the uterus

Clinical Presentation

Typically appear within 24–48 hours following abortion. These include chills, high grade fever, vomiting, malaise, abdominal pain, and foul-smelling vaginal discharge. In some, there may be hemorrhage due to injury to cervix or uterus, undiagnosed cervical pregnancy, uterine atony in advanced gestation, or coagulopathy.

Red Flags

Perforation of the uterus during the abortion typically causes severe abdominal pain and hemorrhage. More concerning are visceral injuries like bowel or bladder injuries which may need urgent laparotomy due to associated hemorrhage. Presence of peritonitis may occur due to spread of infection and present as septic shock.

Evaluation

History

There is history of abortion (medical or surgical) usually carried out by an untrained person or involving use of medicines or substances that have been inserted in the uterus to bring about the abortion. The symptoms arise a few days after use of the abortifacient/surgical procedure. There may be history of other risk factors, chronic diseases, or immunocompromised state. The symptoms may be insidious but progress rapidly as sepsis develops.

Physical Examination

On general examination, the woman has a toxic look with tachycardia, fever, and tachypnoea. If the woman is in shock, hypotension with hypothermia may present. There may be pallor, icterus, ecchymotic patches, anuria, dehydration and altered sensorium.

On abdominal examination, there may be tenderness, and guarding in peritonitis due to visceral injury, or palpable abdominal mass in hematometra (blood accumulation in uterus).

On vaginal speculum examination, there may be evidence of cervical trauma, purulent vaginal discharge, bleeding, or the products of conception may be visible at the cervical os.

On vaginal bimanual examination, there is cervical motion tenderness, uterine and adnexal tenderness, presence of tender adnexal mass suggestive of hematoma. Rectal examination may reveal bogginess due to collection or tenderness and blood staining in cases with bowel injury.

Interpretation of Findings

Pallor and hypotension indicate hemorrhage which may be ongoing. Hyperthermia and tachycardia may present with infection. With onset of sepsis, there is hypothermia and hypotension. Multiorgan involvement may present as renal involvement with anuria or liver involvement with hemolysis. Disseminated intravascular coagulopathy may present with thrombocytopenia and ecchymosis.

Visceral injuries present with tenderness and guarding due to associated peritonitis. Bowel injury due to instrumentation may present as abdominal pain, distension, obstipation, or bloody stools. Injury to urinary bladder may present with suprapubic pain, urinary retention, hematuria, and distension. Hepatic failure and jaundice may ensue due to disseminated intravascular coagulation (DIC) or gangrene. Peritonitis may occur due to spread of infection and present as septic shock with hypothermia, hypotension, oliguria, respiratory distress, or necrotizing infections.

Grading

Based on the extent of spread of infection, septic abortion is graded as follows:

- Grade-I: Infection localized to the uterus
- Grade-II: Infection spreading beyond uterus to pelvic organs and parametrium without signs of generalized sepsis
- Grade-III: Infection spreading beyond pelvis, patients have septicemia with clinical features of fever, hypothermia, tachycardia, tachypnea, and inadequate organ perfusion
- Grade-IV: Patients with septic shock and systolic blood pressure <90 mm Hg.

Investigations

Routine investigations and some specific tests are required to manage cases of septic abortion (**Table 6**). It is important to evaluate for multiorgan dysfunction and development of other complications such as DIC and sepsis.

Laboratory tests may show leukocytosis, thrombocytopenia, hemoconcentration, and intravascular hemolysis (**Table 6**).

Treatment

History and physical examination are crucial for diagnosing septic abortion. Besides routine blood investigations, aerobic and anaerobic blood and vaginal discharge cultures should be obtained to help guide therapy. Ultrasound should also be obtained to look for products of conception in the uterine cavity. In the critical patient, studies looking for DIC are warranted.

TABLE 6: Investigations for septic abortion.	
Routine investigations	
Full blood counts	Serology for HIV, HBsAg, and syphilis
Blood grouping and Rh typing	High vaginal swab culture sensitivity
Renal function test and serum electrolyte	Coagulation profile
Liver function test	Blood culture and sensitivity
Urine microscopy and culture	Blood sugar levels
Ultrasound of abdomen for retained products in uterus, adnexal masses, or free fluid in pelvis	X-ray erect abdomen for gas under diaphragm or multiple air fluid levels in bowel
Special investigations	
Serum lactate—measured within 6 hours of suspected sepsis; ≥4 mmol/L suggests tissue hypoperfusion	
C-reactive protein	
Computed tomography of abdomen and pelvis when ultrasound in inconclusive	
Histopathology and culture sensitivity of products of conception after evacuation	
β-hCG where there is doubt of mismanaged ectopic pregnancy	

(β-hCG: β-human chorionic gonadotropin; HBsAg: hepatitis B surface antigen; HIV: human immunodeficiency virus)

Like other forms of sepsis, resuscitation with intravenous fluids and antibiotics are the mainstay of treatment. Foley catheterization and oxygen support should be given. Vasopressors and blood transfusions are used as needed. The antibiotic regimen selected should cover all potential aerobic and anaerobic pathogens.

Most importantly, prompt evacuation of the infected products is required. This is considered the most critical step in the treatment of septic abortion. Fetal death is inevitable, so procedural intervention should not be withheld even if fetal heart activity is found.

Clinical improvement after fluids, antibiotics, and curettage should be seen within 6 hours. If there is insufficient clinical improvement after such treatment, then a hysterectomy may be necessary. Finally, anti-D immunoglobulin should be administered to all Rh-negative women.

Grade I

Antibiotics should be given as early as possible. Prophylactically antitetanus serum may be given.

Evacuation of the Uterus

As abortion is often incomplete, gentle evacuation should be performed within 24 hours following antibiotic therapy. Early emptying of the uterus not only minimizes the risk of hemorrhage but also removes the nidus of infection. Sedatives and analgesics should be given wherever necessary.

Grade II

Antimicrobial Therapy

A combination of either piperacillin-tazobactam or carbapenem plus clindamycin (IV) gives broadest range of microbial coverage. Empirical therapy is started initially and later changed once culture sensitivity report is available. Other antibiotics such as clindamycin, gentamicin, and metronidazole can also be used as per the clinical scenario.

Surgery

(1) Evacuation of the uterus—Evacuation should be withheld for at least 48 hours when the infection is controlled and is localized, the only exception being excessive bleeding. (2) Posterior colpotomy—When the infection is localized in the pouch of Douglas, pelvic abscess is formed as evidenced by spiky rise of temperature, rectal tenesmus (frequent loose stool mixed with mucus), and boggy mass felt through the posterior fornix. Posterior colpotomy and drainage of the pus relieves the symptoms and improve the general outlook of the patient. (3) Laparotomy—Indicated when uterine perforation, intestinal injury, presence of foreign body, or generalized peritonitis is suspected. Hysterectomy with or without unilateral or bilateral salpingo-oophorectomy may be performed depending upon the pathology. Drainage of pus along with a thorough peritoneal lavage with povidone iodine may be required. Entire bowel length should be examined for any trauma and managed as necessary.

Grade III

Clinical monitoring is to be conducted similar to the management protocols in Grade II. Supportive therapy is directed to treat generalized peritonitis by gastric suction and intravenous crystalloids infusion. Endotoxic shock or renal failure to be managed, if present. Features of organ dysfunction should be carefully guarded against. Patient may need intensive care unit management.

Grade IV

Along with the management protocols of Grade III septic abortion, the patient may even require intensive care, ionotropic or ventilatory support, and other supportive measures like blood transfusion or dialysis which is to be assessed as per the clinical situation.

Complications

Immediate

- *Complications of anesthesia during surgical evacuation*: General anesthesia: Uterine atony leading to severe hemorrhage; local anesthesia: Paracervical block causing accidental intravascular injection of anesthetic agents leading to seizure, cardiopulmonary arrest, and death
- *Neurogenic shock*: Vasovagal syncope produced by stimulation of the cervical canal during dilatation
- *Hemorrhage*: Due to uterine atony in advanced gestational age, cervical laceration, uterine perforation, undiagnosed cervical pregnancy, and coagulopathy
- Acute renal failure

- Pelvic thrombophlebitis
- *Perforation and peritonitis*: Uterine, bladder, and bowel perforation during suction evacuation or dilation of cervix
- Disseminated intravascular coagulation
- Damage to the genital tract and internal organs by the insertion of dangerous objects such as sticks, knitting needles, or broken glass into the vagina or anus.

Sequelae

Septicemia and its associated multiorgan involvement, hepatic failure, paralytic ileus, DIC, and death. Risk of death following complications of unsafe abortions is several hundred times higher.

Remote

- Chronic pelvic pain
- Dyspareunia
- Secondary infertility
- Depression and other psychiatric problems
- Rarely enterovaginal fistula

Prevention and Control

Unsafe abortion can be prevented through:

- Comprehensive sexuality education
- Prevention of unintended pregnancy through use of effective contraception, including emergency contraception
- Provision of safe and legal abortion services
- Maintaining asepsis wherever possible
- Prompt and timely diagnosis and treatment of sepsis

HYPERTENSION IN PREGNANCY

Hypertensive disorders complicate 5–10% of pregnancies and contribute significantly to maternal and perinatal morbidity and mortality worldwide. Not only do these disorders effect pregnancy, they have an important role in long-term disabilities such as cardiovascular and metabolic abnormalities. For the purpose of defining hypertension in pregnancy, the American College of Obstetrics and Gynecology (ACOG) defined criteria of systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg is used. Blood pressure should be repeated to confirm the diagnosis, within 15 minutes if systolic blood pressure ≥160 mm Hg and diastolic blood pressure ≥110 mm Hg or over a few hours if lower. According to the International Society for Study of Hypertension in Pregnancy, hypertensive disorders in pregnancy are classified as follows:

- Chronic hypertension (of any etiology)
- Gestational hypertension—definitive evidence for the preeclampsia syndrome does not develop and hypertension resolves by 12 weeks postpartum
- Preeclampsia superimposed on chronic hypertension
- Preeclampsia and eclampsia syndrome

Of these, chronic hypertension either predates pregnancy or is diagnosed before 20 weeks of gestation whereas gestational hypertension and preeclampsia syndromes develop after 20 weeks of pregnancy.

Chronic Hypertension

Chronic hypertension refers blood pressure ≥140/90 mm Hg either preceding pregnancy or recognized <20 weeks in pregnancy and complicates about 3% of pregnancies. It is usually diagnosed at first visits in early months of pregnancy and since most of the women would not have prepregnancy blood pressure recordings, this reading is used to label the woman as a chronic hypertensive. Those women with persistently high blood pressure ≥140/90 mm Hg after 12 weeks postpartum are also labeled as chronic hypertension, as some women may be missed in pregnancy due to physiological lowering of blood pressure in second trimester when they present late to the clinician for the first time. Women with essential hypertension are usually elderly or overweight with a family history. Few have secondary hypertension with causes usually identifiable before conception. There is increased risk of developing superimposed preeclampsia.

Recently, the American Heart Association and American College of Cardiology have lowered the threshold for normal blood pressure levels to 130/80 mm Hg. Although not used by ACOG for defining pregnancy hypertension at present, there will be in the future, a rise in number women with prepregnancy chronic hypertension.

Chronic hypertension per se results in high morbidity and mortality and increases substantively the risk of cardiovascular disease, coronary heart disease, congestive heart failure, stroke, renal failure, and peripheral arterial disease (**Table 7**).

Etiology/Causes

Chronic hypertension may be primary or secondary. Primary hypertension is idiopathic in origin. Causes of secondary hypertension may be:

- Renal artery stenosis
- Renal parenchymal disease
- Primary aldosteronism

TABLE 7: Complications of chronic hypertension on pregnancy.

Maternal complications	***Fetal complications***
Heart failure	Growth restriction
Hypertensive cardiomyopathy	Preterm birth (spontaneous/ iatrogenic)
Myocardial infarction	Intrauterine fetal demise
Stroke	Neonatal morbidity
Pulmonary edema	Perinatal mortality
Acute kidney injury	Anomalies if exposed to fetotoxic drugs
Placental abruption	
Superimposed preeclampsia and HELLP syndrome	
Development of severe hypertension	
Maternal death	

- Pheochromocytoma
- Cushing's syndrome
- Hypothyroidism/Hyperthyroidism
- Coarctation of the aorta
- Obstructive sleep apnea
- Medication

Pathophysiology

As in normal pregnancies, blood pressure drops in most women with chronic hypertension in early pregnancy and rises again in third trimester. This is noted by reduction of antihypertensive medication needed for control. Women with chronic hypertension are noted to have persistently elevated vascular resistance and reduced intravascular volume expansion. The presentation is further complicated by development of superimposed preeclampsia.

Clinical Presentation

Pregnant women present either with diagnosed essential hypertension or they are diagnosed at first presentation. Development of complications depends largely on the duration and severity of hypertension and whether superimposed preeclampsia develops. Blood pressures ≥160 mm Hg systolic or ≥110 mm Hg diastolic is associated with development of complications. Presence of proteinuria at baseline (≥1 + on dipstick or 30 mg/dL) is a risk factor for development of superimposed preeclampsia and other adversities. Superimposed preeclampsia is diagnosed by worsening hypertension, new-onset proteinuria, neurological symptoms such as severe headaches and visual disturbances, generalized edema, oliguria, and certainly, convulsions or pulmonary edema. Laboratory abnormalities are rising serum creatinine or hepatic transaminase levels, thrombocytopenia, or any of the facets of hemolysis, elevated liver enzyme levels, low platelet count (HELLP) syndrome. For women with chronic hypertension and superimposed preeclampsia with severe features, magnesium sulfate for maternal neuroprophylaxis is recommended.

Red Flags

Around 25% cases of chronic hypertension are complicated by superimposed preeclampsia. Diagnosis is made by worsening hypertension and accompanying new onset proteinuria. Preeclampsia is earlier in onset as compared to previously normotensive women.

Evaluation

History

Onset and duration of hypertension and used of antihypertensive medication (drug, dose, and duration) has to be elicited. In cases of secondary hypertension, history regarding other organ involvement and evaluation of function must be enquired. History regarding comorbidities such as diabetes, thyroid disorders, systemic lupus erythematosus, and thrombophilia are important as the treatment may need modification. Family history of hypertension should be elicited.

Physical examination

Thorough physical examination with accurate blood pressure measurement. Systemic examination should be done to rule out end-organ involvement. Obstetric examination is important to assess fetal growth and development.

Interpretation of Findings

Once the diagnosis is accurately established, systemic examination findings will help in evaluation of organ involvement. History of headache and blurring may indicate severe hypertension. Pulmonary edema presents with fine basal crepitations. Ejection systolic murmurs or added heart sounds may be present too. Renal involvement may present with edema due to hypoproteinemia. Growth restriction of fetus may present as size of uterus smaller than the growth expected at that gestation.

Investigations

In addition to routine antenatal investigations, tests for evaluation of end-organ functioning and prediction of complications are recommended (**Table 8**). Obstetric ultrasound should be done to assess the growth and to rule out embryopathies due to fetotoxic medications.

Treatment

All women with chronic hypertension taking angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be counseled regarding possible teratogenicity (renal failure, oligohydramnios, growth restriction, fetal demise, and skull and limb deformities) of these drugs and be switched to other drugs which are safe in pregnancy. Beta-blockers are not recommended as they are associated with fetal growth restriction when used in latter half of pregnancy. Diuretics too are not recommended for use in pregnancy due to limited data available for safety. Recommended antihypertensive drugs are summarized in **Table 9**.

Women diagnosed first time in pregnancy should have baseline investigations and blood pressure monitoring. They should be advised regarding weight gain, exercise, healthy eating, and dietary salt restriction. Those on medication, if

TABLE 8: Investigations recommended for hypertension in pregnancy.

Test	*Indication*
Full blood counts	Hemoglobin and platelet count
Liver function test	Liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH)] and functions tests [international normalized ratio (INR), serum bilirubin, and serum albumin]
Renal function test	Serum creatinine, electrolytes, and uric acid
Urinalysis and microscopy	Proteinuria (protein: creatinine ratio or albumin: creatinine ratio)
Fundoscopy	Hypertensive retinal changes
Echocardiogram/ echocardiogram	Left ventricular function and cardiomyopathy
Renal ultrasound	When serum creatinine or any of the urine testing are abnormal

TABLE 9: Antihypertensives used in pregnancy.

Drug	*Dosage*	*Comments*
Labetalol α1 and nonselective β-blocker	• 200–2,400 mg/day in 2–4 divided doses • Initial dose usually 100 mg twice daily and increased as needed	• Usually well tolerated • Contraindicated in asthma and congestive heart failure
Nifedipine Calcium channel blocker	20–120 mg/day in divided doses (sustained release preparations)	Tachycardia and headache
Methyldopa Centrally acting α2 agonist	500–2,000 mg/day in 2–4 divided doses	Used when there is intolerance to both labetalol and nifedipine

safe in pregnancy can continue the same. For women not on treatment, start medication if systolic blood pressure is ≥140 or diastolic ≥90 mm Hg. Target blood pressure should be 135/85 mm Hg. It may be helpful to admit to investigate and monitor the blood pressure over 48 hours to rule out other severe conditions.

Labetalol is preferred drug for treatment of hypertension. Nifedipine is used where labetalol is not suitable and methyldopa if both labetalol and nifedipine cannot be used. Low dose aspirin 75–150 mg should be offered once daily from 12 weeks, preferably before 16 weeks. Initial dose of labetalol used is 100 mg twice or thrice a day with titration as needed.

Women with poorly controlled hypertension need follow-up every week for antihypertensive dose adjustment. Those with controlled blood pressure may follow up 2–4 weekly or as deemed necessary.

Delivery should be planned after 37 weeks and before 39 weeks in women with blood pressure <160/110 mm Hg with/without treatment. Corticosteroids for lung maturation may be given for planned births. Trial of vaginal birth should be given. Severe hypertension may be treated with intravenous labetalol or hydralazine and magnesium sulfate should be used for seizure prophylaxis. Those with complications may need earlier delivery after consultation with senior obstetrician and neonatologist.

In the postpartum period, these women are prone to develop pulmonary edema as vascular resistance rises and fluid is mobilized into circulation. Prompt management with diuretics along with blood pressure control should be instituted.

Oral hypertensives can be restarted with the aim to keep blood pressure <140/90 mm Hg and on discharge from the facility, review with physician can be done at 2 weeks and 6 weeks postpartum. Diagnosis is confirmed at 12 weeks when blood pressure remains elevated.

Gestational Hypertension

Gestational hypertension is persistent hypertension >140/90 mm Hg in a previously normotensive woman at or after 20 weeks of gestation, in the absence of features of preeclampsia. Final diagnosis is however made at 12 weeks postpartum when blood pressure has normalized. Around 25% cases go on to develop preeclampsia, more so in women diagnosed early. As in chronic hypertension, gestational hypertension is also a risk factor for future cardiovascular disease.

TABLE 10: Risk factors for gestational hypertension.

Age ≥40 years	*Nulliparity*
Family history of preeclampsia	Interpregnancy interval >10 years
Body mass index (BMI) ≥35 kg/m^2	Multiple pregnancy
Preexisting vascular disease	Previous history of gestational hypertension
Preexisting kidney disease	Previous history of preeclampsia

Etiology/Causes

As for other pregnancy-induced hypertensive disorders, there is no definite etiology for gestational hypertensive. Prevalence is more in women with risk factors (**Table 10**).

Clinical Presentation

Pregnant women presents after 20 weeks of gestation with blood pressure >140/90 mm Hg without proteinuria. The diagnosis is confirmed by repeat blood pressure reading after a few hours. If the blood pressure remains >140/90 mm Hg but <160/110 mm Hg, antihypertensive treatment is started to achieve a target blood pressure of 135/85 mm Hg. Laboratory investigations should be done to rule out hematological or biochemical features suggestive of preeclampsia. Blood pressure and proteinuria should be measured at least twice a week. Once blood pressure is controlled, the woman may follow-up every 2–4 weeks.

If there is severe hypertension, the pregnant woman is admitted and treatment instituted. Blood pressure is repeated every 15–30 minutes till it is <160/110 mm Hg. Daily blood pressure monitoring can be done during hospital stay. Once blood pressure is controlled and laboratory findings are normal, patient can be discharged with follow-up every 2 weeks.

Red Flags

Since these women are at an increased risk of development of preeclampsia, development of new onset proteinuria or abnormal laboratory findings may suggest development of the same. At every antenatal visit, home blood pressure recordings should be assessed along with evaluation for headache, blurring of vision, and epigastric pain which may indicate preeclampsia (**Table 11**).

TABLE 11: Differentiating features of preeclampsia and gestational hypertension.

Findings	*Preeclampsia*	*Gestational hypertension*
Onset	>20 weeks	>20 weeks
Proteinuria	Present	Absent
Thrombocytopenia (platelets $<10^5/mm^3$)	Present	Absent
Serum creatinine >1.1 mg/dL	Present	Absent
Liver transaminases twice of normal	Present	Absent
Headache	Present	Absent
Visual disturbance	Present	Absent

Evaluation

History

Assessment regarding risk factors such as family history and hypertension in previous pregnancy should be done. History of any medical comorbidity such as diabetes and vascular diseases should be elicited.

Physical examination

Thorough systemic examination should be done to rule out any end-organ involvement and also to rule out preeclampsia.

Interpretation of Findings

Raised blood pressure may be the only finding in most cases. With severe hypertension or development of preeclampsia, findings suggestive of end-organ damage such as pulmonary edema, proteinuria, and abnormal laboratory findings may be present.

Investigations

Other than routine antenatal investigations, investigations are done at baseline to evaluate disease severity and end-organ damage (**Table 12**). Obstetric examination and assessment of fetal well-being to be done at every antenatal visit and growth assessment by ultrasound at 2–4 weekly.

Treatment

Labetalol is the drug of choice started in twice or thrice a day dosage and titrated as needed. In presence of contraindication, nifedipine or methyldopa may be used. Home blood pressure records should be maintained and warning signs explained. Follow-up every 2 weeks with records is adequate if blood pressure is controlled. Termination can be done after 37 weeks of gestation.

In women presenting with severe hypertension, intravenous labetalol or hydralazine may be used. Once controlled, oral medication may be started. If blood pressure remains elevated or preeclampsia develops and termination is decided, corticosteroid for fetal lung maturation should be given and magnesium sulfate should be considered for neuroprotection. Mode of delivery can be decided according to the obstetric indication. Blood pressures should be controlled during labor. Postpartum period should be watched for development of pulmonary edema and managed.

TABLE 12: List of investigation for gestational hypertension.

Full blood counts	*Urinalysis and microscopy*
Liver transaminases	Lactate dehydrogenase
Prothrombin time	Serum creatinine
Urea and electrolytes	Fundus examination

In postpartum period, antihypertensive treatment may be continued as required. Start medication if >150/100 mm Hg in those not on medication. Medicine should be gradually tapered with physician review at 2 and 6–8 weeks.

Preeclampsia

The most dreaded of all hypertensive disorders in pregnancy, the preeclampsia syndrome, has an incidence of 2–5% though it contributes most to morbidity and mortality related to hypertension. On the global front, it is estimated over 70,000 women and 500,000 babies die each year due to its complications and the burden of near miss is nearly 100-fold. It is a pregnancy-specific disorder that affects every organ system in the body and is associated with cardiovascular complications in later life.

The diagnosis of preeclampsia is made by the presence of new onset hypertension >140/90 mm Hg after 20 weeks of gestation either with proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, and fetal growth restriction. Some cases may be diagnosed for the first time in intrapartum or early postpartum period.

Etiology/Causes

Numerous etiologies have been proposed, yet no definite cause has been established for development of preeclampsia. The most accepted theory is of placental implantation with abnormal trophoblastic invasion of uterine spiral arteries. Unlike in normal pregnancies where placental trophoblasts invade the decidua and extend into the walls of the spiral arteriole replacing the endothelium and muscular walls to create a large caliber low-resistance vessel, in preeclampsia, there is defective placental implantation characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts. This results in a small caliber vessel with high resistance to flow. Antiangiogenic factors have a role to play in this defective remodeling. With this, there is endothelial damage, intimal hyperplasia, and medial necrosis leading to atherosclerotic changes in placental vessel walls on microscopy. All these culminate in a systemic inflammatory response with clinical onset of hypertension and multiorgan involvement.

Another theory postulated is immune maladaptation of the mother to paternally derived antigens. This leads to graft-versus-host reaction with inflammation at uteroplacental interface. This is supported by incidence of preeclampsia being higher in first pregnancy when the woman is exposed to paternal antigens, and the severity of the disease being more in multiple pregnancy and molar pregnancy where the load of paternally derived antigens is higher.

Endothelial cell dysfunction resulting from release of placental factors due to placental ischemia is another proposed theory for preeclampsia. Antiangiogenic and metabolic factors

TABLE 13: Risk factors for preeclampsia.	
Age >35 years	Nulliparity
Body mass index (BMI) >30 kg/m^2	Multifetal pregnancy
Chronic hypertension	Prior preeclampsia
Diabetes mellitus	Prior abruption
Chronic kidney disease	Assisted reproduction
Systemic lupus erythematosus	Prior stillbirth
Antiphospholipid antibody syndrome	Male fetus

and other inflammatory leukocyte mediators [tumor necrosis factor α (TNFα) and interleukins] are thought to provoke systemic endothelial cell injury. There is formation of reactive oxygen species with toxic free radicals causing endothelial dysfunction leading to prostaglandin imbalance and finally ending in placental atherosclerosis with microvascular coagulation.

Genetic association of preeclampsia is well established and the disease has strong familial predisposition. Numerous genes have been studied for their association, the important ones being methylenetetrahydrofolate reductase, factor V Leiden, angiotensin-converting enzyme gene, various human leukocyte antigens, and many more. The syndrome is usually polygenetic origin with phenotypic expression dependent on environmental influences as well. Certain clinical risk factors if present have strong premonitory significance and need further evaluation (**Table 13**).

Pathophysiology

Abnormal trophoblast invasion in women who develop preeclampsia causes placental ischemia with release of certain antiangiogenic factors and substances which cause injury of systemic endothelial cells and activation which is central to pathogenesis of preeclampsia. This endothelial activation causes endothelial leakage and interferes with many intrinsic functions of the endothelium such as anticoagulation and release of nitric oxide. Activated endothelium releases substances that promote coagulation and reduced prostacyclin and nitric oxide increases sensitivity to vasopressors. Due to widespread arterial vasospasm, there is rise in blood pressure. Along with reduced blood flow and endothelial leak, there is progressive tissue ischemia and necrosis leading to end-organ damage with clinical features.

Endothelial dysfunction, vasospasm, and ischemia lead to the manifestation of pathophysiological changes in all organ systems beginning early in pregnancy which progress throughout pregnancy with multiorgan involvement.

In the cardiovascular system, there is ventricular hypertrophy with diastolic dysfunction as a result of increase in afterload due to hypertension which can be evaluated on echocardiography. Also, there is marked hemoconcentration due to limited volume expansion and endothelial activation which causes a fall in the cardiac preload. These women are extremely sensitive to volume of intravenous fluids transfused and can develop pulmonary edema compounded by these factors.

Overt thrombocytopenia (platelets <100,000/mm^3) and hemolysis result from endothelial disruption with platelet adherence and fibrin deposition (microangiopathic hemolysis). Hemolysis can be evaluated by elevated serum lactate dehydrogenase, reduced haptoglobin levels, increased bilirubin levels, and presence of schizocytes, spherocytes, and reticulocytosis in peripheral blood smear. Together with elevated liver transaminases these form part of the HELLP syndrome.

In the kidneys, there is reduced perfusion due to marked increase in resistance in the afferent glomerular arterioles and decreased filtration due to glomerular endotheliosis. As a result, there is elevated serum creatinine and uric acid. Acute tubular necrosis occurs frequently with coexisting placental abruption HELLP syndrome and postpartum hemorrhage.

Liver involvement ranges from mild periportal hemorrhage to hepatocellular necrosis to massive infarction and liver failure. There may be only mild elevation of aspartate transaminase or alanine transaminase in mild cases whereas levels up to 2,000 U/L have been reported in severe cases. Rarely, a subcapsular hematoma may form and rupture causing hemorrhage.

In the brain, there is cerebral edema due to hyperperfusion with endothelial damage, and, infarction due to vasospasm and ischemia. Rise in blood pressure exceeds the cerebrovascular autoregulatory capacity with forced vasoconstriction and vasodilatation which leads to capillary damage and causes edema. The occipital and parietal lobes are usually involved which is apparent on imaging as posterior reversible encephalopathy syndrome. Cerebral symptoms can present as confusion, lethargy, visual blurring, obtundation, coma, or seizures in eclampsia. Visual symptoms of blurring, diplopia, and scotoma result from either occipital lobe edema or retinal detachment or infarction.

Clinical Presentation

Pregnant woman presenting with blood pressure >140/90 mm Hg after 20 weeks of pregnancy accompanied by proteinuria or any systemic findings is diagnosed as preeclampsia. The blood pressures should be rechecked after a few hours to make a diagnosis. Proteinuria, once the sine qua non of preeclampsia, is now not considered pathognomonic of this condition. In absence of proteinuria, presence of any abnormal laboratory values suggestive of preeclampsia is included in the diagnosis (**Table 14**).

Preeclampsia is classified as nonsevere and severe depending on presence of severe hypertension, rapidly deteriorating laboratory parameters, or features of impending eclampsia (**Table 15**). However, this is now considered redundant as a seemingly "nonsevere" case may rapidly progress to a severe form of the disease.

Red Flags

Blood pressures systolic ≥160 mm Hg or diastolic ≥110 mm Hg or presence of any hematological or biochemical abnormalities are concerning. In presence of symptoms of impending eclampsia, one needs to be more vigilant and institute prompt treatment to prevent worsening of the maternal condition.

Evaluation

History

On presentation, it is important to ask regarding presence of any symptoms indicating features of severity. History of headache

TABLE 14: Criteria of diagnosing the preeclampsia.

Criteria	*Diagnosis of preeclampsia*	*Comments*
Blood pressure	• >140/90 mm Hg after 20 weeks • Confirm by repeat blood pressure measurement in a few hours	Previously normotensive woman
Proteinuria	≥300 mg/24 hours or urine protein: creatinine ratio ≥0.3 or dipstick 1 + persistent	Automated dipstick recommended, if not available visual dipstick used
Hematological complications	Thrombocytopenia—platelet count <150,000/mm^3, disseminated intravascular coagulation (DIC), and hemolysis	
Renal disease	Creatinine level >1.1 mg/dL or doubling of baseline	No history of previous renal disease
Liver involvement	Serum transaminases double of normal	With or without right upper quadrant or epigastric pain
Pulmonary edema		
Cerebral or visual symptoms	Headache or visual disturbances: Eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata	
Uteroplacental dysfunction	Fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth	

TABLE 15: Indicators of preeclampsia severity.

Systolic blood pressure	*≥160 mm Hg*
Diastolic blood pressure	≥110 mm Hg
Headache	New-onset headache
Visual disturbances	Present
Upper abdominal pain	Epigastric or right upper quadrant pain
Oliguria	<400 mL/24 h
Serum creatinine	>1.1 mg/dL
Serum transaminases	>70 IU/mL
Pulmonary edema	Present
Fetal growth restriction	Present

TABLE 16: Recommended investigations for preeclampsia.

Recommended investigations	*Importance*
Complete blood count	Anemia and thrombocytopenia
Urine proteins	Diagnosis/quantification of proteinuria
Renal function tests	Serum creatinine levels and uric acid levels
Liver function test	Serum transaminases and bilirubin level
Lactate dehydrogenase	Hemolysis for diagnosis of HELLP syndrome
Coagulation profile	With low platelet counts
Fundoscopy	Papilledema and other hypertensive changes
Obstetric ultrasound	Fetal well-being

(HELLP: hemolysis, elevated liver enzyme levels, and low platelet count)

not relieved by medication, visual disturbances, scotomas, flashes of light suggesting aura, blurring of vision, pain in epigastric or right upper quadrant, and recent weight gain need to be inquired. History of presence of risk factors, chronic or gestational hypertension, and use of antihypertensive medicines has to be asked. History of medical conditions such as diabetes, chronic kidney disease, thyroid disorders, lupus, and thrombophilia must be ruled out. One must also ask about family history of hypertension. Obstetric history regarding multiple fetuses, hydramnios or molar pregnancy should be elicited.

Physical examination

Thorough physical examination with measurement of blood pressure, pulse, respiratory rate, temperature, pallor, and edema to be evaluated. It is important to assess the level of consciousness and visual symptoms and evaluate any dyspnea which is out of proportion to that physiologically expected. Measure the weight and assess the weight gain since last visit. Systemic examination to assess for pulmonary edema, congestive cardiac failure such as tachypnoea, presence of basal crepitations, and raised jugular pressure should be assessed. Obstetric examination is done to assess the period of gestation and well-being.

Interpretation of Findings

Presence of any features of severity will label the condition as severe preeclampsia which is ominous.

Investigations

Investigations recommended in preeclampsia, apart from routine, help in establishment of diagnosis as well as classification of severity of the condition (**Table 16**).

Treatment

For women presenting with blood pressures 140/90–159/109 mm Hg, admit if there are any concerns for maternal or fetal well-being such as presence of clinical features

suggestive of severe disease. This will also give an opportunity to investigate and watch for disease progression. Detailed examination should be done with assessment for features of worsening. Daily weight measurement and proteinuria quantification to be done. Blood pressure to be monitored 4 hourly. Start antihypertensive medication to achieve blood pressure <135/85 mm Hg with frequent monitoring (**Table 17**). All relevant investigations must be done. Proteinuria should be reevaluated if new symptoms develop. Fetal assessment with cardiotocography, ultrasound, and Doppler to be done at the time of admission. Once blood pressure is controlled and blood tests are reassuring, the woman can be discharged if the pregnancy is remote from term and there are no immediate indications for delivery, with advice on home blood pressure monitoring and sensitization regarding warning symptoms. Follow-up can be done on fortnightly basis with good control.

Pregnancy can be allowed to progress till 37 weeks with mild preeclampsia with good blood pressure control on medication when delivery by induction or cesarean section for obstetric indication is done.

Women presenting with blood pressure >160/110 mm Hg or symptoms of headache, blurring of vision, epigastric pain, and need urgent admission. Blood pressure should be controlled with injectable labetalol, hydralazine, or oral nifedipine with monitoring every 15–30 minutes. If blood pressure falls <160/110 mm Hg, maintenance therapy with oral antihypertensives to be given with investigations repeated alternate day to assess disease progression. Fetal evaluation to be done once the condition of patient is stable to assess maturity and well-being. Corticosteroid coverage can be advised if <34 weeks of gestation to enhance fetal lung maturity, should it become necessary to terminate the pregnancy earlier. Decision to terminate the pregnancy should be taken only after discussion with the critical care team and neonatologist. If high blood pressure persists despite medication, there are features of impending eclampsia or laboratory reports are ominous, delivery is considered after stabilization of the mother. Magnesium sulfate should be considered for seizure prophylaxis (**Box 3**).

For those women whose blood pressure is controlled on more than one drug and laboratory reports do not indicate immediate need for intervention, pregnancy can be continued up to 34 weeks of gestation when delivery should be planned after corticosteroid cover (**Box 4**). Till the termination is planned, hospital visits should be weekly with blood pressure monitoring and assessment of fetal well-being with obstetric ultrasound and umbilical artery Doppler weekly. Approach to preeclampsia is summarized in **Flowchart 2**.

Eclampsia

Preeclampsia complicated by generalized tonic-clonic seizures is eclampsia and has poor implications for maternal and perinatal outcome. Usually preceded by severe preeclampsia,

BOX 3: Indications for magnesium sulfate prophylaxis in severe preeclampsia.

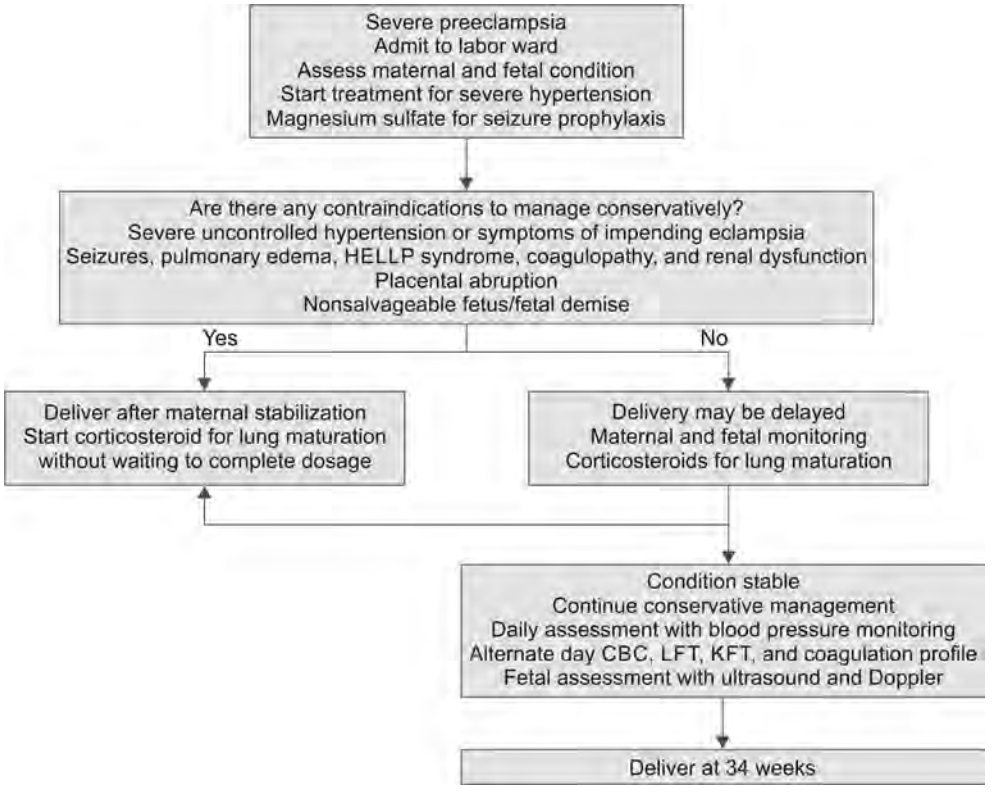
- Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg
- Proteinuria ≥2 + by dipstick in a catheterized urine specimen
- Serum creatinine >1.1 mg/dL
- Platelet count <100,000/mm^3
- Aspartate aminotransferase (AST) elevated two times above upper limit of normal range
- Persistent headache or visual symptoms (scotoma, blurring, and diplopia)
- Persistent epigastric or right-upper quadrant pain

BOX 4: Indications for termination of pregnancy <34 weeks in preeclampsia after maternal stabilization.

- Blood pressure uncontrolled despite using three antihypertensive drugs at optimal dosage
- Presence of pulmonary edema with oxygen saturation (SpO_2) <90%
- Progressive worsening of liver function, renal function, thrombocytopenia, or disseminated intravascular coagulation (DIC)
- Persistent neurological symptoms of headache, visual symptoms, or seizures
- Placental abruption
- Reversal of diastolic flow in umbilical artery on Doppler study, fetal heart rate abnormalities detected on cardiotocography or intrauterine demise

TABLE 17: Therapy for control of severe hypertension.

Drug	*Dosage*	*Side effects*
Hydralazine	• Dilute 20 mg hydralazine in 20 mL of water for injection • Initial 5 mg intravenous (IV) bolus dose, repeat 5 mg dose at 20 minutes. If blood pressure not controlled and third dose of 5 mg after another 20 minutes • Record blood pressure every 10 minutes • If still not controlled after three doses, start infusion at 5 mg/hour dose	Maternal hypotension and fetal distress
Labetalol	• Initial 10 mg dose, repeat at 10–15 minutes as 20 mg and then 40 mg to 80 mg, if no response. Maximum dose of 300 mg • Record blood pressure every 10 minutes	Contraindicated in asthma and congestive heart failure
Nifedipine	• Initial 10 mg immediate release dose, repeat 30–45 minutes with second 10 mg dose • Record blood pressure every 15 minutes • If severe hypertension persists, switch to injectable antihypertensive	Tachycardia and headache


Severe preeclampsia
Admit to labor ward
Assess maternal and fetal condition
Start treatment for severe hypertension
Magnesium sulfate for seizure prophylaxis
Are there any contraindications to manage conservatively?
Severe uncontrolled hypertension or symptoms of impending eclampsia
Seizures, pulmonary edema, HELLP syndrome, coagulopathy, and renal dysfunction
Placental abruption
Nonsalvageable fetus/fetal demise
Yes
No
Deliver after maternal stabilization
Start corticosteroid for lung maturation
without waiting to complete dosage
Delivery may be delayed
Maternal and fetal monitoring
Corticosteroids for lung maturation
Condition stable
Continue conservative management
Daily assessment with blood pressure monitoring
Alternate day CBC, LFT, KFT, and coagulation profile
Fetal assessment with ultrasound and Doppler
Deliver at 34 weeks

(CBC: complete blood count; HELLP: hemolysis, elevated liver enzyme levels, and low platelet count; KFT: kidney function test; LFT: liver function test)

FLOWCHART 2: Approach to preeclampsia.

convulsions can occur in the antenatal or postnatal period. In the antenatal period, eclampsia occurs usually in the last 3 months of pregnancy closer to term. In postnatal period, seizures occur usually within 48 hours of birth though cases have been reported even 7 days after delivery.

All pregnant women presenting with seizures should be considered to be eclampsia until proven otherwise. In women presenting with focal neurological deficits, atypical eclamptic seizures and prolonged comatose state, alternate diagnosis should be sought.

Clinical Presentation

Generalized seizures, sometimes violent enough to injure the woman, last about a minute followed by gradual waning of contraction intensity. The eclamptic phase is sometimes preceded by a state of aura with marked headache, visual symptoms such as flashes or scotomas, confusion or altered consciousness. Post an episode of seizure, the woman may regain consciousness completely in some time or remain unconscious or comatose. In some, there is a state of combative semiconsciousness. Rarely coma may persist and condition deteriorates after further seizures resulting in death. If seizures continue despite all interventions (status epilepticus), there is emergent need for sedation or general anesthesia to prevent anoxia.

Due to spasm of all muscles in the body during a convulsion, tongue bite can occur there, thus, the need to protect the airway. Also, after convulsion, the tongue may fall back and obstruct the upper airway due to secretions. There is also a risk of aspiration of secretions or vomitus postconvulsion leading to aspiration pneumonitis or Mendelson's syndrome. Due to spasm of respiratory muscles, there is anoxia, hypercarbia, and lactic acidosis with transient tachypnoea to compensate for CO_2 retention. Other organs may be affected as in severe preeclampsia.

Pulmonary edema may occur due to ventricular failure from raised blood pressure (cardiogenic edema) or injudicious use of intravenous fluid or aspiration of gastric contents (altered pulmonary capillary permeability).

Cerebrovascular hemorrhage may lead to neurological defects or even cause death if massive. A devastating complication, it is more common in women with chronic hypertension where there are Charcot-Bouchard aneurysms in the deep penetrating arteries of the lenticulostriate branch of middle cerebral arteries which rupture during hypertensive crises.

Visual impairment results from occipital lobe edema or retinal detachment. It is usually reversible within 1–2 weeks.

Posteclamptic convulsion, there is higher chance of onset of labor with rapid progression. Fetal bradycardia is common after seizure due to acidosis and usually recovers by 5 minutes.

Red Flags

Death may occur from status epilepticus nonresponsive to treatment, cerebral edema with transtentorial herniation, massive cerebral hemorrhage, pulmonary edema, pulmonary embolism, hepatic rupture due to subcapsular hematoma, acute hepatic/renal failure, congestive cardiac failure, and DIC.

Treatment

Delivery of the fetus is the definitive treatment of preeclampsia and eclampsia. However, when the woman has convulsed, it is important to stabilize her condition before termination of pregnancy which is done irrespective of ability of the fetus to be salvaged.

When a pregnant woman presents with seizures, immediately check the vitals and turn in lateral decubitus position to prevent aspiration. Care should be taken to prevent the woman from injuring herself should a seizure recur. A mouth gag or padded tongue blade can be inserted to prevent tongue bite during fit. Airway assessment for patency to be done and suctioning to clear any secretions is done. Respiratory rate and oxygen saturation are assessed and endotracheal intubation is done for those not able to maintain saturation. Oxygen is given at 8–10 L/min if saturation in low. A quick history is obtained and examination done. Magnesium sulfate is given to prevent further seizures along with medicine to control blood pressure. Per urethral catheterization is done. Obstetric assessment for mode of termination of pregnancy is done. Cesarean section is done for obstetric indications and status epilepticus nonresponsive to treatment, if immediate vaginal delivery is not possible. It is a good practice to deliver an eclampsia patient in 12 hours to improve maternal outcome.

The mainstay of eclampsia treatment is use of magnesium sulfate to prevent further convulsions or even forestall convulsions in severe preeclampsia. It is administered either by intramuscular route as intermittent injections or intravenous route as continuous infusion; the doses used are same for eclampsia and preeclampsia. The treatment has to be continued till 24 hours after delivery or last seizure, whichever is later (**Table 18**).

Importance of assessment of deep tendon reflexes cannot be overemphasized. At serum magnesium levels >10 mEq/L which may be the only indication of levels above normal range. At levels >12 mEq/L, respiratory depression (respiratory rate <10 or SpO_2 <92%) and arrest ensues. Treatment with calcium gluconate or calcium chloride, 1 g intravenously (10 mL of 10% over 10 minutes), along with discontinuation of further magnesium sulfate, usually reverses mild-to-moderate respiratory depression and these should be readily available in labor ward settings.

Urine output monitoring (>30 mL/hour) gives an idea of renal function and thus monitored every 4 hours. Since $MgSO_4$ is renally excreted, magnesium toxicity can occur with impaired renal function. Even with suboptimal renal function, loading dose should not be skipped as it helps in achieving a therapeutic serum level. Maintenance doses, however, will depend upon renal function, and when serum creatinine is >1 mg/dL, it is advisable to do serum magnesium levels to monitor toxicity and guide further dosage.

With administration of $MgSO_4$, there is transient fall in vascular resistance and mean arterial pressure with increase in cardiac output presenting as flushing.

Magnesium sulfate readily crosses over to the fetus and causes transient fetal heart rate changes such as reduced variability and decelerations. Few other adverse effects have been reported such as hypotonia yet overall, it has been found to be protective against development of cerebral palsy, especially in low birth weight babies.

Another important facet of eclampsia management is treatment of severe hypertension which may result in cerebral hemorrhage or hypertensive encephalopathy or even cause convulsions in severe preeclampsia. It is recommended that therapy be started to bring systolic blood pressure <160 mm Hg and diastolic blood pressure <110 mm Hg. Labetalol, hydralazine, and nifedipine (oral) are used for management of severe hypertension as discussed previously.

Diuretics must be used judiciously in cases with pulmonary edema, which is probably the only indication for use in preeclampsia and eclampsia.

TABLE 18: $MgSO_4$ regimen for eclampsia treatment.

	Intramuscular regimen (Pritchard regimen)	***Intravenous regimen (Zuspan regimen)***
Loading dose	• 4 g $MgSO_4$ as 20% v/w solution intravenously at rate not exceeding 1 g/min • Follow promptly with 10 g $MgSO_4$ 50% v/w solution, 5 g as deep intramuscular in upper outer quadrant of each buttock by 3 inch 20-gauge needle	4–6 g $MgSO_4$ in 100 mL normal saline over 15–20 minutes
Repeat convulsions after 15 minutes	Give additional 2 g $MgSO_4$ as 20% v/w solution intravenously at rate not exceeding 1 g/min	
Maintenance dose	Every 4 hours, 5 g $MgSO_4$ 50% v/w solution as deep intramuscular in alternate buttock	1–2 g/hour maintenance in 100 mL intravenous fluid/infusion
Prerequisites for maintenance doses	• Patellar reflex is present • Respiration is not depressed • Urine output over last 4 hours is >100 mL	• Deep tendon reflexes present • Serum magnesium levels done 4–6 hourly to maintain between 4 and 7 mEq/L • Serum magnesium levels if creatinine >1 mg/dL
Maternal observations	Respiratory rate and blood pressure every 30 minutes, maternal pulse hourly, urine output hourly, deep tendon reflexes 2 hourly, and fetal heart rate continuous monitoring	
Pain relief	1 mL of 2% lidocaine can be added to the intramuscular preparation	
Discontinue	24 hours after delivery or last fit whichever is later	24 hours after delivery or last fit whichever is later

Both vaginal birth and cesarean section are possible in cases of eclampsia. For vaginal birth, intravenous fluids should be used cautiously to avoid any fluid overload when using oxytocin infusion for labor augmentation. Second stage of labor has to be cut short by using vacuum or forceps for assisting birth. For the purpose of cesarean section, general, epidural, and combined spinal-epidural are acceptable provided that careful approach is adopted to manage the complications arising due to each method. Due to limited plasma volume expansion of pregnancy, these women may not be able to tolerate moderate amount of blood loss at childbirth and second stage has to be managed well to prevent excessive bleeding. Blood loss can be estimated from hematocrit and managed appropriately with crystalloids and blood transfusion.

HELLP SYNDROME

HELLP syndrome is an acronym for hemolysis, elevated liver enzymes, and low platelet counts and occurs in about 7.5% of all pregnancies, more commonly in those complicated by severe preeclampsia and eclampsia. It may develop during the antepartum period more so in the third trimester and also in the postpartum period. Majority (80%) of women with HELLP have hypertension and proteinuria.

Two classification systems are used for grading of HELLP syndrome as follows:

1. *Tennessee classification*:
   i. Complete syndrome—platelets <100,000/mm^3, liver transaminases >70 IU/L, and lactate dehydrogenase >600 IU/L
   ii. Incomplete syndrome—one or two of platelets <100,000/mm^3, liver transaminases >70 IU/L, and lactate dehydrogenase >600 IU/L
2. *Mississippi classification:*
   i. Class 1—platelets < 50,000/mm^3, liver transaminases >70 IU/L, and lactate dehydrogenase >600 IU/L
   ii. Class 2—platelets 50,000–100,000/mm^3, liver transaminases >70 IU/L, and lactate dehydrogenase >600 IU/L
   iii. Class 3—platelets 100,000–150,000/mm^3, liver transaminases >40 IU/L, and lactate dehydrogenase >600 IU/L

Etiology

Similar to the pathogenesis of preeclampsia, there is endogenous release of factors leading to endothelial injury with activation of the coagulation and complement cascade. There is also decrease in endothelium-derived prostacyclin and nitrous oxide increasing the response to vasopressors. There is widespread microvascular injury with hemolytic anemia, elevated liver enzymes due to periportal hepatic necrosis and thrombocytopenia due to consumption by microthrombi.

Pathophysiology

Microangiopathic hemolysis results in abnormal forms of red cells in peripheral smear (schizocytes, burr cells, and fragmented cells). There is compensatory haematopoiesis which can be seen as reticulocytosis. Due to hemolysis, there is an increase in lactate dehydrogenase level, fall in hemoglobin, low haptoglobin, and rise in unconjugated bilirubin levels. Liver enzymes (aspartate and alanine transaminases) are elevated as a result of hepatic necrosis and increased hemolysis. Thrombocytopenia results from consumption due to platelet aggregation and microthrombi formation.

Clinical Presentation

Majority of cases being associated with hypertensive disorders are diagnosed in these women by laboratory investigations. There may be no symptom at all and diagnosis is made on the basis of presence of anemia, platelet count <100,000/mm^3, raised liver transaminases, and bilirubin and elevated lactate dehydrogenase levels.

In symptomatic women there may be hypertension and proteinuria with epigastric or right upper quadrant pain, nausea, vomiting, headache, edema, weight gain, and rarely jaundice.

Maternal complications such as eclampsia, acute renal failure, disseminated intravascular coagulopathy, placental abruption, cerebral hemorrhage, pulmonary edema, hepatic infarction or parenchymal hemorrhage, and subcapsular hematoma may occur. Mortality can occur in 1–3% cases.

Neonatal morbidity and mortality are also increased. There is a higher incidence of growth restriction, prematurity, perinatal asphyxia, and stillbirths. Neonatal thrombocytopenia also occurs in a few cases. Mortality is higher in preterm deliveries.

Red Flags

Large hepatic hematoma can even rupture and cause shock and death. Epigastric pain radiating to shoulder, transaminases >1,000 IU/L, presence of fever, and abdominal distension warrant imaging and prompt management.

Treatment

Management of HELLP is largely supportive. Careful observation of parameters and correction of anemia and coagulopathy is required. Antihypertensives to control blood pressure in women with preeclampsia are needed to prevent worsening. Delivery is the definitive therapy for HELLP. In mild cases, pregnancy may be continued with meticulous monitoring till reasonable fetal maturity is achieved. Corticosteroids for fetal lung maturation should be used in pregnancy <34 weeks of gestation. Those presenting early on with HELLP (<26 weeks of gestation) are advised termination. Prolonged conservative management may have poor fetal and maternal outcomes.

Large hepatic hematomas or those presenting with rupture and hemodynamic instability may need surgery or hepatic artery embolization for management. Liver transplant is a last resort in those who do not respond to standard management.

PLACENTA PREVIA

Placenta previa is placental implantation in the lower uterine segment. This may be near or even cover the internal cervical os. Placental location may change during pregnancy as the lower uterine segment grows in the latter half, and so the diagnosis. Moreover, lack of any defined landmark makes it even more challenging to correctly locate the placental edge which may vary falsely with the bladder filling. Placenta previa is defined using ultrasonography as a placenta developing within the lower uterine segment.

Classification

Conventionally, placenta previa has been graded according to the relationship between the lower placental edge and the internal os of the uterine cervix.

- *Grade I or minor previa*: Lower edge inside the lower uterine segment;
- *Grade II or marginal previa*: Lower edge reaching the internal os;
- *Grade III or partial previa*: Placenta partially covered the cervix;
- *Grade IV or complete previa*: Placenta completely covered the cervix.

Grades I and II are categorized as "minor" placenta previa whereas grades III and IV are "major" placenta previa.

A newer classification which is widely accepted now is as follows:

- *Placenta previa*—the internal os is covered partially or completely by placenta
- *Low-lying placenta*—implantation in the lower uterine segment and placental edge is <2 cm from the internal os
- *Partial previa*—placental edge reaches but does not cover the internal os
- *Total previa*—placenta covers the internal cervical os.

Partial and total previa are considered as major degrees of previa and a high cesarean section rate is associated with these.

Any class of placenta previa may change in labor with cervical dilatation due to relative change in relation of the placental edge with cervical margin.

Epidemiology

The incidence of placenta previa varies from 0.3 to 1 out of 300–400 births.

Etiology

There are many theories about development of placenta previa.

Dropping Down Theory

The fertilized ovum drops down in uterine cavity and is implanted in the lower segment. Poor decidual reaction in the upper uterine segment and failure of zona pellucida to disappear in time can be a possibility. Persistence of chorionic activity in the decidua capsularis and its subsequent development into placenta results in formation of lesser degrees of placenta previa. Defective decidua results in spreading of the chorionic villi over a wide area in the uterine wall to get nourishment which forms membranous placenta encroaching onto the lower segment, common with morbidly adherent placentas. Big surface area of the placenta as in multiple fetuses may encroach onto the lower segment. Placenta previa is associated with many risk factors (**Table 19**).

TABLE 19: Risk factors for placenta previa.

Advanced maternal age	Cigarette smoking
Increasing parity	Cocaine use
Multiple pregnancy	Endometritis
Previous placenta previa	Tumors of uterus distorting contour
Prior cesarean delivery	Assisted reproduction
History of uterine curettage	Short interpregnancy intervals

Clinical Presentation

Placenta previa may be asymptomatic and only an incidental finding on routine ultrasonography. In symptomatic patients, painless bleeding is the most characteristic event. Bleeding usually begins without warning or pain in a woman who has had an uneventful pregnancy course (sentinel bleed/warning hemorrhage) and rarely profuse. There is no associated pain unless labor starts simultaneously. There is no associated inciting factor such as fall, trauma, or coitus. Many cases present for first time in labor, more often with major degrees of previa, due to inevitable shearing of placenta as cervix dilates. Fetal distress is unusual unless the hemorrhage is severe enough to cause maternal hypovolemic shock. The first episodes with small bleeds occur < 30 weeks in a third of cases, between 30 and 35 weeks in another third and beyond 36 weeks in the remaining.

Red Flags

Presence of pain that is usually continuous, symptoms of pre-eclampsia such as raised blood pressure, headache, visual disturbances or epigastric pain, sudden decompression of an overdistended uterus as in hydramnios, history of hypertension, and thrombophilias, all may be suggestive of an ominous form of antepartum hemorrhage "placental abruption" where the separation of placenta occurs leading to hemorrhage.

In 10% cases, both these forms of antepartum hemorrhage may coexist.

Massive hemorrhage may cause exsanguination and present as hypovolemic shock which needs prompt management with resuscitation, blood transfusion, and termination of pregnancy even if the fetus is nonviable, which if not done, can even result in death of the pregnant woman.

Evaluation

History

Unprovoked, painless, apparently causeless, and recurrent bleeding usually points to the diagnosis of placenta previa. Establish the amount, color of bleed, and history of any precipitating factors. Obstetric history should be established regarding past pregnancies, previous cesarean sections, hemorrhage in previous pregnancies, gestational age at present, multiple fetuses, preeclampsia in current or previous pregnancies, and placental localization on ultrasonography. Enquire about any hypertensive disorders, thrombophilia, and uterine fibroids. Ask about perception of fetal movements as the fetus may be dead in case of heavy bleeding.

Physical Examination

A quick examination is done to assess the general condition of the woman. Shock with altered sensorium presents when bleeding has been heavy. The woman is pale and the pallor is usually proportionate to the amount of blood loss which should be estimated. Check for vitals, blood pressure, pulse rate, and temperature. Assess for need of blood transfusion. Start resuscitation simultaneously with intravenous fluid through two wide bore cannulas and draw blood for grouping and crossmatching and other investigations.

Systemic examination is done followed by obstetric examination. Abdominal examination is done to determine the size of uterus, contour, consistency, and presence of tenderness. Fetal presentation, uterine contractions, and presence of fetal heart sound are established. Vulval examination to assess any ongoing bleeding and a gentle speculum examination to rule out any local causes of bleeding are done. Per vaginal digital examination is best avoided for fear of torrential hemorrhage.

Interpretation of Findings

As the dictum goes, all cases of vaginal bleeding in late pregnancy are presumed to be placenta previa unless proven otherwise. Shock out of proportion suggests alternate diagnosis such as placental abruption or rupture uterus. Preeclampsia and hypertension, when present, may mask the shock and give a false impression of the amount of blood lost.

Uterus height corresponds to the period of gestation in previa, whereas, if more, may suggest concealed abruption. Uterus tone is increased in cases of placental abruption along with tenderness and fetal parts are felt with difficulty. Uterus may not be palpable in cases of rupture and fetal parts are superficially felt. Malpresentations with nonengagement of fetal head are common in cases of placenta previa. Fetal heart sounds may be absent in massive hemorrhage in previa or concealed abruption and rupture uterus. After initial resuscitation and stabilization of patient, investigations are done (**Table 20**).

Treatment

Antenatal care, including hospitalization, should be tailored to individual woman's needs and social circumstances depending on distance from hospital and availability of transportation, previous bleeding episodes, laboratory reports, and acceptance of receiving donor blood or blood products.

Women with *asymptomatic* placenta previa confirmed on ultrasound in late pregnancy and managed at home should be counseled about risks of obstetric hemorrhage, preterm delivery, and need access to the hospital in case bleeding starts.

Significance of "warning hemorrhage" should not be ignored. A course of antenatal corticosteroid therapy is recommended prior to 34 weeks of gestation in women at higher risk of preterm birth. Counseling should also include need for blood transfusion and need of intensive care monitoring. Delivery should be considered between 36 and 37 weeks of gestation. Prevention and treatment of anemia during the antenatal period is recommended for women with placenta previa or a low-lying placenta as for any pregnant woman. Minor degrees of placenta previa may have uneventful vaginal delivery but cesarean section in recommended for major previas.

Those who are *symptomatic* may be managed depending on whether the bleeding is continuing, amount of bleeding, and effects of bleeding on the woman.

TABLE 20: Investigations for placenta previa.

Full blood counts	Bleeding time and clotting time
Blood urea and serum creatinine	Clot retraction time
Blood sugars	PT and aPTT
Urine routine and microscopy	Fibrin degraded products
Liver function test	Kleihauer–Betke test in Rh negative
Ultrasonography for localization of placenta—transabdominal/transvaginal or transperineally	
Doppler or magnetic resonance imaging in cases with previous uterine scars to diagnose morbidly adherent placenta	

(aPTT: activated partial thromboplastin time; PT: prothrombin time)

Expectant Management

The aim is to continue pregnancy for fetal maturity without compromising the maternal health. Expectant management can be offered only if there is availability of blood transfusion and facilities for cesarean section round the clock.

The pregnant woman should be in good health (hemoglobin >10 g/dL; hematocrit >30%) and pregnancy <37 weeks with no ongoing vaginal bleeding. Fetal well-being muse be assured using cardiotocography and ultrasound. Routine assessment for blood loss and fetal surveillance is done. Hemoglobin is built up and the blood loss is replaced by adequate crossmatched blood transfusion. This is ideal in hospital setting but some prefer home care when there is compliance and weekly follow-up is possible. This can be continued up to 37 weeks of pregnancy when the fetal maturity is achieved. Expectant management is discontinued if there is recurrent/continuing brisk hemorrhage, fetus is dead or congenitally malformed on investigation, labor onset and where another cause of bleeding such as abruption is identified. Steroid therapy is indicated when the duration of pregnancy is <34 weeks.

Acute Management

Definitive management (delivery) is done if patient is in exsanguinated state on presentation, bleeding occurs ≥37 weeks of pregnancy, onset of labor, there is continuing moderate bleeding, fetal distress or fetal death/congenital malformation incompatible with life, and any obstetric indication where vaginal delivery is contraindicated.

Initial resuscitation with intravenous fluids and blood transfusion is done. Clinical assessment is important to decide the mode of delivery. Cesarean delivery is preferred for all women with major degrees of placenta previa, in women with profuse bleeding, or obstetric contraindication for vaginal birth.

Vaginal delivery may be considered where placenta edge is clearly away from the internal cervical os on sonography after vaginal examination in a double setup arrangement in the operation theater prepared for cesarean section. Should vaginal delivery be considered safe, artificial rupture of membranes with oxytocin augmentation is done with careful watch for bleeding and vitals.

For cesarean section, informed consent is taken for surgery and performed in presence of a senior obstetrician and senior anesthetist. Uterine incision should be decided depending on placental localization or presence of adherent placenta. Elective sections are associated with better maternal and perinatal outcomes and are preferred. Regional anesthesia is considered safe and is associated with lower risks of hemorrhage than general anesthesia for cesarean delivery in women with placenta previa or a low-lying placenta. Blood loss should be assessed and crossmatched for possible transfusion.

Hysterectomy may be done as a life-saving procedure in some cases.

Complications

Morbidly adherent placentas are serious complication associated with placenta previa. Venous thromboembolism is associated with prolonged inpatient care. Other complications include malpresentations, intrapartum and postpartum hemorrhage, preterm labor, and sepsis. Coagulation defects are rare complications of placenta previa. Fetal hemorrhage, low birth weight, prematurity, intrauterine asphyxia, or birth injury.

PRELABOR RUPTURE OF MEMBRANES

"Prelabor rupture of membranes" (PROM) is the rupture of the fetal membranes before onset of labor. This is classified further depending on duration of pregnancy as: *Preterm prelabor rupture of membranes (PPROM)*—before 37 completed weeks and before onset of labor, *term prelabor rupture of membranes (term PROM*)—after 37 completed weeks but before onset of labor, and *previable prelabor rupture of membranes (previable PROM)*—rupture of membranes before onset of labor and before period of viability (23 weeks completed). PROM complicates nearly 10% of all pregnancies. Approximately two-thirds of the patients with PROM are deliver within the next 4 days and the rest within 1 week. An estimated 80% of term PROM begin labor within 24 hours and nearly 95% within 72 hours. Though the exact etiology can be a combination of various factors, following are the risk factors associated with PROM (**Table 21**).

Pathophysiology

Prelabor rupture of membranes may occur because of an alteration in structure or tensile strength of membranes or an alteration in the biochemical milieu of the membranes although the exact pathogenesis is still unclear. The amniotic membranes are a connective tissue structure and their tensile strength depends on the composition, degradation, and quality of their collagen, which increases until 20 weeks and then plateaus until week 39 when it starts to dramatically decrease. Incidence is high in women with connective tissue disorders, tobacco smoking, nutritional deficiencies, and intra-amniotic. Prostaglandins, glucocorticoids, and relaxin hormone facilitate rupture of the membranes.

TABLE 21: Risk factors of prelabor rupture of membranes (PROM).

Maternal factors	Maternal smoking, caffeine intake, and low socioeconomic status
Nutrition	Deficiency of copper/vitamin C, and low body mass index
Immunological	Collagen vascular disorders
Infectious	Vaginal colonization by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and group B streptococci
Previous pregnancy	History of preterm delivery or PROM
Present pregnancy	Vaginal bleeding in the first and second trimesters, short cervix (<2.5 cm) on ultrasonography, positive fetal fibronectin in cervicovaginal fluid

Clinical Presentation

The characteristic presentation is complaint of watery discharge per vagina which may be continuous or intermittent. There is no associated pain, fever, itching, or odor associated with the discharge.

Red Flags

Prolonged rupture of membranes can lead to ascending infection in the uterus and development of chorioamnionitis (**Table 22**). This requires early delivery to prevent development of maternal and fetal sepsis. This may present with a nonreactive fetal cardiotocography and absence of fetal breathing movements.

Evaluation

History

History should include duration of leaking, type of discharge, associated foul smell, fever, abdominal pain, and presence of infection elsewhere. One must also confirm the duration of pregnancy by dates and early scans. Enquire about fetal well-being and perception of movements. Ask regarding previous preterm births or premature membrane rupture in a prior pregnancy. Presence of any chronic illness or connective tissue disorders should be ruled out.

Physical Examination

A general physical examination is to be done with recording of blood pressure, pulse rate, temperature, and respiratory rate. A systemic examination should be done. Obstetric examination should include abdominal examination to confirm the uterus size, presentation and lie, presence of uterine contractions, and assess for any tenderness. Fetal heart rate auscultation is to be done. A vaginal speculum examination is done to confirm the diagnosis and to assess the characteristics of the fluid. Digital vaginal examination should be avoided unless the woman is in labor.

Interpretation of Findings

Presence of watery discharge through cervical os is characteristic. Fever, tachycardia, uterine tenderness, and foul-smelling discharge are suggestive of chorioamnionitis.

TABLE 22: Clinical features of chorioamnionitis.

Fever (>100°F)	Fetal tachycardia >160 bpm
Maternal tachycardia >100/min	Uterine tenderness
Foul odor of the amniotic fluid	Nonreactive fetal cardiotocography
Laboratory features of chorioamnionitis	
Maternal leukocytosis >15,000	C-reactive protein >2.7 mg/dL
High vaginal swab may show microbial growth	Ultrasonography may suggest absent fetal breathing movements

Investigations

Other than routine antenatal investigations, some specific tests may be done in cases of PROM—full blood count (including total and differential leukocyte count), C-reactive protein, and high vaginal swab for culture. Ultrasonography for fetal well-being may also show reduced amniotic fluid measurement which is suggestive but not diagnostic of PROM.

Some laboratory tests are available to diagnose PROM which include placental alpha macroglobulin-1 (PAMG-1), insulin-like growth factor binding protein-1 (IGFBP-1), and pH of amniotic fluid to help diagnose PROM and are helpful but not easily available.

Treatment

Essentially involves inpatient management. After assessment of fetal well-being and ruling out infection, further management includes antibiotics, corticosteroids for fetal lung maturity, monitoring for features of chorioamnionitis and other possible complications, and, delivery if indicated. Decision to deliver will depend upon gestational age, presence of infection, uterine contractions, fetal well-being, lung maturity, and availability of facility for newborn care.

Antibiotics

Erythromycin 250 mg 6 hourly for 10 days or earlier if labor onset or intravenous ampicillin followed by oral amoxicillin or erythromycin is recommended for prevention of infection.

Corticosteroids

The predominant risks for patients with PROM between 24 and 34 weeks are respiratory distress/hyaline membrane disease, sepsis, and intraventricular hemorrhage. Administration of glucocorticoids is beneficial if there is no clinical or subclinical chorioamnionitis.

Neuroprophylaxis

Magnesium sulfate should be given for neuroprophylaxis in PROM before 32 weeks of pregnancy, given up to 24 hours.

Tocolysis

Tocolytic agents do not significantly prolong the latency period in patients with PROM, may be useful in patients with contractions at the time of admission who may deliver before receiving the benefit of glucocorticoid treatment.

For patients with PROM before 34 completed weeks, management should be expectant unless an indication for delivery is present. The risk of expectancy is infection, but in the majority of cases infection is diagnosed early and has no serious effects on mother or fetus.

Those women who present beyond 34 weeks need to be evaluated and management has to be individualized depending upon the fetomaternal condition and presence of infection or risk factors. Termination has to be done at 37 completed weeks.

When PROM presents after 24 weeks, expectant management should be offered.

Expectant management will include the above and daily maternal and fetal monitoring. Investigations should be done biweekly to diagnose infection and include leukocyte counts, C-reactive protein, and vaginal swabs weekly.

Contraindications for expectant management are chorioamnionitis, abruptio placenta, labor onset, and fetal distress.

Delivery

In most cases of PROM, labor tends to begin spontaneously in a few hours to days. Tocolysis should be given and labor augmentation avoided in preterm PROM to give the room for steroid cover. In case of PROM, or preterm PROM where membrane rupture has been for a long duration and corticosteroid coverage has been done, or preterm RPOM crossed 34 completed weeks, vaginal delivery can be achieved by induction with oxytocin or prostaglandins. Cesarean section should be reserved for obstetric indications such as fetal distress or malpresentations. Antibiotic coverage should be done with observation for signs of chorioamnionitis. For cases of previable PROM, counseling regarding the prognosis is important. Induction of labor can be done if the woman is well counseled and desires so. If the woman opts for expectant management, antibiotics should be given while watching for chorioamnionitis and steroids can be given once the pregnancy crosses period of viability. It is important to counsel that two-thirds will deliver within 1 week of PROM and survival rate of extremely premature babies is extremely poor (**Table 23**).

PRETERM LABOR

Preterm labor is presence of uterine contractions of sufficient intensity and frequency to bring about changes in the uterine cervix (dilatation and effacement) before 37 completed weeks of pregnancy and after the period of viability. "Suspected preterm labor" is when there are signs and symptoms of possible preterm labor but labor has not established yet. "Diagnosed preterm labor" is suspected preterm labor with a diagnostic test positive for preterm labor. "Established preterm labor" is when cervical dilatation is ≥4 cm with regular uterine contractions. The prevalence widely varies and ranges between 10% and 15% and contributes majorly to perinatal morbidity and mortality. Many factors contribute to development of preterm labor (**Table 24**).

TABLE 23: Complications of prelabor rupture of membranes (PROM).

Maternal complications	*Fetal complications*
Chorioamnionitis	Preterm labor and prematurity
Abruptio placenta	Pulmonary hypoplasia
Cesarean section due to malpresentations/cord prolapse	Intraventricular hemorrhage and cerebral palsy
Postpartum endometritis	Neonatal sepsis
Maternal sepsis	Fetal skeletal malformation
Retained placenta	Risk of trauma due to operative interference
Rarely maternal death	Death due to prematurity, sepsis, and cord prolapse

Pathophysiology

The components contributing to preterm labor are cervical changes, activation of the decidual membranes, and uterine contractions. The whole process may progress rapidly or develop over weeks. Cervical changes are evident as effacement of the cervix and membrane activation results in the presence of fetal fibronectin in the cervicovaginal secretions (**Fig. 1**).

Clinical Presentation

Women who develop preterm labor may have some nonspecific warning features a few days prior to onset of labor. Clinically, preterm labor is the occurrence of regular uterine contractions (≥4 in 20 minutes or ≥8 in 1 hour) and cervical changes (effacement ≥80% and dilatation ≥1 cm) in women with intact fetal membranes and gestational age <37 weeks.

Threatened preterm labor is characterized by regular and frequent (10/hour) uterine contractions, cervical dilatation <1 cm, and short cervix (<2.5 mm) by transvaginal ultrasound examination.

TABLE 24: Etiology of preterm labor.

Maternal factors	• Stress, smoking, substance and alcohol abuse, maternal age <18 or >40, low body mass index, low prepregnancy weight, poor nutrition, and low socioeconomic status • Medical and surgical illness such as acute fever, acute pyelonephritis, diarrhea, and acute appendicitis • Chronic diseases such as hypertension, nephritis, diabetes, decompensated heart lesion, and severe anemia • Genital tract infection such as bacterial vaginosis, beta-hemolytic *Streptococcus*, *Bacteroides*, *Chlamydia*, *and Mycoplasma*
Past pregnancy related	Previous preterm labor, cervical incompetence, cervical surgeries, multiple induced second trimester abortions, uterine anomalies, and multiple pregnancies
Present pregnancy	Multiple gestation, antepartum hemorrhage, premature rupture of the membranes, chorioamnionitis, polyhydramnios, inadequate prenatal care, and extrauterine infections

Red Flags

Chorioamnionitis, as a result of prolonged membrane rupture or itself a cause of preterm labor, may present with fever >100.4°F, tachycardia, foul-smelling discharge, uterine tenderness, fetal tachycardia (>160/min), increases C-reactive protein and leukocytosis, and may need augmentation of labor (**Table 25**). Presence of massive placental abruption also may need augmentation if coexistent with preterm labor. Medical conditions such as uncontrolled diabetes may also be a contraindication to arrest preterm labor.

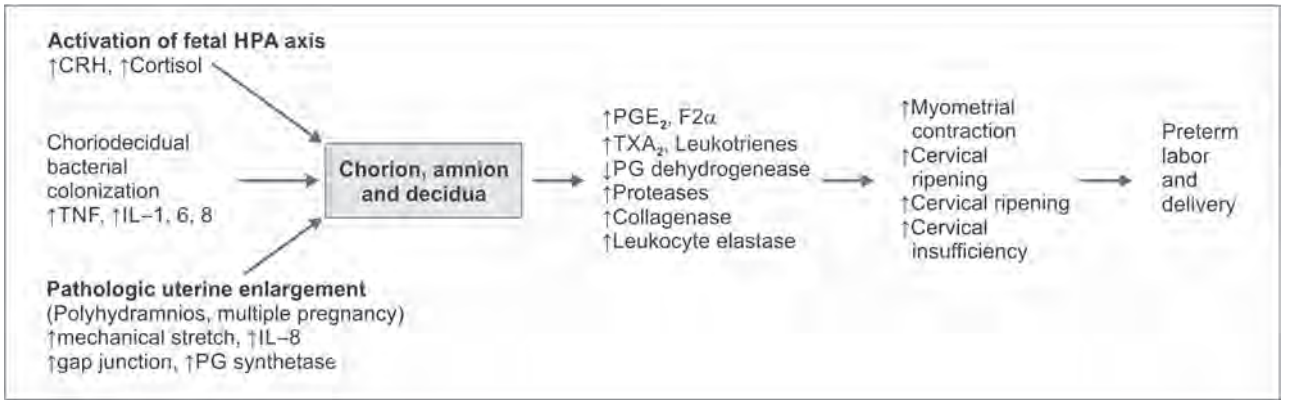
Evaluation

History

Ask regarding onset and progress of pain, duration and frequency of contractions, heaviness or dragging sensation, perception of fetal movements, complaints of discharge or leaking per vagina, and fever. Confirm the duration of pregnancy by dates and early scans. Ask about previous pregnancies and whether there has been any previous preterm delivery. Enquire about any chronic illnesses and previous surgeries, especially cervical procedures such as conization, cervical amputation, large loop excision of transformation zone (LLETZ), or previous cervical cerclage. Personal history of smoking, substance abuse, and physical abuse should be elicited.

TABLE 25: Red flags of preterm labor.

Warning symptoms	***Warning signs***
Lower abdominal cramps	Uterine contractions
Low and dull backache	Leaking per vagina
Pressure/heaviness	Shortening of cervix
Increase/change in vaginal discharge	Thinning/effacement of lower uterine segment
Abdominal cramps	Engagement of presenting part



(CRH: corticotropin-releasing hormone; HPA: hypothalamic–pituitary–adrenal; IL: interleukin; PG: prostaglandin; PGE_2: prostaglandin E_2; TNF: tumor necrosis factor; TXA_2: thromboxane A_2)

FIG. 1: Etiopathogenesis of preterm labor.

Physical Examination

A quick and thorough general examination is done with assessment of vitals followed by systemic examination. Obstetric assessment is done to ascertain the uterine fundal height which should correspond to the gestational age of pregnancy, fetal lie and presentation, uterine contractions and fetal heart sound. Vaginal examination is done to assess the status of membranes, cervical dilatation, and effacement.

Interpretation of Findings

Presence of regular uterine contractions and cervical dilatation and thinning are suggestive of labor.

Prediction of Preterm Labor

Some clinical, biochemical, and radiological investigations are used to identify high risk of preterm birth (**Table 26**).

Investigations

Other than routine investigations in pregnancy, some specific investigations may be required in cases of preterm labor (**Table 27**).

Management

The management includes: (1) To prevent preterm onset of labor, if possible; (2) To arrest preterm labor, if not contraindicated; (3) Appropriate management of labor; and (4) Effective neonatal care.

Bed rest is advisable to prevent premature rupture of membrane. Delivery by lower segment cesarean section (LSCS) does not prevent periventricular-intraventricular hemorrhage compared with vaginal birth. Intensive clinical monitoring with continuous cardiotocography (CTG) is ideal. Repeated digital examinations should be avoided to prevent infection.

TABLE 26: Prediction of preterm labor.

Fetal fibronectin	Swabs from cervicovaginal secretions tested for fetal fibronectin between 24 and 37 weeks, if positive, predict preterm labor in next 2–3 weeks
Salivary estradiol levels	Increases levels of salivary estradiol can predict preterm labor
Cervical length measurement by transvaginal scan	Short cervical length <25 mm can predict preterm labor risk

TABLE 27: Investigations for preterm labor.

Full blood count	Cardiotocography for fetal heart rate
Urine routine microscopy	Ultrasonography for fetal well-being
High vaginal swab for culture	Cervical length estimation
Vaginal fluid pH	C-reactive protein

Corticosteroids

Steroid administration reduces the incidence and severity of respiratory distress syndrome and hence, neonatal morbidity and mortality. Recommended corticosteroids are injection betamethasone 12 mg, two doses 24 hours apart or injection dexamethasone 6 mg, four doses 12 hours apart. Delivery should be delayed using tocolysis for minimum 12 hours for maximum effect of steroid, although optimal benefit begins 24 hours after therapy and lasts for 7 days, but first dose should be administered irrespective of possibility of administration of a second dose. Single course of steroids is recommended.

Tocolytic Agents

These are used to delay delivery to achieve lung maturity or facilitate transfer to another facility, but maintenance tocolysis is not recommended in routine practice. Commonly used ones are presented in **Table 28**. Before starting tocolytic agent one should rule out any contraindication to tocolytic therapy (**Table 29**).

Antibiotics

In case of preterm labor, antibiotics are recommended when there is associated rupture of membranes (prevention of group B *Streptococcus* infection in fetus). Erythromycin 250 mg every 6 hours is preferred for maximum of 10 days or till labor sets in. Those allergic to erythromycin may be given oral penicillin. 5–10% of patients in preterm labor may have infection outside uterus, mostly in the urinary tract and they should be treated by appropriate antibiotics.

Rescue Cervical Cerclage

It is a surgical procedure where stitch is applied to the cervix in women with cervical dilatation with unruptured membranes to prevent preterm births. There should not be any uterine contractions, bleeding, infection, and fetus should be viable.

Prophylactic Vaginal Progesterone and Cervical Cerclage

Prophylactic vaginal progesterone can be offered to women diagnosed as having short cervical length on ultrasound but no history of preterm births. Cervical cerclage is offered to women with cervical length is ≤25 mm on transvaginal sonography and are at risk of preterm birth (previous history of preterm birth, uterine anomalies, and symptomatic).

Management of Preterm Labor

- Bed rest advisable to prevent rupture of membranes
- Strong sedatives avoided
- Repeat vaginal examinations to be avoided
- Ideally continuous fetal heart tracing
- Fetal scalp electrodes should be avoided
- Delivery preferably in a hospital with specialized neonatal unit in presence of senior obstetrician and pediatrician
- Episiotomy should be considered to minimize head compression
- Prophylactic forceps should not be used
- Cord clamping to be done early if resuscitation is needed or may be delayed for up to 3 minutes

TABLE 28: Commonly used tocolytic drugs.

Drug	*Dosage*	*Comments/side effects*
Nifedipine (calcium channel blocker)	• 20–30 mg orally stat followed by same dose after 30 minutes, if contractions persist • Maintenance 10–20 mg 6 hourly for 48–72 hours (maximum 160 mg/24 hours)	Contraindicated in maternal heart disease and hypotension; stop if pulse rate >120/min, blood pressure <100/60 mm Hg or SpO_2 <95%
Terbutaline (β agonist)	0.25 mg subcutaneous (S/C) every 20 minutes to 3 hours	Tachycardia, chest pain, palpitations, and headache
Isoxsuprine (β agonist)	• 4 ampules (40 mg) in 500 mL of 5% dextrose 0.2–0.5 mg/min intravenous (IV) over 10 hours • Maintenance 0.1–0.3 mg/min IV over 12 hours	Tachycardia, chest pain, palpitations, and headache
Magnesium sulfate	• 4–6 g IV over 20 minutes followed by 2–3 g/hour as continuous infusion for 24 hours/delivery • Neuroprotective at <32 weeks	Monitor with urine output, respiratory rate, and deep tendon reflexes
Atosiban (oxytocin receptor antagonist)	• 6.75 mg intravenously stat over 1 minute followed by infusion of 18 mg/hour for 3 hours and then 6 mg/hour for up to 45 hours • Maximum duration 48 hours and maximum dose 330 mg	Chest pain, palpitations, tachycardia, hypotension, dyspnea, nausea, vomiting, and headache

TABLE 29: Contraindications of tocolytic therapy.

Advanced labor (cervix >4 cm dilated)	Fetal demise
Abruptio/placenta previa	Fetal maturity >34 weeks
Features of chorioamnionitis	Acute fetal distress
Severe preeclampsia and eclampsia	Congenital malformations
Severe anemia	Hyperthyroidism

TABLE 30: Neonatal complications in preterm babies.

Respiratory system	Hyaline membrane disease and apnea of prematurity
Central nervous system	Intraventricular hemorrhage and hypoxic–ischemic encephalopathy
Biochemical changes	Hypoglycemia, hypocalcemia, and hypomagnesemia
Cardiovascular system	Patent ductus arteriosus
Hepatobiliary system	Jaundice and necrotizing enterocolitis
Ocular	Retinopathy of prematurity
Systemic complications	Hypothermia, septicemia, hypoxia, and acidosis

Neonatal Complications in Preterm Babies

Preterm neonates are predisposed to many complications and need intensive monitoring (**Table 30**). Particularly important are hyaline membrane disease due to lung immaturity and septicemia. The neonate may need intensive care with ventilatory support, oxygen, and surfactant therapy. Prevention of sepsis, acidosis, and electrolyte imbalance should be practiced to prevent morbidity.

Prevention

Primary care is aimed at reducing the incidence of preterm labor by treating the high-risk factors. Secondary care includes screening tests for early detection and prophylactic treatment (tocolytics and cervical cerclage in women with short cervix). Tertiary care is aimed to reduce the perinatal morbidity and mortality after the diagnosis (use of corticosteroids/surfactant therapy).

SUMMARY

Obstetric emergencies can arise at any point in time and it is important to diagnose the condition and institute prompt treatment as needed. The early half of pregnancy can have complications related to miscarriages or infection arising as a result of unsafe abortions. Nearly 10 lakh abortions are carried out in India annually and almost 10 women die per day due to related complications. Diagnosis of abortion and treatment of related complications is thus, of utmost importance. Since the patient is first attended by the emergency physician, it is imperative that early pregnancy complications be addressed. Pregnancy is often missed or overlooked so it is advisable to ask regarding the last menstrual period in a woman of reproductive age group and carry out a urine pregnancy test whenever in doubt. Liaising with the on-call gynecologist can be helpful.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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157 CHAPTER

Comorbid Conditions and Pregnancy

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INTRODUCTION

Many medical conditions can present in pregnancy, either as a preexisting condition or arising during pregnancy. As a result of the complex interactions between the mother, fetus, disease, and the treatment many medical problems become complicated. Chronic medical conditions if not managed well pose a serious threat to the mother's health and poor fetal outcome. The mother is the first priority in any medical emergency since the fetus is dependent on her for physiologic support. Complex demography and lifestyle factors are responsible for increasing prevalence of medical problems in pregnancy. Older women are more likely to have acquired medical disorders. Medical conditions are the leading causes of maternal death. The physiologic changes occur in pregnancy makes symptom onset or rapid decompensation of previously present medical illness during pregnancy. Certain chronic medical condition poses a serious threat to the mother health or result in a poor fetal outcome. The incidence of pregnancy with chronic disease is increasing day by day. The following medical conditions pose a serious threat to both mother and fetal outcome (**Table 1**).

DIABETES

Diabetics cause various complications in pregnancy and also give rise to acute complications of diabetes. The incidence of diabetes with pregnancy is increasing day by day. Three-fourths of pregnant patients with diabetes have either gestational diabetes or type 2 diabetes mellitus (T2DM) diagnosed through prenatal screening. Of the remaining 25%, 1% has preexisting type 1 diabetes mellitus (T1DM) and the remaining are T2DM patients. Pregnant diabetes women are at increased risk for spontaneous abortion, particularly patients with poor glycemic control in pregnancy, preexisting vascular disease, and preeclampsia. Preexisting diabetes and gestational diabetes are at increased risk for complication during pregnancy. The common complications occurring because of diabetes in pregnancy are: Pregnancy-induced hypertension (PIH), preterm labor, spontaneous abortion, pyelonephritis, and diabetic ketoacidosis (DKA). The American College of Obstetrician and Gynecologists recommends the following goals for maintaining euglycemia in pregnant diabetic patients: A fasting blood glucose concentration of <95 mg/dL and a 2-hour postprandial glucose concentration <120 mg/dL. Initial stage of gestational diabetes can be managed with diet and if it is high then there is need of oral hypoglycemic drugs like metformin. Insulin therapy is necessary for some patients with gestational diabetes and for preexisting diabetes. Among patients with preexisting T1DM and T2DM patients, the need for insulin increases throughout the courses of pregnancy. Usually all T2DM patients are switched to insulin as soon as possible to ensure appropriate glycemic control. There are concerns over the safety of oral hypoglycemic agent in pregnancy. In general, during the first trimester, the initial insulin requirement is 0.7 units/kg/day. By late pregnancy, patients generally require 1 unit/kg/day. Neutral Protamine Hagedorn (NPH)/regular insulin combination are still first-line insulin therapy.

Pregnant patients are at increased risk of DKA, and DKA can occur more rapidly, and at lower glucose levels, than in nonpregnant patients. DKA should be considered for any pregnant diabetic patient who is ill appearing and/or has a blood glucose level ≥180 mg/dL. Treatment of DKA in pregnancy includes supplemental oxygen, left lateral decubitus positioning, and usual DKA care: Isotonic fluid resuscitation to correct volume deficits, administration of continuous insulin, correction of electrolyte abnormalities, and treatment of the underlying cause.

Mild hypoglycemia (glucose <70 mg/dL and able to follow commands) is treated with some oral feed. Severe hypoglycemia (glucose <70 mg/dL with unable to follow command) should

TABLE 1: Comorbid conditions of concern during pregnancy.

Endocrine	• Diabetes • Thyroid diseases
Cardiovascular	• Chronic hypertension • Gestational hypertension • Peripartum cardiomyopathy • Thromboembolism
Central nervous	Epilepsy
Respiratory	Asthma

be treated with 50 mL of 50% dextrose in water intravenous (IV), with 1–2 mg of glucagon given intramuscular (IM), or subcutaneous if IV access is delayed. Subsequently, the patient should be given 5% dextrose solution IV at 50–100 mL/h.

THYROID DISEASES

Hyperthyroidism

Hyperthyroidism in pregnancy increases the risk of preeclampsia, congenital anomalies, and neonatal morbidity. Treatment is with propylthiouracil (PTU). Patients on PTU are at risk for purpuric rash and agranulocytosis. Thyroid storm can presents with fever, volume depletion, or cardiac decompensation manifesting as high-output heart failure.

Hypothyroidism

The most common cause of hypothyroidism worldwide is iodide deficiency. In iodine-replete areas, the most common cause is postautoimmune thyroiditis, such as Hashimoto's thyroiditis. Overt hypothyroidism is often associated with infertility, so most cases seen during pregnancy are less severe. When signs and symptoms do occur, they are generally the same as those in the nonpregnant state. Myxedema coma is extremely rare, but should be considered along with other causes of coma in a pregnant patient. There is an increased incidence of adverse maternal and fetal effects such as preeclampsia, placental abruption, low birth weight, and an increased risk of stillbirth in women with clinical hypothyroidism. Postpartum thyroiditis is characterized by transient hyperthyroidism and/or hypothyroidism in the postpartum period. The diagnosis of hypothyroidism during pregnancy should be suspected when the patient exhibits edema, dry skin, hair loss, and a prolonged relaxation phase of deep tendon reflexes. Confirmation of hypothyroidism is based on an elevated serum thyroid-stimulating hormone (TSH) level, relying on trimester-specific TSH reference ranges.

CARDIOVASCULAR DISEASES

Hypertensive disorder is the most frequent cardiovascular events occurring in 6–8% of pregnancies. Older pregnant women experience an increased rate of antepartum and intrapartum complication mainly in comorbid with cardiovascular diseases. Cardiac disease in pregnant women can be worsened in pregnancy due to increase in blood volume, along with the increases in preload, cardiac output, and oxygen consumption.

Chronic Hypertension and Hypertensive Emergencies

Hypertension is the most common medical problem in pregnancy occurring in 6–8% of pregnancies. In normal pregnancy, blood pressure falls by around 10 mm Hg in the first half of pregnancy, and then gradually returns to prepregnancy levels by term. High blood pressure in pregnancy can be in two forms. It may be a preexisting hypertension called chronic hypertension or it can develop during pregnancy as PIH. Treatment is often considered for chronic hypertension if blood pressure >140/90 mm Hg measured on two occasion before 20 weeks of gestation. Chronic hypertension is associated with adverse perinatal outcome including preeclampsia, intrauterine growth restriction (IUGR), and placental abruption. The severity of maternal blood pressure at 20 weeks is associated with worse outcome. Treatment of mild-to-moderate chronic hypertension in pregnancy has no proven fetal benefit. Excessively lowering of the blood pressure is not recommended because it causes adverse perinatal outcome due to decreased placental perfusion. Pharmacological treatment is indicated if blood pressure is persistently >150–160/100–110 mm Hg in order to prevent maternal end-organ damage.

Chronic hypertension during pregnancy is usually treated with labetalol, nifedipine, or methyldopa. Drugs such as angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors are avoided. The β-blocker atenolol has been associated with IUGR. Thiazide diuretics can exacerbate the intravascular fluid depletion of preeclampsia so in such case it should be discontinued.

Gestational Hypertension

Gestational hypertension is a provisional diagnosis used for a heterogenous group of women including: (1) Those that will eventually develop proteinuria during the pregnancy and be diagnosed with preeclampsia, (2) Those who will have persistent hypertension after 12 weeks postpartum and be diagnosed with chronic hypertension, and (3) Those who do not develop preeclampsia and whose blood pressures normalize postpartum.

Preeclampsia is associated with increased risk of developing new onset hypertension, coronary artery disease, cerebrovascular disease, and chronic kidney disease. If preeclampsia develops before 34 weeks, the risk is increased up to eightfold. If pharmacological treatment is required, labetalol (nonselective α- and β-blocker) or modified-release nifedipine (calcium channel blocker) are the first-line drugs in pregnancy. Methyldopa and amlodipine are second-line options. Drugs such as ACE inhibitors, angiotensin II receptor blockers, and spironolactone are contraindicated in pregnancy and during preconception should be switched to an alternative agent. However, ACE inhibitors can be reintroduced postpartum and are safe when breastfeeding.

Peripartum Cardiomyopathy

The incidence of peripartum cardiomyopathy (PPCM) is between 1 in 3,000 and 4,000 births. Mortality of PPCM is high from 5 to 20%. By definition, PPCM is heart failure developing in the last month of pregnancy or within 5 months of delivery in a woman without another identifiable cause of the heart failure. The etiology of PPCM remains unknown but evidence points to myocarditis, perhaps due to a weakened immune response to viral infection of the myocardium. Initial diagnosis may be delayed because the sign and symptoms of systolic dysfunction including dyspnea, fatigue, tachypnea, and lower extremity edema are common in the last month of pregnancy and immediate postpartum period. Standard congestive heart failure treatment (includes ACE inhibitors) is contraindicated in pregnancy and excess diuresis (risk of uteroplacental insufficiency) should be avoided in pregnancy. Future pregnancies are at risk for recurrent and life-threatening

PPCM. Women whose cardiac function does not recover fully should be discouraged from conceiving again.

Thromboembolism

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are the common diseases causing maternal morbidity and mortality. Venous thromboembolism (VTE) refers to both DVT, a blood clot in the venous system of the lower extremities, and PE, a clot that breaks loose and lodge in the pulmonary arteries. Advance maternal age, increasing parity, multiple gestation, operative delivery, prolong bed rest, and obesity are the risk factors to thromboembolism during pregnancy. The relative risk of VTE in pregnancy is increased fourfold to sixfold compared with the general population. Cesarean section further increases this risk. DVT and PE are treated with unfractionated or low molecular weight heparin at usual doses. Warfarin is contraindicated during pregnancy as should direct oral anticoagulant such as rivaroxaban. Thrombolysis is considered in massive life-threatening PE; however, pregnancy is not a contraindication to thrombolysis.

Valvular Heart Disease and Pregnancy

Mitral stenosis and regurgitation followed by aortic valve disease are the common valvular comorbid conditions associated with pregnancy. Effects of coexisting valvular disease on pregnancy depend on the type and severity of the valvular lesions. Mild-to-moderate valvular lesions with the New York Heart Association (NYHA) Class I/II are generally associated with good outcome for mother and fetus. Advanced valvular lesions such as mitral stenosis (NYHA more than class I) and severe aortic stenosis are associated with ventricular dysfunction and pulmonary hypertension (**Table 2**). Significant maternal mortality is observed in patient with prosthetic valve and on anticoagulants. Expert cardiologist consultation and directed therapy required in valvular heart disease and pregnancy.

TABLE 2: Risk stratification in pregnant women with valvular heart disease.

Low risk	• Aortic stenosis with EF > 50% mean gradient <25 asymptomatic • Aortic or mitral regurgitation asymptomatic or mild symptoms • Mitral valve prolapses EF > 50% with mild/moderate regurgitation • Mild/moderate stenosis without severe pulmonary stenosis • Mild-to-moderate pulmonary stenosis
High risk	• Symptomatic mitral stenosis NYHA Class II–IV • Severe aortic stenosis (irrespective of symptoms) • Mitral/aortic regurgitation NYHA Class III–IV • Severe LV dysfunctions <40% • Severe pulmonary hypertension • Mechanical prosthetic valve

(EF: ejection fraction; LV: left ventricular; NYHA: New York Heart Association)

ASTHMA

Asthma is one of the most common chronic medical problems in pregnancy, with a prevalence of between 3.7 and 9.4 %. Maternal asthma is associated with an increased risk of preeclampsia or eclampsia, premature contractions, cesarean section, low birth weight, and small for gestational age status. Maternal respiratory function changes can make it more difficult to recognize the decompensating pregnant asthmatic patient. During the course of pregnancy, tidal volume, and minute ventilation increase by 45% resulting in an average partial pressure of carbon dioxide (pCO_2) of 32 mm Hg. The kidneys compensate and maintain an average bicarbonate level of 19 mEq/mL, which results in a compensated respiratory alkalosis with a serum pH between 7.40 and 7.45. Many adverse perinatal outcomes caused by asthma are thought to be due to fetal hypoxia. Both the American College of Obstetrics and Gynecology (ACOG) and National Asthma Education and Prevention Program have clearly stated that it is safer to use asthma medications to treat pregnant women than to allow severe asthma symptoms and exacerbations to occur during pregnancy. Acute asthma presents with cough, wheezing, and dyspnea. The standard treatment for a pregnant asthmatic patient is the same as that for a nonpregnant patient with an asthma exacerbation. Supplemental oxygen should be given to all mothers with oxygen saturation below 95%. Inhaled short-acting β2-agonists are the first-line treatment for an asthma exacerbation and can be given continuously, if needed, for a severe exacerbation. Long-acting selective β2-agonists and inhaled corticosteroids, with budesonide being the preferred agent, can be added as controller medications on discharge from the ED. Nonselective β-agonists such as epinephrine are generally avoided because of concern for their effect on placental blood flow. Terbutaline sulfate 0.25 mg subcutaneous can also be used when not better with above treatment. Second-line agents for asthma control (e.g., cromolyn sodium) are considered safe in pregnancy. Magnesium has been shown to improve respiratory function in pregnant females with severe asthma exacerbations without adverse fetal outcomes.

EPILEPSY

Management of epilepsy in pregnancy has two main aspects. First, epilepsy may have adverse outcome on pregnancy (and vice versa); secondly, antiepileptic drugs (AEDs) exposure may adversely affect the fetus as well. Maternal mortality is 10-fold higher in patients with epilepsy than in those without the disorder. Epilepsy is also associated with an increased risk of obstetric hemorrhage, hypertensive disorders of pregnancy, and fetal growth restriction. Hepatic and renal clearance of many drugs is increased in pregnancy. Lamotrigine, in particular, may require significant dose increases in pregnancy. All AEDs are teratogenic but the risks of uncontrolled epilepsy almost always outweigh the risks to the fetus posed by these medications. Sodium valproate should be switched to an alternative drug preconception because sodium valproate carries the highest risk of fetal malformations. Even if alternate antiepileptics are used through pregnancy, careful monitoring and counseling are required to communicate the benefits and risks to the mother.

SUMMARY

Maternal mortality and morbidity resulting from treatable medical conditions is increasing day by day, despite a marked decrease in overall maternal mortality. Preconception counseling is the most important part to explain them about the continuation of the same medication or to change in medication with risk benefit background. Prompt recognition of acute illness and optimal treatment of chronic conditions is of clear benefit, and most drugs and many radiological investigations can be used in pregnancy to manage medical conditions in pregnancy.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Emergency Delivery

Sangeeta Kaushik Sharma

INTRODUCTION

Emergency department (ED) is challenging and dynamic place where time bound emergencies are imminent. The management of childbirth is usually the responsibility of obstetricians and is not always available in-house in most of EDs, as they need to be called from outpatient department (OPD) or operation theater (OT) in daytime and from their home in nighttime. So, emergency physician should be prepared of managing obstetric emergencies and procedures of labor and basic steps of parturition, if situation occurs. Apart from this, emergency physician should be aware of various possible complications during labor such as malpresentation, shoulder dystocia, multiple deliveries, and be able to perform various maneuvers for shoulder dystocia and breech presentation. Labor is a process that begins with the onset of repetitive and forceful uterine contractions sufficient to cause dilation of the cervix and ends with delivery of the infant and placenta.

PREHOSPITAL CARE

If such a situation occurs outside the hospital then arrangements must be made to transport the pregnant to the nearby hospital safely and promptly. Under Janani Suraksha Yojana for pregnant, Indian Government is providing free transport facility to all pregnant women in labor pains, to nearby hospital for urgent delivery round the clock 24 hours. During prehospital care: (1) Provide oxygen, (2) Obtain intravenous (IV) access, (3) Transfer the patient in left lateral recumbent position, use this position especially if the expectant mother's blood pressure is low (pressure on vena cava reduces the return to the heart), and (4) Prepare for field delivery, because little can be done to prevent the birth.

EMERGENCY DEPARTMENT CARE

Evaluation of Pregnant Female

Apart from history and physical examination of pregnant female few points to be noted such as prenatal history, frequency of contractions, any vaginal discharge or bleeding, and focused examination to determine fetus presentation (**Fig. 1**).

Abdominal Examination and Steps to Ascertain the Presentation

This is very important to know which part of the fetus is near the birth canal. Sterile vaginal examination is carried out to know which part of fetus body (head, shoulder, buttock, and feet) is the presenting part. Shoulder will be the presentation in transverse lie. Abdominal examination carried out by Leopold maneuver (**Figs. 2A** to **D**).

Vaginal Examination

Lithotomy position is maintained while doing vaginal examination. Prepare the part (cleaning with povidone-iodine); vulva and perinial area for examination. Sterile gloved hand should be used to examine the vagina and effacement (**Figs. 3A** to **C**—measured through 0–100%) and cervical dilatation is assessed (10 cm cervical os indicate full dilatation). After examination of cervix, head of fetus [station of head –5 to +5 (**Fig. 4**)] is determined in relation to ischiatic spine. When the head is at the level of ischial spine this is leveled as 0 and as head progress further to birth canal it is levels as +5.

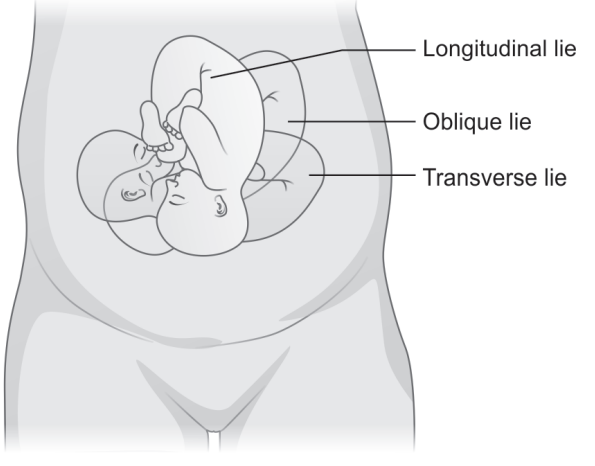
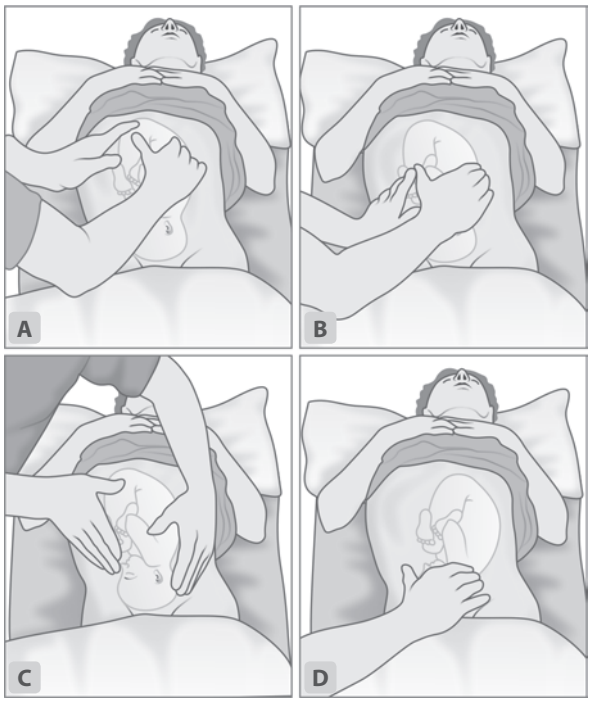
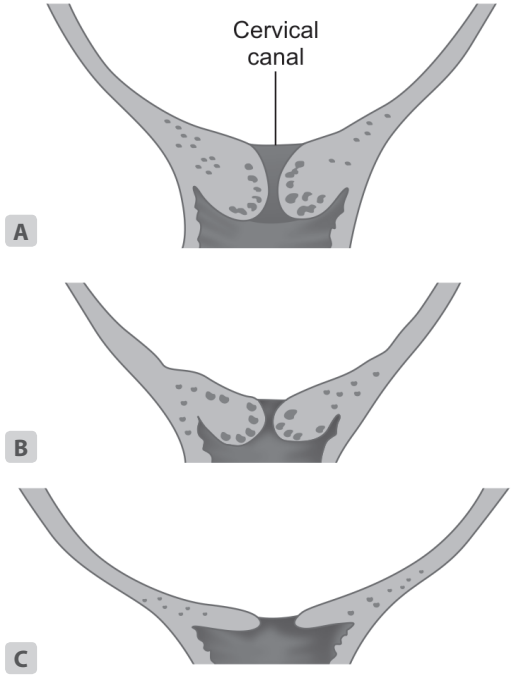


FIG. 1: Various presentation of fetus.



FIGS. 2A TO D: Leopold maneuver for abdominal examination in pregnant female. (A) Palpate fundus part; (B) Palpate lateral part of abdomen to find the back of fetus; (C) Palpate other lateral part; (D) Palpate presenting part.



FIGS. 3A TO C: Effacement of cervix. (A) 0%; (B) 50%; (C)100%.

Emergent Vaginal Delivery/Labor

Labor is defined as the initiation of regular and rhythmic contractions that results in serial cervical dilatation and effacement and categorized into four stages. *First stage (stage of cervical dilatation)* begins with onset of regular contraction and end with complete dilatation; latent (0–3 cm) → active (4–7 cm) → transitional (8–10 cm). *Second stage (stage of expulsion)*

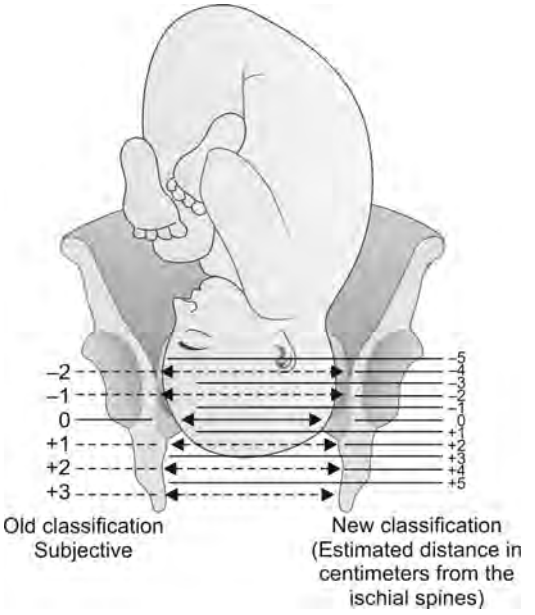


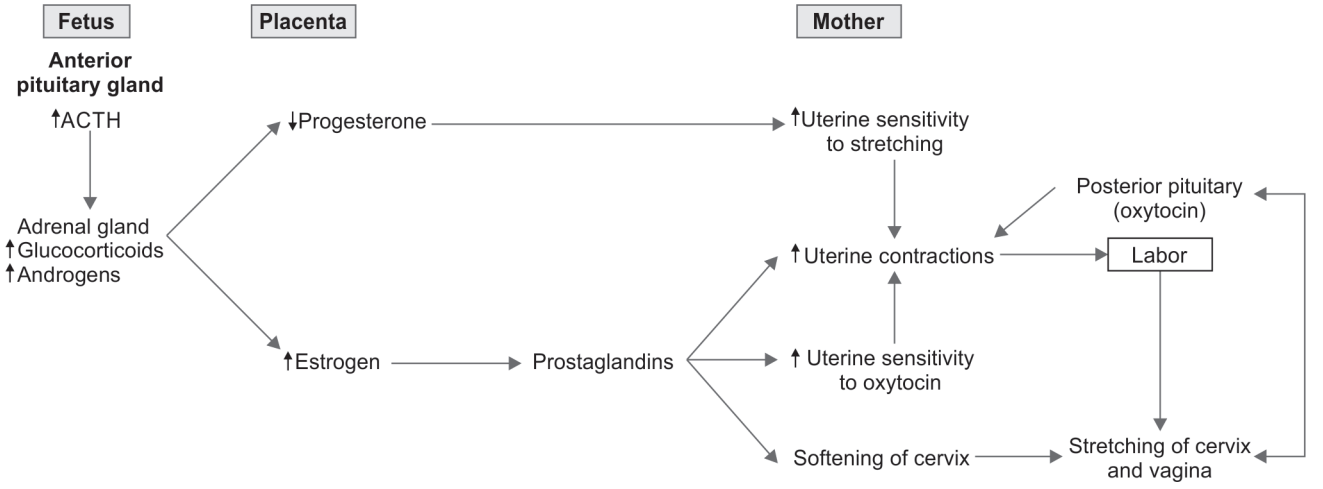
FIG. 4: Station of head.

begins with complete cervical dilatation and end with delivery fetus. *Third stage (placental stage)* begins immediately after fetus is born and ends when placenta is delivered. *Fourth stage (maternal stabilization stage)* begins after delivery of the placenta and continues for 1–4 hours after delivery. Various hormonal factors are believed to have role in initiation of process of labor as shown in **Figure 5**.

A reliable sign of impending child labor is shown. The appearance of a slight amount of vaginal blood-tinged mucus is a good indication that labor will begin within the next 24 hours and sequence of labor will start and obstetrics and pediatric consult should be requested without delay. The loss of more than a few milliliters of blood at this time, however, must be regarded as being due to a pathological process like placenta previa or abruptio placenta. Adequate equipment should be arranged easily accessible for use at any time. List of equipment for labor is given in **Box 1**.

Patient should be placed in lithotomy position, if head is visible in vaginal opening or vulvar area (crowning), physician should be ready for the emergency delivery. Once the fetus head is crowning, delivery is performed by using the Ritgen maneuver. Important steps for safe delivery are shown in **Figure 6**.

Neonate neck should be checked for the umbilical cord around the neck, gently pull it around the head if cord around the neck is present. Deliver the child and shoulder by giving gentle traction and then rest of the baby will come out quickly. Be careful at this time as baby is slippery at this time. Suction the mouth and nose of the baby. Place the double clamp on the cord about 7–10 cm away from the baby and cut the clamp between the cord. If the child starts breathing and moving and appears to be in good health, hand over the baby to nursing personnel. In case of thick meconium, intubate the baby with 3.0 size endotracheal tube, then perform suction and stimulate the baby. Guide the placenta for delivery, do not try to pull the placenta. Mother and baby can be moved to the obstetrics ward for follow-up care if both are healthy and do not require further resuscitation.



(ACTH: adrenocorticotrophic hormone)

FIG. 5: Possible role of hormonal factors in labor.

Box 1: Essential equipment for labor.

- Sterile gloves
- Sterile gown
- Towels
- Hemostats
- Placenta cord clamps
- Surgical scissors
- Suction bulb
- Infant nasogastric tube
- Syringes
- Neonatal air bag
- Needles
- Gauzes
- Neonatal warmer

Placenta Delivery

This may take 5–15 minutes after the delivery of fetus; bleeding is inevitably occurred when placenta separates and give uterus massage for contraction. Manual removal is mandatory if placenta does not descend and mother asked to push down or cough to increase the intra-abdominal pressure. Once placenta is delivered, stop abdominal massage and start the oxytocin infusion [20 U (2 mL/L)] at the rate of 10 mL/minute until uterus is well contracted and bleeding is stopped. Infusion of oxytocin titrated to 1–2 mL/minute until to shifted recovery unit. Mother should be kept under careful observation for 1 hour as bleeding may reoccur.

Episiotomy

Episiotomy is the incision given to the posterior vaginal wall to enlarge the vaginal introitus and facilitates smooth passage of fetal head (**Fig. 7**). Earlier it was thought that episiotomy can prevent vaginal tear and head trauma, but it is not showing better outcome and associated with bleeding, hematoma, infections incontinence, and lacerations. Now selective approach is used and only recommended in selective cases such as breech presentation, shoulder dystocia, preterm labor, and imminent perineal tear.

After the fetal delivery episiotomy can be repaired. Vaginal canal should be inspected closely for any other reason of bleeding and should be corrected and hemostasis achieved first before repair of episiotomy. Site is adequately prepared and cleaned and sutured with 2-0 or 3-0 absorbable sutures.

COMPLICATED DELIVERY

Often high-risk deliveries occur in ED in higher population of without access of care, those of unaware and denial of pregnancy. Obstetric patient presenting to ED usually have little or no prenatal care.

The emergency physician needs to expect the unexpected during a delivery, including precipitous delivery, shoulder dystocia, malpresentation, umbilical cord emergencies, hemorrhage, and multiple gestations. Additional ED nursing staff, doctors, obstetrician, and pediatrician should be called to ED. Arrange and open the kit for delivery and neonatal care, turn on infant warmer, and prepare resuscitation equipment. Wear personal protective equipment (gown, mask, eye protection, gloves, and shoe covers). Obtain IV access in the mother so that oxytocin, fluids, blood, and other medications may be administered as needed during the delivery. Keep the patient and family well informed.

If the infant is not crowning (head bulging at the perineum), a brief vaginal examination performed with a sterile–gloved hand. Various abnormal presentations of abnormal deliveries such as face, foot, hand, arm, or breech presentations are obvious on palpation (**Fig. 8**). These unexpected presentations can be problematic for the delivery in the ED, because they require special expertise.

UMBILICAL CORD PROLAPSE

Obstetrician should be called and the mother prepared for emergency cesarean section. However, if labor has progressed far enough that vaginal delivery is imminent, it should be performed as the most rapid method of delivery. If delivery is not imminent, as arrangements are being made for the

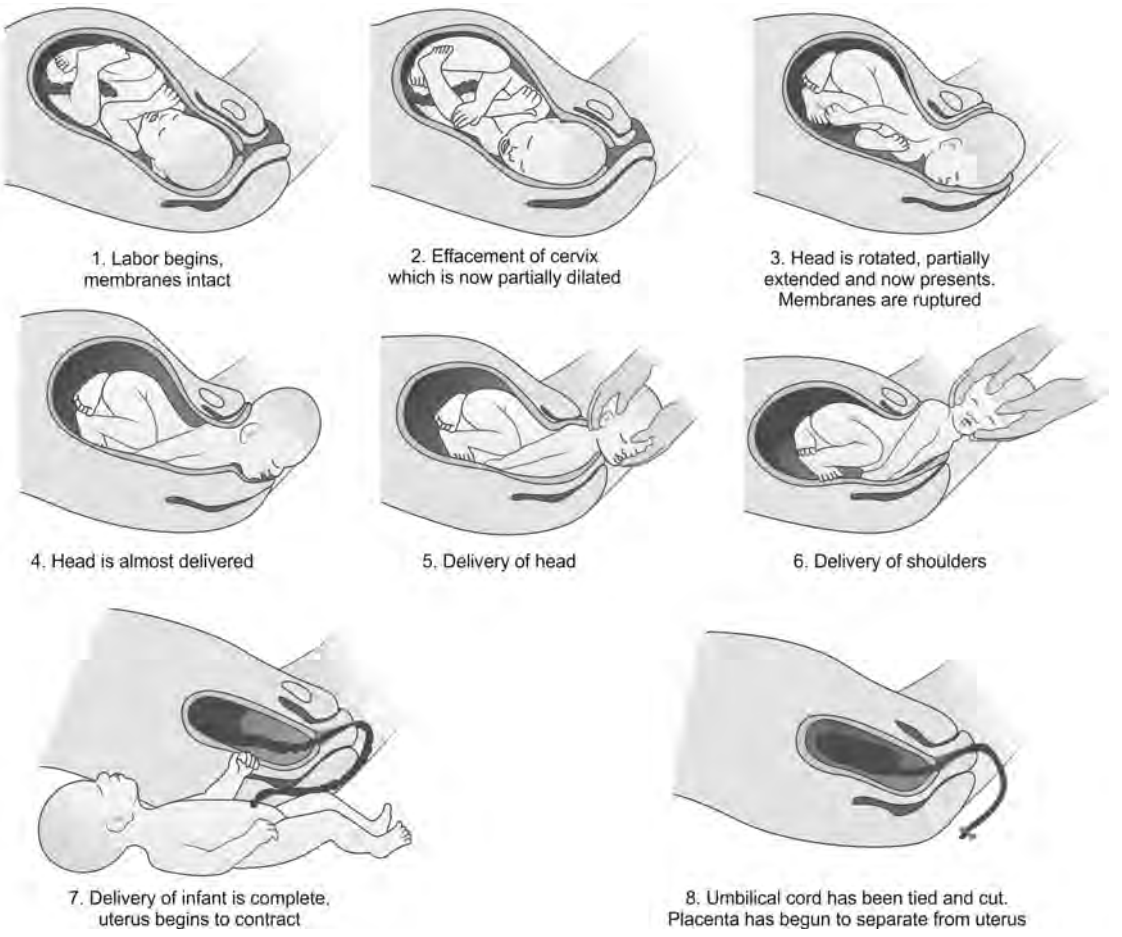

1. Labor begins, membranes intact
2. Effacement of cervix which is now partially dilated
3. Head is rotated, partially extended and now presents. Membranes are ruptured
4. Head is almost delivered
5. Delivery of head
6. Delivery of shoulders
7. Delivery of infant is complete, uterus begins to contract
8. Umbilical cord has been tied and cut. Placenta has begun to separate from uterus

FIG. 6: Steps for safe delivery in emergency department.

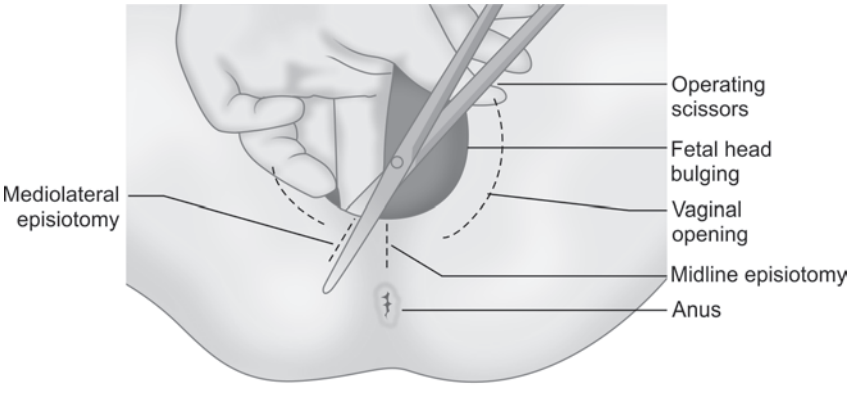


FIG. 7: Episiotomy modalities.

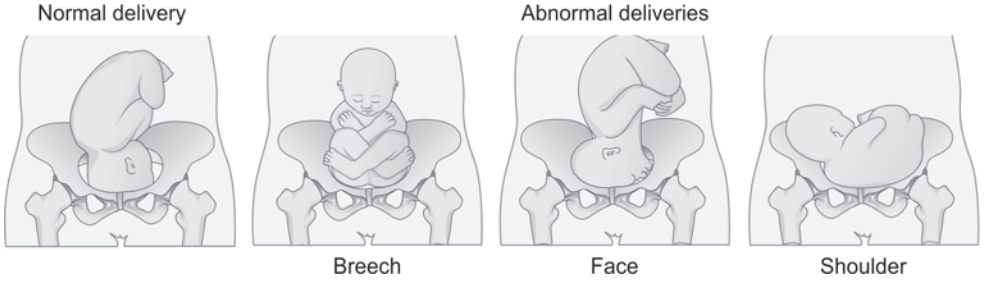


FIG. 8: Abnormal presentations of deliveries.

operation room, care should be focused on reducing pressure on the prolapsed cord. The cord should not be manipulated as this can induce vasospasm and subsequent fetal hypoxia. Instruct the mother not to push. The patient should be transported to the operating room and prepared for surgery with the provider's hand still in the vagina. Instillation of 500–700 mL normal saline into the bladder via Foley catheter may also help lift any presenting fetal parts off the cord.

CESAREAN SECTION

It is one of the oldest surgical procedures to preserve the fetal life. Every emergency physician must be aware of this procedure. Though most experience obstetrician should perform this procedure and neonatologist presence is mandatory.

Common indications for cesarean section procedures are malpresentation such as breech, brow, face posterior or transverse lie, and cord prolapse. Medical conditions where cesarean section such as cardiac, pulmonary, thrombocytopenia, active herpes simplex virus, human immunodeficiency virus infection, congenital anomalies, pelvic tumor, placenta previa, placental abruption, and vasa previa. Emergent cesarean section is indicated in perimortem condition (mother in cardiac arrest). Prolonged resuscitation is not beneficial to mother and fetus, so every attempt should be made to complete this surgical procedure within 4 minutes to save the fetal life. Decrease in time from maternal death to delivery, enhanced the possibility of neonatal survival. Rapid extraction of infants while avoiding any injury to mother and infants is the primary goal in perimortem condition. When this is so important, emergency physician should be aware of the minimum equipment required for the procedure. Essential equipment for perimortem cesarean section are retractors, clamps, vascular clamps or hemostats, neonatal resuscitation kit: neonatal air bag, intubation tray, suction bulb, warmer, curved scissors, blades #10, blood gas syringe, and suture. Perimortem cesarean section technique is described in **Figure 9**.

First a vertical incision is made in ventral aspect of the abdomen. Second, identify the bladder, place a bladder retractor. Third vertical incision made with the scalpel in the uterus. With a scissors, extend the incision inferiorly. Extract the fetus head, suction the pharynx, and deliver the fetus completely. Important to note complications of cesarean section surgical procedure are bladder injury (common) followed by bowel injury, fetal injury, neonatal neurological injury, maternal bleeding, and infections.

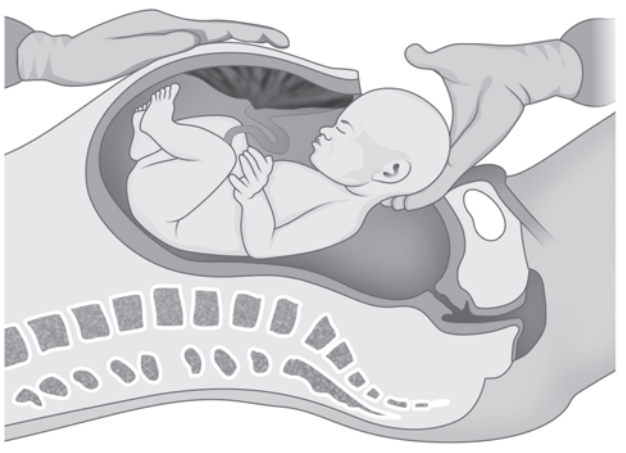


FIG. 9: Perimortem cesarean section.

POSTPARTUM COMPLICATIONS

Risk factors for the postpartum complications are cesarean delivery, prolonged rupture of membrane, prolonged labor, and bladder cauterization. These risk factors described earlier leads to complications such as mastitis, upper respiratory infection, urinary tract infection, thrombophlebitis, hematoma, abscess formation, endometritis, perineal cellulitis, and hemorrhage.

Postpartum Hemorrhage

An emergency physician should give attention to amount of blood loss during and after the delivery. Bleeding can be subtle and constant and can be life-threatening if go unnoticed. More than 500 mL of maternal blood during vaginal delivery is considered as postpartum hemorrhage. Multiple risk factors are identified for this condition such as prior history of postpartum hemorrhage, multiple deliveries, polyhydramnios, prolonged labor, and coagulopathy. Differential diagnosis includes uterine atony, cervical or uterine laceration/rupture, and retain products of conception. Management includes hemodynamic evaluations, initiation of blood products, volume expanders, and identify cause and their treatment.

Uterine Atony

Uterine atony is the most common cause of postpartum hemorrhage after prolonged labor and overdistension. Uterus feels soft and boggy with vaginal bleeding. Treatment of choice is uterotonic drug oxytocin 10–40 U in 1 L of crystalloid and given in infusion. Second-line drugs are methylergonovine 0.2 mg intramuscular and carboprost (prostaglandin derivatives) 0.25 mg intramuscular. Two-hand uterine massage can also be done. If these measures fail to control the postpartum hemorrhage, invasive measures such as embolization and surgery are indicated.

Placenta Previa

Placenta previa is a third trimester obstetric complication in which placenta abnormally (partially or completely) covers the internal cervical os. *Symptoms*: Bright red painless recurrent vaginal bleeding. S*igns:* Soft pain-free uterus easy to feel fetus, often high head breech or transverse lie no fetal distress. No recommendations for digital per vaginum (PV) examination, often fetus is not affected by the first small bleed, but because of high risk after emergency resuscitation shift immediately to obstetric department.

Abruption of Placenta

It means premature separation of placenta. *Symptoms*: Abdominal pain, bleeding, and severe shock. *Signs*: Shock spasm of uterus fetal part hard to feel, often no fetal heart sound. All emergency protocol should be considered to shift the patient to obstetric emergency unit.

Uterine Inversion

Forceful traction of umbilical cord during placental delivery causes uterine inversion. Although uterine inversion is uncommon but present with severe abdominal pain and produce shock due to vaginal bleeding and can be life-threatening if left untreated. Physical examination reveals absence of palpable uterus and protruding mass on vaginal examination. Hemodynamic stabilization and repositioning of the uterus is required in this situation.

SUMMARY

Every emergency physician should have sound knowledge of the emergency delivery and common obstetrics complications and emergencies. First principles of obstetrics emergencies are the same as with any other emergency, maintain circulation, airway, and breathing. Left uterine displacement of gravid uterus to prevent aortocaval compression. If patient is in second stage of labor, deliver the baby with all due precautions. If time permits, shift the patient to obstetric unit after primary resuscitation.

MULTIPLE CHOICE QUESTIONS

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159 CHAPTER

Resuscitation in Pregnant

Vijaya Banu Mohan, Dodiy Herman, Benita Florence

INTRODUCTION

Resuscitation in pregnancy has few unique aspects and consideration when to compared to normal adult resuscitation as it involves resuscitation of two patients—pregnant woman and fetus. It is important to be familiar with the physiological changes in pregnancy which impact the resuscitation.

PHYSIOLOGICAL CHANGES IN PREGNANCY

The resuscitation modifications begin as early as in first trimester which peak at the second trimester and stays the same until labor. These are based on the anatomical and physiological and anatomical changes during the course of pregnancy. The changes during pregnancy and their implications are tabulated in **Table 1**.

CRITICALLY ILL MATERNAL PATIENTS

Any patient requiring admission to intensive care unit (ICU) because of pregnancy-specific conditions (sepsis, hemorrhage, and hypertensive emergencies in pregnancy), medical or surgical conditions unrelated to pregnancy (asthma, diabetes, and trauma), and conditions worsening in pregnancy (cardiac conditions, anemia, and autoimmune conditions). The crucial part in the prevention of cardiac arrest in critically ill patient is the prompt quick response.

MATERNAL COLLAPSE

It is an acute critical event due to cardiorespiratory or central nervous system involvement leading to reduced or absence conscious level during any stage of pregnancy up to 6 weeks after labor. If maternal collapse is not managed effectively then it can lead to cardiac arrest.

TABLE 1: Anatomical and physiological changes in pregnancy and their associated implications.

Systems	*Changes during pregnancy*	*Implications*
Airway	Edema/friability of upper airway	Difficult to perform bag mask ventilation
	Edema to pharynx and larynx	• Difficulty in laryngoscopy • Small diameter • ET tube may be needed
Breathing	• Diaphragm elevation by 4 cm • Reducing FRC	• High thoracostomies • Hypoxia can develop quickly
	Oxygen consumption is increased by increased by 20% to meet the oxygen demands of maternal and fetal organs	Hypoxia develops soon, hence maintain saturation > 94%
	Increased tidal volume and minute ventilation	Partial pressure of carbon dioxide is reduced leading to respiratory alkalosis. Normal $PaCO_2$ can mean impending respiratory failure
Circulation	• Cardiac output increased by 30–40% • Increased heart rate • Plasma volume increased by 30% • Uterine blood flow increased by 10–20% • Blood pressure reduces in the second trimester	Masking the effecting of sepsis

Continued

Continued

Systems	*Changes during pregnancy*	*Implications*
	Aortocaval compression starting from 20 weeks	• Hypotension on supine position • Avoid access in lower extremities • Decreases the effectiveness of CPR
	Diaphragmatic elevation and apex of heart moved to left	• Changes in ECG—left axis deviation • Q waves in lead III • ST depressions in inferolateral leads • T-wave changes—flattened or inverted
Other changes	Relaxation of lower esophageal sphincter	Risk of aspiration
	Changes in bile composition (lithogenic)	Prone for cholelithiasis
	Plasma volume increase by 50% and 30% increase in red cell mass	Physiological anemia leading to reduced oxygen carrying capacity to tissue, more impact during CPR
	Increase in clotting factors and vWF	Hypercoagulable state—increased risk of venous thromboembolism
	Dilatation of ureteropelvic system—physiological hydroureteronephrosis and increased vesicoureteric reflux	Increased pyelonephritis
	Vaginal pH decreases	Increased chance of chorioamnionitis

(CPR: cardiopulmonary resuscitation; ECG: electrocardiogram; FRC: functional residual capacity; $PaCO_2$: partial pressure of carbon dioxide; vWF: von Willebrand factor)

MATERNAL CARDIAC ARREST

Cardiac arrest in pregnancy is rare. It occurs in 1:30,000 pregnancies. Resuscitation in cardiac arrest in pregnancy is unique and has few modifications as it involves two patients—mother and fetus. Effective resuscitation of the mother is often the best way to improve fetal outcome. It may need resuscitative hysterotomy if return of spontaneous circulation (ROSC) is not obtained in 4 minutes. One of the study done in UK revealed about one-fourth of the cardiac arrest in pregnancy were secondary to anesthesia and the all those patients survived.

Causes

The causes of maternal collapse or cardiac arrest can be classified as obstetric causes and nonobstetric cause (**Table 2**).

TABLE 2: Causes of maternal cardiac arrest.

4H	**H**ypoxia	• Acute myocardial infarction (MI) • Cardiomyopathy • Anaphylaxis • Aortic dissection • Aspiration
	Hypovolemia	Hemorrhage: • Antepartum hemorrhage • Postpartum hemorrhage • Uterine rupture • Coagulopathy • Surgical • Trauma Other shocks like: • Anesthesia • Septic • Neurogenic
	Hypo/hyperkalemia Other electrolyte imbalance	• Less likely • Oxytocin can cause hyponatremia
	Hypothermia	Less likely
4T	**T**hromboembolism	• Amniotic fluid embolism • Pulmonary embolism • Acute myocardial infarction • Air embolism
	Toxicity	• Magnesium • Local anesthesia
	Tension pneumothorax	Trauma
	Tamponade	Trauma
Preeclampsia/eclampsia		

APPROACH TO CRITICALLY ILL OBSTETRIC PATIENT

Like any standard approach, initial assessment should be done in airway, breathing, circulation, disability, and exposure (ABCDE) approach. Good maternal resuscitation provides good fetal care. So, it is imperative to follow the general standards of resuscitation. Resuscitation has the highest priority than the evaluation of the cause.

- Oxygen to maintain saturation >95%
- Insert two large bore intravenous (IV) access above the level of diaphragm
  - Treat hypotension with isotonic IV fluids and care should be taken that volume resuscitated is 50% more than the fluid required by nonpregnant person
  - If fluid unresponsive vasopressor should be considered as uterine blood flow is pressure dependent

- Early antibiotics, if sepsis is considered
- *Investigations*:
  - Bloods—full blood count (FBC), urea and electrolyte (U&E), liver function test, coagulation profile, crossmatch, fibrinogen, and fibrin degradation products
  - Chest X-ray—to look for pulmonary edema and acute respiratory distress syndrome (ARDS)
  - Electrocardiogram (ECG)
- Involve obstetrician, anesthetist, and neonatologist at the earliest
- If hemorrhage—crossmatch four to six units of blood
- If coagulopathy—liaise with hematologist to correct with platelet fresh frozen plasma (FFP) and cryoprecipitate transfusion
- Early transfer to intensive treatment unit (ITU)
- Deliver the baby

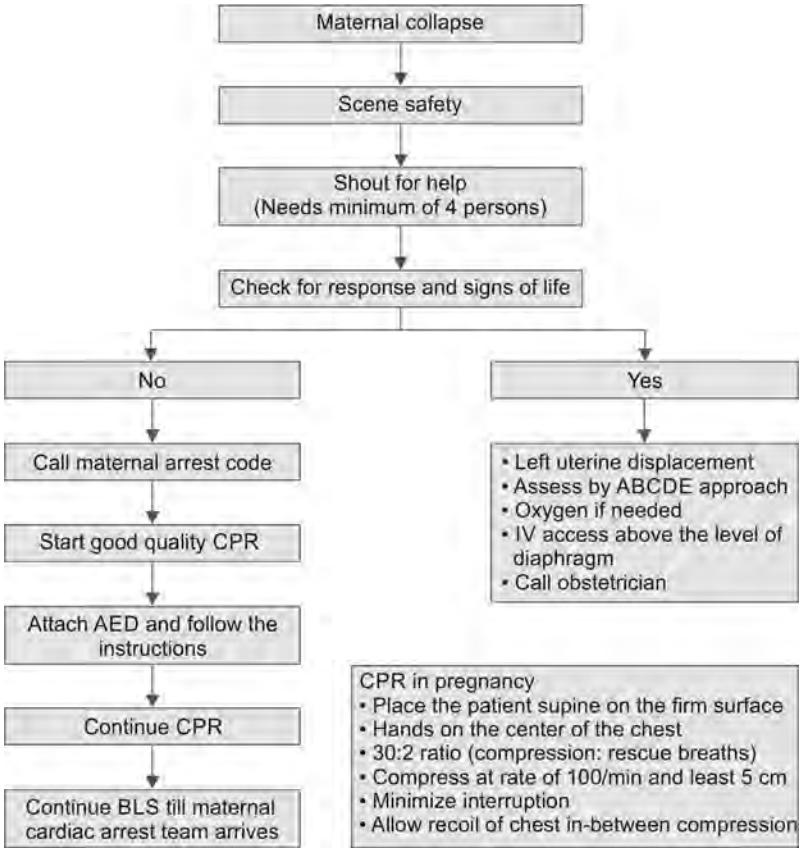
APPROACH TO MATERNAL CARDIAC ARREST

Whenever there is a maternal cardiac arrest, basic life support (BLS) (**Flowchart 1**) should be commenced immediately as basic emergency care is crucial with few modifications. Make the patient lie in supine position over the back board. Check for the response. If the patient is unresponsive with no breathing or abnormal breathing, obstetric emergency code should be activated. For BLS, minimum of four persons are needed. Automated external defibrillator (AED) and crash cart to be obtained. Check for pulse for not >10 seconds. If no pulse palpable then start chest compression as per standard adult resuscitation guidelines. Care should be taken to ensure good quality CPR with minimal interruptions. Bag mask ventilation (BMV) with 15 L of oxygen using two-hand technique to be provided—two breaths for 30 compressions each lasting for 1 second. Care should be taken to avoid excessive ventilation. AED should be used to analyze the rhythm and provide shock. If the patient is above 20 weeks of gestation, aortocaval compression can restrict the effectiveness of CPR, manually displace the uterus to left (pull the uterus to left) (**Fig. 1**). Left lateral tilt between 15° and 30° if feasible. This can be achieved with Cardiff wedge, pillow, or sand bags.

Advanced Life Support

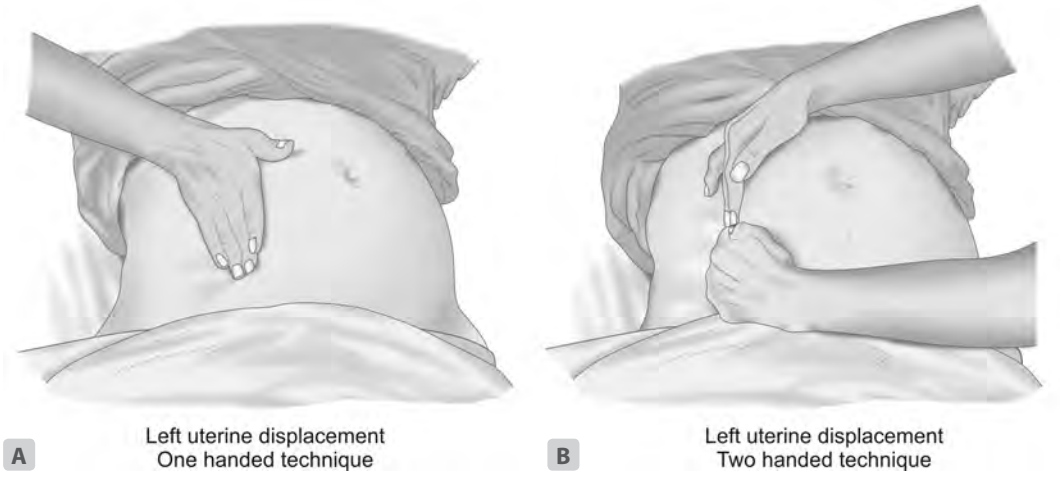
Every hospital should have the specific method to activate the maternal cardiac arrest code [advanced life support (ALS)] (**Flowchart 2**). One code call to all necessary resuscitation responders is needed. Ideal maternal cardiac arrest team should consist of:

- Emergency physician and nurse/critical care physician and nurse/internal medicine physician and nurse
- Obstetrician and obstetric nurse
- Anesthetist, especially if obstetric anesthetist if available and nurse
- Neonatologist and nurse

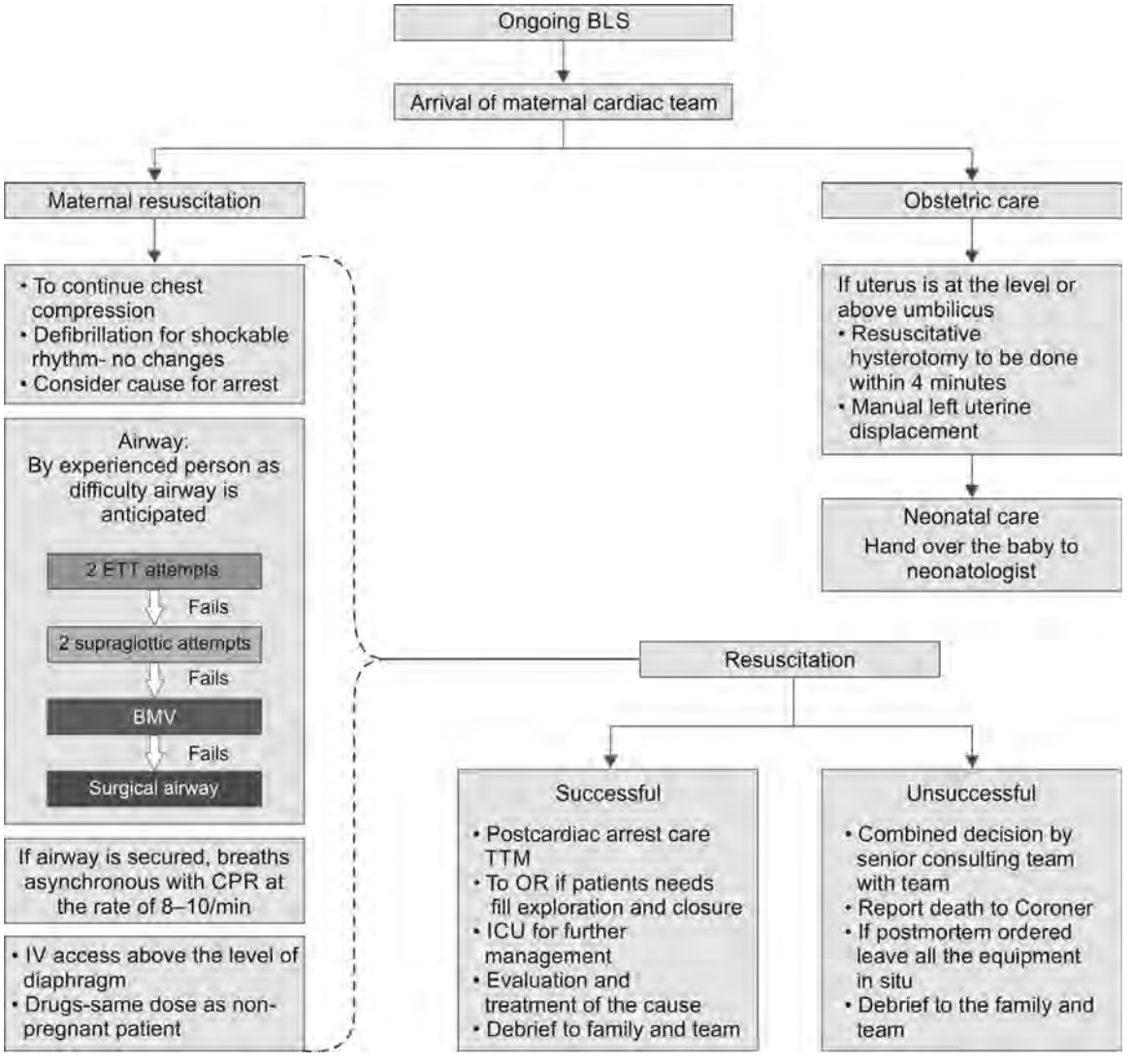

Maternal collapse
Scene safety
Shout for help
(Needs minimum of 4 persons)
Check for response and signs of life
No
Yes
Call maternal arrest code
Start good quality CPR
Attach AED and follow the instructions
Continue CPR
Continue BLS till maternal cardiac arrest team arrives
• Left uterine displacement
• Assess by ABCDE approach
• Oxygen if needed
• IV access above the level of diaphragm
• Call obstetrician
CPR in pregnancy
• Place the patient supine on the firm surface
• Hands on the center of the chest
• 30:2 ratio (compression: rescue breaths)
• Compress at rate of 100/min and least 5 cm
• Minimize interruption
• Allow recoil of chest in-between compression

(ABCDE: airway, breathing, circulation, disability, and exposure; AED: automated external defibrillator; BLS: basic life support; CPR: cardiopulmonary resuscitation; IV: intravenous)

FLOWCHART 1: Basic life support algorithm for pregnant.



FIGS. 1A AND B: (A) Left Uterine displacement, one hand technique. (B) Two hand technique (More than 20 weeks gestational size or uterus is palpable or visible).


Ongoing BLS
Arrival of maternal cardiac team
Maternal resuscitation
Obstetric care
• To continue chest compression
• Defibrillation for shockable rhythm- no changes
• Consider cause for arrest
If uterus is at the level or above umbilicus
• Resuscitative hysterotomy to be done within 4 minutes
• Manual left uterine displacement
Neonatal care
Hand over the baby to neonatologist
Airway:
By experienced person as difficulty airway is anticipated
2 ETT attempts
Fails
2 supraglottic attempts
Fails
BMV
Fails
Surgical airway
Resuscitation
If airway is secured, breaths asynchronous with CPR at the rate of 8–10/min
• IV access above the level of diaphragm
• Drugs-same dose as non-pregnant patient
Successful
• Postcardiac arrest care TTM
• To OR if patients needs fill exploration and closure
• ICU for further management
• Evaluation and treatment of the cause
• Debrief to family and team
Unsuccessful
• Combined decision by senior consulting team with team
• Report death to Coroner
• If postmortem ordered leave all the equipment in situ
• Debrief to the family and team

(BLS: basic life support; BMV; bag mask ventilation; CPR: cardiopulmonary resuscitation; ETT: endotracheal tube; ICU: intensive care unit; IV: intravenous; OR: operating room; TTM: targeted temperature management)

FLOWCHART 2: Advanced life support (ALS) for pregnant.

As maternal cardiac arrest involves adult resuscitation, obstetric care and neonatal resuscitation, team leader for each should be allocated. Overall a team leader for the cardiac arrest should communicate with all the team leaders.

Airway: Maternal cardiac arrest is one of the situations in adult resuscitation which requires definitive airway at the earliest by an experienced person. Alternate measures if definitive airway fails, surgical airway should be followed.

Breathing: BMV connected to 15 L oxygen.

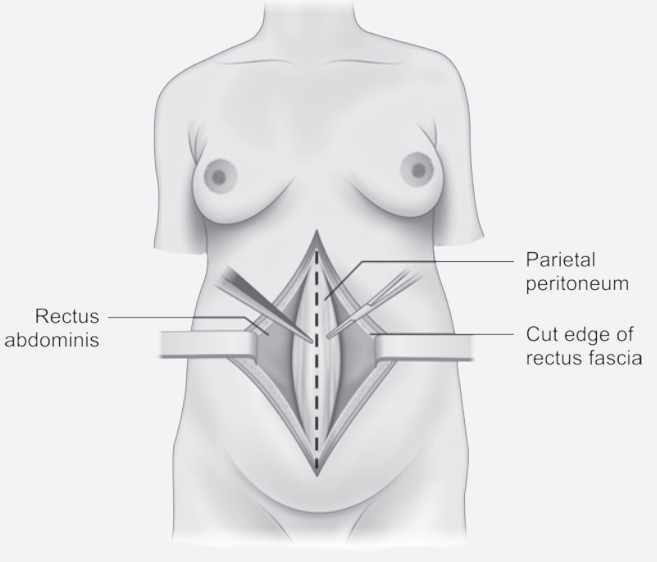
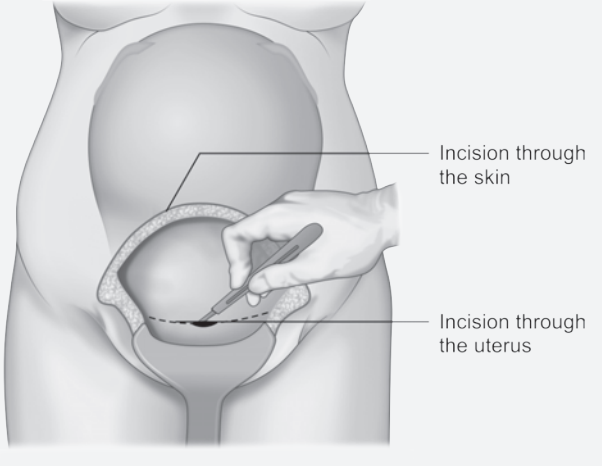
Circulation: IV access above diaphragm.

Defibrillation and drugs: Standard resuscitative guidelines should be followed as there are no modifications. Reversible causes for the cardiac arrest should be considered.

Resuscitative Hysterotomy

It is also called as perimortem cesarean delivery (PMCD) (**Table 3**). It is usually done in patients who are >20 weeks pregnant or uterus is above the level of umbilicus. During maternal cardiac arrest, if ROSC is not obtained within 4 minutes, it is necessary to deliver the baby as this relieves the occlusion of inferior vena cava (IVC) by the uterus and thereby improving the cardiac output. Delivery also improves the thoracic wall compliance and this improves CPR effectiveness. It is preferred to do it in the place where the maternal resuscitation is carried out. Shifting the patient to the operating room (OR) will cause delay in all the crucial resuscitations. It can be carried out with a scalpel and scissor as waiting for the surgical equipment will cause unnecessary delay.

TABLE 3: Resuscitative hysterectomy.

Recommended equipment	***Steps of resuscitative hysterotomy***
• Sterile gloves • Fixed blade scalpel • Sterile scissors • Umbilical cord clamps • Antiseptic	• With continuing maternal resuscitation and manual left uterine displacement, if antiseptic solution is available, pour over the abdomen • Make an incision over the abdomen—vertical incision (preferred over Pfannenstiel) from xiphisternum to pubic symphysis as it allows more space for visualization • Incision from skin to peritoneum • Make vertical incision over the uterus from fundus to lower segment of uterus • Stretch the uterine incision through fingers to allow the easy access to the delivery • Deliver the baby after cutting the cord between the two umbilical clamps. Hand over the baby to neonatologist • Deliver the placenta • Uterus to be closed in layers followed by closure of abdomen as done in regular manner • Oxytocin and antibiotics can be considered • Foley's catheter can be placed
Incisions	
	
	

MANAGEMENT AFTER RESUSCITATIVE HYSTEROTOMY

It depends on the outcome of resuscitation. If ROSC obtained after resuscitative hysterotomy, the patient should be managed in the ICU unless an operation is need. In that situation, patient has to be shifted to OR for full exploration and closure. Target temperature management has to be maintained along with other standard ICU care. Cause of arrest should be evaluated and treated. If the resuscitation is unsuccessful, a combined decision to be made by the senior consulting team in liaison with the team leader. This should be informed to the coroner and if postmortem is required all the equipment should be left in situ. If the abdomen is open with uterus and placenta in situ, it should be left open and covered with dressing. Team and family debriefing have to be done irrespective of the outcome. Neonatal resuscitation is beyond the scope of this chapter.

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism (AFE) is one of the rare causes of cardiac arrest in pregnancy. AFE is an obstetric condition characterized by the triad of cardiovascular collapse, hypoxic respiratory failure, and coagulopathy. It is also commonly associated with neurologic symptoms (encephalopathy/coma/seizures) with persistent neurologic deficits in survivors. Low incidence of syndrome is may be due underestimation and diagnosis by exclusion and also due to underreporting. Significant mortality and morbidity is associated with AFE, and emergency physician should be aware about this clinical situation as resuscitation considerations differ slightly from other causes of cardiopulmonary collapse.

Risk Factors

Risk factors associated with increased risk of AFE include advanced maternal age (35 years or older), placental abnormalities (previa, accreta, abruption, and rupture), medical induction of labor, operative deliveries (cesarean delivery, forceps-assisted delivery, vacuum-assisted delivery, and termination of pregnancy), amniocentesis, trauma, eclampsia, cervical lacerations, prolonged gestation, male fetus, and multiple gestations.

Pathogenesis

The traditional theory of developing the AFE start with any stressful factors which causes breach in the physical barriers between mother and fetus, with amniotic fluid entering the maternal circulation, amniotic fluid embolization into the pulmonary vasculature, resulting in mechanical obstruction of pulmonary capillaries, but this is not observed in all cases of AFE nor proven in multiple animal studies.

More recent studies suggest that AFE is similar to abnormal immunologic response with complement activation and release of endogenous proinflammatory mediators. This abnormal host response is similar to those found in anaphylactic shock or endotoxin-mediated septic shock. Some experts use the term "anaphylactoid syndrome of pregnancy" more accurately describes the physiologic diagnosis, although it has not been widely accepted.

Timing and Clinical Presentation

Most of AFE occurs during labor, but can occur during immediate postpartum period till 48 hours postpartum period also.

Cardiovascular Collapse

Pulmonary vasoconstriction, followed by severe pulmonary arterial hypertension and right ventricular (RV) failure (cor pulmonale) is the initial response to hypoxia. Echocardiographic evidence of RV strain and leftward deviation of the intraventricular septum may be present. Hypoxia, acidosis, and hypercapnia if not treated timely may further worsen pulmonary vasoconstriction. Specific treatments for pulmonary hypertension (sildenafil, inhaled nitric oxide, and inhaled or IV prostacyclin) and RV support with inotropes (dobutamine and milrinone) are effective. As a result of RV failure or due direct effect from amniotic fluid or other mediators left ventricular (LV) failure may also occur. LV failure may clinically present as hypotension and pulmonary edema, which can be treated with vasopressors and diuretics, respectively, along with inotropes for increased cardiac contractility.

Hypoxic Respiratory Failure

More than 90% of patient may present as hypoxia which is an early finding. Severe ventilation and perfusion mismatch from the initial embolism and cardiogenic pulmonary edema cause early hypoxia. Later hypoxia may be due to noncardiogenic pulmonary edema from alveolar capillary leakage of a proteinaceous exudative edema containing amniotic fluid debris, consistent with acute respiratory distress syndrome. Encephalopathy and neurologic injuries can also be observed due to hypoxia in survivors. Bradycardia may be observed on fetal monitoring due to hypoxia.

Coagulopathy

Amniotic fluid embolism-induced coagulopathy is most likely multifactorial. Disseminated intravascular coagulation (DIC) is present in 80–85% of cases. Amniotic fluid activates platelet aggregation decreases whole blood clotting time. Extrinsic pathway of the clotting cascade is also get activated by procoagulant components of amniotic fluid (namely tissue factor III), leading to a consumptive coagulopathy. Hemorrhage caused by DIC may be manifested by bleeding from venipuncture or surgical sites, and vaginal bleeding with concomitant uterine atony.

Diagnosis

Amniotic fluid embolism represents a clinical syndrome; there are no clear diagnostic laboratory markers. Diagnosis is by exclusion rather than being based on histopathologic examination. Tests such as a complete blood count, coagulation, and cardiac biomarkers are nonspecific. Laboratory manifestations of DIC (such as prolonged prothrombin and partial thromboplastin times, and decreased fibrinogen levels) may be present. Chest radiographs reveal nonspecific findings such as diffuse bilateral opacities. Evidence of RV strain and leftward deviation of the intraventricular septum can be noted on echocardiogram examination. Differential diagnoses

to consider include puerperal sepsis, thromboembolic pulmonary embolism, air embolism, aspiration pneumonitis, myocardial infarction, and eclampsia.

Management

Patient should be treated in ICU, treatment is supportive and should include multidisciplinary team including maternal-fetal medicine, critical care, anesthesia, and respiratory therapy. Critical care management is focused on hemodynamic support (mechanical ventilation, vasopressors, and inotropes). Avoid excessive crystalloid fluid administration. In the case of cardiac arrest, a presumptive diagnosis of AFE standard high-quality CPR with advanced cardiovascular life support (ACLS) protocols should continue. Both medical and surgical management may be required in AFE coagulopathy. Medical management includes transfusion strategies to maintain a platelet count >50,000/mm^3, a normal activated partial thromboplastin time and international normalized ratio, and a fibrinogen level >200 mg/dL. Early and aggressive transfusion, including activation of a massive transfusion protocol (hemostatic resuscitation in a 1:1:1 ratio) in severe hemorrhage could improve outcomes. Other pharmacologic therapies such as recombinant factor VIIa, fibrinogen concentrates, tranexamic acid, and prothrombin complex concentrates can also be considered. Massive crystalloid resuscitation may result in a dilutional coagulopathy and increased intravascular hydrostatic pressures, which could worsen bleeding.

Mortality and Outcome

Multiorgan failure, massive hemorrhage, and cardiac arrest are the main causes of death.

SUMMARY

Resuscitation of the pregnant patient presents unique challenges. Being knowledgeable about maternal physiologic changes and the distinctive underlying etiology of cardiac arrest in pregnancy is essential in providing high-quality and potentially lifesaving care for both mother and fetus. Maternal resuscitation needs teamwork among adult resuscitation team, cesarean delivery of the fetus, and neonatal resuscitation within 5 minutes. Simulation training and drills can help in improving the teamwork, communication, and belief in managing the maternal cardiac arrest and resuscitative hysterotomy.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Pediatric and Neonatal Transport

Trevor L Tredway

INTRODUCTION

Of the several hundred million emergency department (ED) visits across the United States (US), about 20% of those involve pediatric patients. A great majority of the seriously ill or injured pediatric patients are treated at EDs in community hospitals. When the medical care and/or resources for the patient exceeds what is available at these community hospitals that necessitates transfer to a higher level of care. These situations have helped lead to the development of pediatric and neonatal transport medicine. As more children undergo interfacility transport, it is important to understand the basic concepts of pediatric and neonatal transport.

REFERRING AND RECEIVING HOSPITAL RESPONSIBILITIES

The federal government established the Emergency Medical Treatment and Labor Act (EMTALA) in the Consolidated Omnibus Budget Reconciliation Act (COBRA) of 1985. EMTALA states that every hospital must examine, treat, and stabilize anyone presenting to the ED for medical care. After the medical screening is completed, it may be determined that the patient requires care that exceeds the hospital's existing capabilities. At this time, they can make the decision to transfer the patient to a higher level of care. This decision to transfer cannot be based on the patient's ability to pay and must be within the hospital's own guidelines as well as state and federal regulations.

The referring hospital is responsible for contacting the receiving hospital to arrange the transfer. This initial contact should occur as early as possible in the case. The referring hospital needs to discuss with the family the reason for the transfer and should obtain verbal consent that they are in agreement with the transfer. All appropriate forms, records, labs, and imaging should also be transferred with the patient to comply with EMTALA regulations. The best practice is for these referring hospitals to have established policies and agreements with the receiving hospitals.

The EMTALA also states that any hospital cannot refuse to accept appropriately transferred patients when they have the capacity to treat and manage the patient. Most tertiary care pediatric hospitals have existing policies and procedures to expedite transfers from referring hospitals. In addition, a majority of tertiary care pediatric hospitals have their own pediatric and neonatal transport teams in-house.

CRITERIA FOR TRANSFER

It is up to the referring facility to determine which pediatric or neonatal patient must be transferred to a higher level of care. Again this is most commonly when the patient's needs have exceeded the medical care and resources for their facility. Below is a list of common situations that would require transfer (**Box 1**).

MODE OF TRANSPORT

The mode of transport for the patient should be determined in the communication between the referring and receiving facilities. The mode of transportation should take in account the condition of the patient and their risk for deterioration, the distance between facilities, the weather conditions, and the cost. Air transport of a stable patient a short distance is likely

BOX 1: Criteria for transfer.

- Status post cardiopulmonary arrest
- Respiratory distress or failure
- Depressed or deteriorating neurologic exam or status
- Shock that is not responding adequately to treatment
- Serious cardiac rhythm disturbances leading to inadequate perfusion
- Children with severe electrolyte or metabolic disturbances (i.e., DKA)
- Children with life threatening ingestion or exposure to toxic substances
- Children that have sustained major traumatic injuries leading to circulatory, respiratory, or neurologic compromise

(DKA: diabetic ketoacidosis)

not necessary or cost effective. The main modes of transport are ground ambulance, rotor-wing aircraft (helicopter), or fixed-wing aircraft.

Ground ambulance is the most often used mode of pediatric and neonatal transport. The major advantages to this mode are that it provides a stable working space for the transport team and it is relatively safe in most weather conditions. The major disadvantage to ground ambulance is the speed at which the patient can be brought from the referring hospital to the receiving hospital. If the distance between the two facilities is large, it may take several hours to transport the patient via ground. For a patient that is critically ill or injured a long transfer between facilities may increase their risk of morbidity or mortality.

Over the past several years, rotor-wing transport has become a more popular way to transport patients to the ED. This includes transfers from referring facilities as well as patients brought directly from accident scenes. Rotor-wing ambulances have the main advantage of providing an expeditious transport of the most critically ill or injured patients. However, this mode is limited significantly by weather conditions. This includes the weather near both facilities in addition to the weather at the time of departure and the time of the return trip. The safety of the aircrew and the transport team takes priority when determining whether this mode of transport can be used.

Fixed-wing transport of patients is less commonly used and mainly for those patients that are being transferred between facilities that are very long distances apart. This mode of transportation requires the availability of an airport for landing in addition to ground transportation to and from the hospitals. Thus, fixed-wing transport carries additional costs compared to ground ambulance or rotor-wing aircraft.

TRANSPORT TEAM

Together with determining the mode of transport, the type of team to transport the patient should be discussed between the referring and receiving facilities. These teams may be basic life support (BLS), advanced life support (ALS), or specialized pediatric and neonatal transport teams. All involved in this discussion should have adequate knowledge of the capabilities of the particular teams in terms of pediatric equipment as well as procedural skills.

The advances in interfacility transport of pediatric patients have led to the development of specialized teams. These specialized teams are designed to safely and effectively transport and render care to patients. The specialized teams are usually staffed by dedicated pediatric critical care nurses and respiratory therapists or paramedics. All team members undergo education and training in pediatric and neonatal ALS. It is the responsibility of the medical director for the transport team to confirm all transport team personnel have received appropriate training and are maintaining their procedural skills.

Depending on the needs during the transport of the patient an emergency medicine or critical care physician can be added to the team. These specialized teams are able to bring advance pediatric care to the patient rapidly and provide continuous care during the transport to the receiving facility. Transport team members have to be able to communicate well with their medical control and must be able to work in highly stressful situations. It has been shown that transport between facilities by specialized pediatric and neonatal transport teams were associated with improved outcomes including survival rates as well as fewer unplanned events during the transport.

PATIENT MONITORING AND CARE

Current technology allows most pediatric and neonatal transport teams to provide hospital-based monitoring. Standard monitoring of the patient during transport includes continuous monitoring of heart rate, respiratory rate, pulse oximetry, and blood pressure. Additionally, most teams also provide continuous monitoring of end-tidal CO_2. Certain aspects of patient monitoring may be determined by the patient's underlying condition and/or their status during transport.

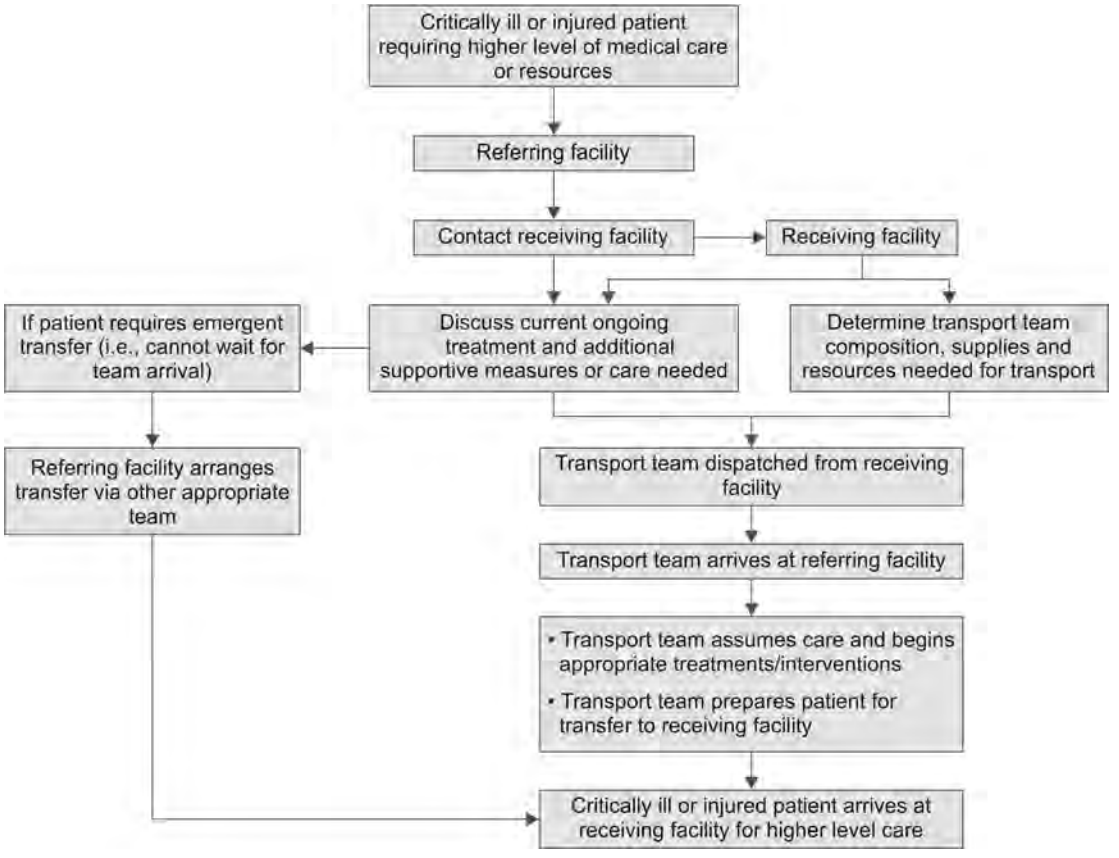
Newborns and neonates provide a unique situation for transport between facilities. In these situations, it is extremely important to maintain the body temperature of the infant during the transport. Therefore, many of these transports take place with specialized teams and the use of transport incubators. The transport incubator with its portable power supply functions like an incubator in the ICU and allows the transport team to have a limited temperature gradient within small environment.

During transport of a patient the teams should be able to provide appropriate specialized critical care treatment and interventions. Teams must have the essential medical equipment, medical devices, and medications immediately available and accessible to them during the transport of the ill or injured patient. Since many hospitals do not own or operate their own ambulances or aircraft, all of the above items need to be easily portable and checked prior to departure for the transport.

The teams need to be able to manage the airway, provide sedation, manage shock, and provide resuscitative efforts if required. Much of the care is determined by the patient's underlying condition along with their current clinical status. Point of care laboratory monitoring is also important during transport between facilities. Laboratory values such as serum glucose, serum electrolytes, hemoglobin, hematocrit, and blood gas measurements are necessary during long transports. Since many of these patients are critically ill or injured continuous and accurate monitoring is required as their clinical status can change rapidly.

SUMMARY

The transfer of children between facilities requires the team to provide continuous stabilization and care throughout. This is different from most emergency medical service (EMS) providers who routinely transport patients from the medical scene to the hospital. The ultimate goal is to bring ED/intensive care unit (ICU) care to the patient sooner. With the appropriate knowledge, preparation, and skills, the interfacility transfer (**Flowchart 1**) of critically ill or injured pediatric or neonatal patients can take place safely and expeditiously to attain improved outcomes.


Critically ill or injured patient requiring higher level of medical care or resources
Referring facility
Contact receiving facility
Receiving facility
If patient requires emergent transfer (i.e., cannot wait for team arrival)
Discuss current ongoing treatment and additional supportive measures or care needed
Determine transport team composition, supplies and resources needed for transport
Referring facility arranges transfer via other appropriate team
Transport team dispatched from receiving facility
Transport team arrives at referring facility
• Transport team assumes care and begins appropriate treatments/interventions
• Transport team prepares patient for transfer to receiving facility
Critically ill or injured patient arrives at receiving facility for higher level care

FLOWCHART 1: Pediatric and neonatal interfacility transport.

MULTIPLE CHOICE QUESTIONS

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161 CHAPTER

Pediatric Resuscitation

Mohammad Anzal Rehman, Thiagrajan Jaiganesh

INTRODUCTION

Across the world, 6.2 million children under 15 years of age lost their lives in 2018. While this represents a relative decline from previous years (14.2 million in 1990), pediatric mortality remains considerably high, with many deaths still occurring due to preventable causes.

In the United States alone, approximately 20% (28 million of a total of 139 million) of all emergency department visits in 2017 comprised patients aged under 15. Therefore, emergency physicians around the world as frontline healthcare providers have to be proficient in identifying, assessing, and managing critically ill children.

SYSTEMATIC APPROACH TO THE CRITICALLY ILL CHILD

Initial Assessment and Evaluation of the Sick Child

Children are unique. Triage parameters ordinarily implemented for adults may not appropriately gauge the severity of the disease due to their continually evolving anatomy and physiology. Signs and symptoms could be subtle and could easily mask an impending deterioration. Vital signs could be falsely reassuring, and an over-reliance could result in an untoward outcome.

In 2000, the American Academy of Pediatrics (AAP) introduced a unique method of evaluating the pediatric patient: the pediatric assessment triangle (PAT) (**Fig. 1**). The three elements of the triangle: (1) Appearance, (2) Work of breathing, and (3) Circulation, can be used to reliably identify the "sick" child with underlying states of shock and cardiopulmonary compromise.

Assessing PAT could be carried out from a distance without upsetting the child, potentially eliminating the difficulties and confounders associated with examining a crying, fidgety child.

- *Appearance*: Inspect the child's appearance and evaluate the level of consciousness by assessing *T*one, *I*nteractiveness, *C*onsolability, *L*ook/gaze, and *S*peech/cry *(TICLS)*.
- *Work of breathing*: Observe for audible breath sounds (stridor and wheezing), positioning (e.g., sniffing or tripod position can indicate respiratory distress), retractions, breathing patterns, and rate.
- *Circulation*: Assess the child's perfusion status by checking skin color (pallor, mottling, and cyanosis), surface temperature and any signs of bruising or bleeding.

Any abnormality noted in one or more segments of the PAT necessitates immediate action and intervention. If, however, no significant abnormalities are found in the initial impression, subsequent triage, and evaluation should attempt to obtain the following vital sign measurements alongside initiation of the primary survey:

- Respiratory rate
- Blood pressure
- Heart rate
- Temperature
- With the possible inclusion of:
  - Pulse oximetry
  - Point-of-care blood glucose, particularly in children with altered level of consciousness

PRIMARY SURVEY

Proceed with primary survey in children when there is no obvious life-threatening condition on initial impression. The primary survey is designed as a sequential airway, breathing,

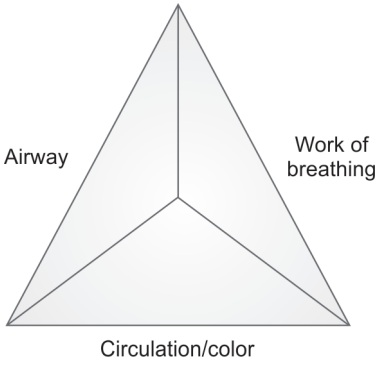
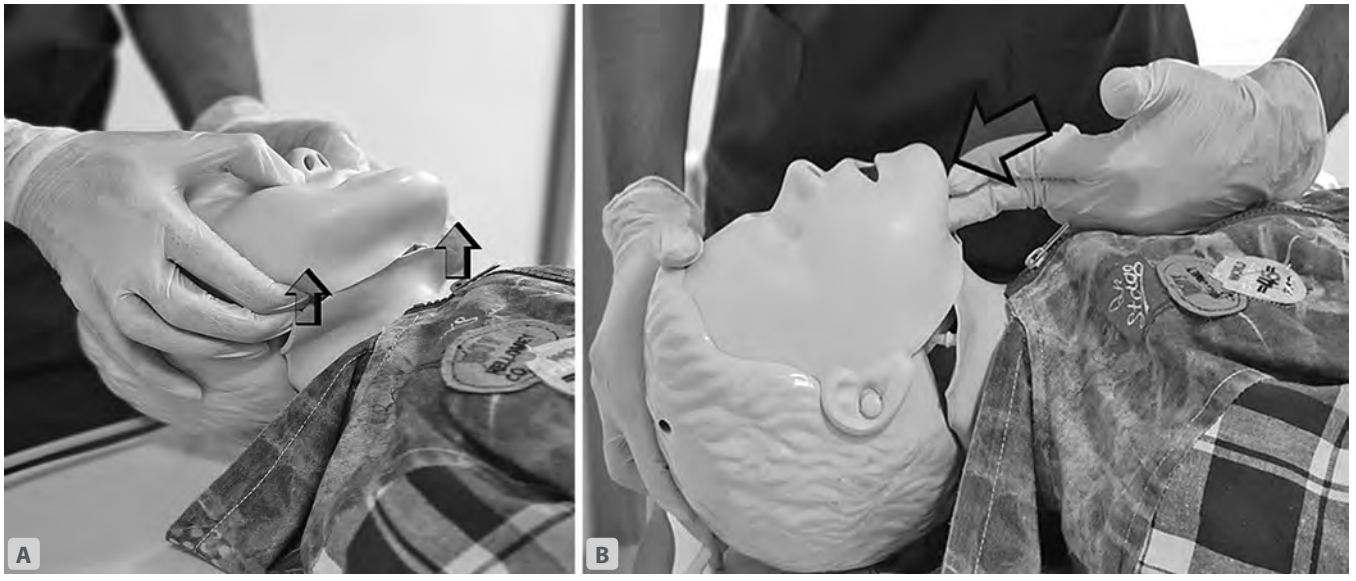


FIG. 1: Pediatric assessment triangle (PAT).



FIGS. 2A AND B: (A) Jaw thrust; (B) head tilt–chin lift.

circulation, disability, and exposure (ABCDE) approach to assessment and evaluation. Note that the correction of any abnormalities identified during the primary survey takes priority over the completion of the survey and/or vital signs measurement.

Airway

Evaluation of the airway primarily revolves around the assessment of its patency. To determine if the airway is patent (open):

- Observe for chest rise or abdominal breathing
- Listen or feel near the mouth and nose for breath sounds or air movement
- Assess for signs of upper airway obstruction such as hoarseness or stridor

If you determine that the patient is not breathing or is gasping, continue with pulse check and proceed with pediatric advanced life support (PALS) protocols for respiratory/cardiac arrest.

If you find signs suggestive of upper airway obstruction, such as increased respiratory effort, retractions, interspersed periods of apnea, abnormal sounds such as snoring or stridor, you may open and maintain the airway using the following interventions:

Simple Measures

- Positioning—a responsive child is made more comfortable with the elevation of the bed. **Figures 2A** and **B** depict the opening of the airway of an unresponsive child, either using the head tilt–chin lift or jaw thrust maneuvers (use this if a cervical injury is suspected). During these maneuvers, apply pressure only on bony prominences as depicted and not on soft tissues. Alternatively, the unconscious child can be turned to their side to aid the airway opening. Assess the effectiveness of any airway maneuver that has been carried out.
- Use appropriately sized airway adjuncts such as oropharyngeal and nasopharyngeal airways to maintain patency. Blood and or vomitus (noisy, gurgling respiratory effort) can be suctioned off under direct vision using a Yankauer catheter to restore airway patency. If a foreign body is suspected as the cause of obstruction, the same can be removed using McGill's forceps and direct laryngoscopy.
- *Foreign body obstruction*: Children <1 year of age can be given five back slaps alternating with five chest thrusts to relieve the obstruction (**Flowchart 1**). In comparison, children >1 year can be given abdominal thrusts (**Flowchart 2**). In the case of an unresponsive patient, proceed with the initiation of the emergency response system, and start basic life support.

Advanced Measures

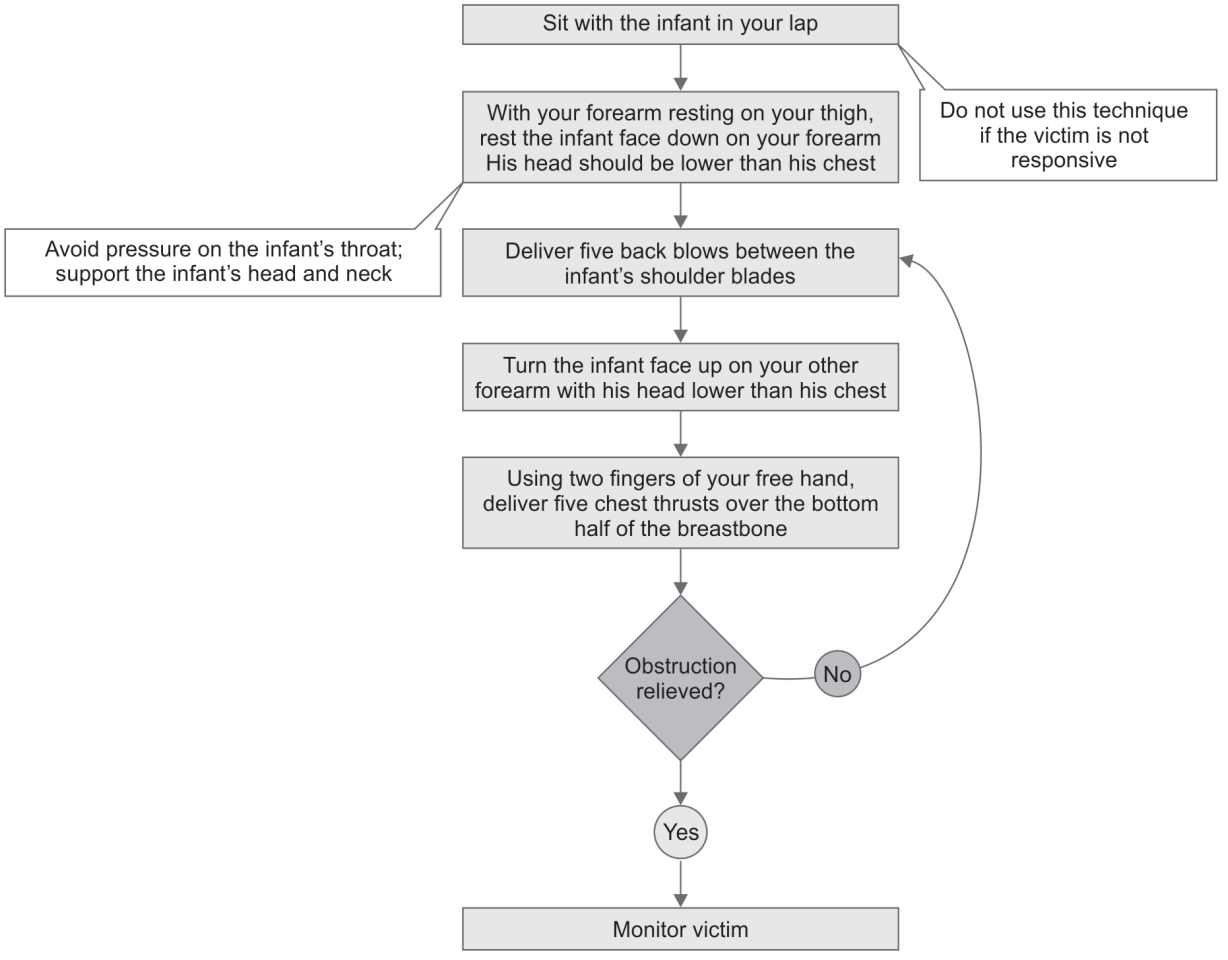
Advanced airway management techniques may be required if the child is unable to protect their own airway and or there is a risk of aspiration. These involve the insertion of an advanced airway devices, such as a laryngeal mask airway or endotracheal intubation and cricothyrotomy and require expertise.

Several anatomic and physiologic differences come into play with the pediatric airway, particularly in the first 2 years of life, compared with conventional variables in an adult airway. These unique characteristics include a large occiput, head, tongue, tonsils, adenoids and stomach, more anterior airway, narrow subglottic region, and small cricothyroid membrane, creating potential challenges during airway management, such as difficulties with positioning, obstruction, vocal cord visualization, and bleeding risk.

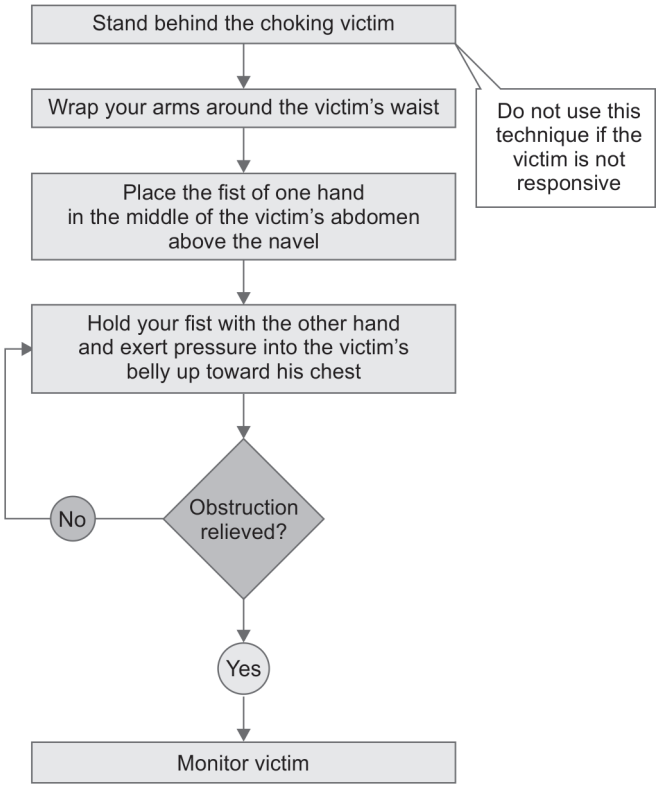
Breathing

Consider the following components during the assessment of breathing in the pediatric patient:

- Respiratory rate and pattern (normal respiratory rate differs with age)—irregular patterns, fast (tachypnea), slow (bradypnea), or absent respiration (apnea) indicates underlying abnormality and may even signal impending arrest. **Table 1** shows the normal resting respiratory rate for different age groups.
- Increase in respiratory effort—nasal flaring, retractions, head bobbing, or "seesaw respirations" (chest and abdomen


Sit with the infant in your lap
Do not use this technique if the victim is not responsive
With your forearm resting on your thigh, rest the infant face down on your forearm His head should be lower than his chest
Avoid pressure on the infant's throat; support the infant's head and neck
Deliver five back blows between the infant's shoulder blades
Turn the infant face up on your other forearm with his head lower than his chest
Using two fingers of your free hand, deliver five chest thrusts over the bottom half of the breastbone
Obstruction relieved?
No
Yes
Monitor victim

FLOWCHART 1: Infant choking algorithm.


Stand behind the choking victim
Do not use this technique if the victim is not responsive
Wrap your arms around the victim's waist
Place the fist of one hand in the middle of the victim's abdomen above the navel
Hold your fist with the other hand and exert pressure into the victim's belly up toward his chest
Obstruction relieved?
No
Yes
Monitor victim

FLOWCHART 2: Child choking algorithm.

TABLE 1: Normal resting respiratory rate.

Age range	*Normal respiratory rate*
0–12 months	30–60/min
1–3 years	24–40/min
4–5 years	22–34/min
6–12 years	18–30/min
13–18 years	12–16/min

move with inverse proportion during respiration), all of which could imply underlying issues with airway resistance, obstruction or lung compliance.

- Chest expansion and air movement—check for asymmetric chest rise and listen for any sounds of abnormal air entry, such as inspiratory stridor (suggestive of tracheal or laryngeal airway obstruction), expiratory wheezing (suggestive of lower airway obstruction), crackles, or grunting (expiration against a partially closed glottis).
- Central cyanosis is a late sign and occurs when oxygen saturations are below 70%.
- Pulse oximetry may be incorporated here to assess oxygen saturation and guide administration of supplemental oxygen, with care taken to interpret readings in conjunction with your assessment as well as clinical signs and symptoms of the patient.

- CO_2 monitors help to identify hypercapnia which could result in drowsiness or unconsciousness. They help monitor both ventilation and confirm endotracheal tube placement.

Circulation

The approach to assessing circulation involves the evaluation of the following parameters:

- *Heart rate, rhythm, and pulse*: The management of abnormal (tachycardia and bradycardia) or absent pulse (cardiac arrest) is discussed in more detail later in this chapter. Briefly, a central pulse should ideally be assessed. In infants, feel for the brachial artery and in older children feel for the carotid or femoral pulse. Tachycardia can be a sign of pain, respiratory distress, infection, or shock. Bradycardia is often a late sign of shock and suggestive of a preterminal state. **Table 2** depicts the normal heart rate for different age groups. In the absence of a palpable pulse, or a rate of <60 beats/min, chest compressions should be started immediately. This assessment should take no longer than 10 seconds.
- *Central capillary refill time*: Checked over the sternum and normal is <2 seconds.
- *Skin color and temperature*: A change in color (pallor, mottling, and cyanosis) with or without changes in surface temperature can indicate problems with perfusion.
- The blood pressure may be incorporated here, with care taken to reference normal variances with age, usually to check for hypotension, which is an important marker for shock or impending arrest.

TABLE 2: Normal heart rate.

Age range	*Normal heart rate*
0–3 months	80–205/min
4 months–2 years	75–190/min
2–10 years	60–140/min
Over 10 years	50–100/min

TABLE 3: Glasgow coma scale (GCS)—total score/15.

Motor response (best) Score/6	• Spontaneous movement, obeys commands—6 • Localizes pain—5 • Withdraws from pain—4 • Flexion with pain (decorticate) —3 • Extension with pain (decerebrate) —2 • No motor response—1
Verbal response (best) Score/5	• Oriented—5 • Confused—4 • Inappropriate words—3 • Incomprehensible sounds—2 • No verbal output—1
Eye opening score/4	• Spontaneous eye opening—4 • Opens to speech—3 • Opens to pain—2 • No eye opening—1

Disability

This component of the primary survey integrates a rapid assessment of the child's level of consciousness and responsiveness, indirectly correlating with cerebral perfusion and neurologic status.

Two popular methods of pediatric rating level of consciousness are the AVPU (alert, voice, painful, and unresponsive). Response scale and the more widely used Glasgow coma scale (GCS) (**Table 3**).

In addition to the above, pupillary assessment and response to light can provide information regarding brainstem function. Very dilated or pinpoint pupils with sluggish reactions are suggestive of a possible overdose of benzodiazepines or opiates, respectively. Unreactive dilated pupils following trauma may indicate raised intracranial pressure and compression of the ophthalmic nerve. A blood glucose test should be incorporated in this segment to detect and guide management for potential hypoglycemia. Hypoglycemia may present as seizures, while hyperglycemia may present vomiting and malaise or concurrent infection.

Exposure

Finally, all assessments should involve undressing the child to expose and examine the entire body adequately. However, it is crucial to be conscious that children lose heat rapidly due to their high body surface area. Pyrexia and or hypothermia could suggest an infective cause. Petechiae and or purpura could suggest life-threatening bacteremia. Bruising (patterned, multiple areas and stages, particular sites), cigarette burns, etc., could indicate a nonaccidental injury.

Upon completion of the primary survey and when all life-threatening conditions have been addressed, proceed to secondary assessment.

SECONDARY SURVEY

Once a primary assessment is complete, with the child not requiring any immediate action or intervention, evaluation should proceed to the secondary survey, which includes a focused history and physical examination. We are emphasizing repeated assessments for any changes in clinical status during the examination.

Focused history: *SAMPLE mnemonic*:

- *S*igns and symptoms at onset of condition (e.g., dyspnea, fever, and vomiting)
- *A*llergies to food and/or drugs
- *M*edications taken regularly at home and/or accessible to child, including last dose of known medication
- *P*ast medical history—Overview of comorbid conditions, past surgeries, underlying health issues, and immunization status
- *L*ast meal consumed, with time elapsed since up to presentation
- *E*vents leading up to current illness

Focused Physical Examination

Based on the patient's clinical signs and presumed cause of illness, the physician should attempt to focus his examination primarily to areas of suspected dysfunction or injury (e.g., a patient that is in respiratory distress should have an

FIG. 3: Broselow—length-based resuscitation tape.

examination focused around the chest and upper airway, including heart and breath sounds).

Adjuncts to Initial Assessment

Various tools can help provide specific information alongside an evaluation of the critically ill pediatric patient, so long as they do not interfere with or delay emergent intervention. These include, but are not limited to, the following: electrocardiograms (ECG), chest X-rays (CXR), arterial or venous blood gases (A/VBG).

The majority of critically ill children present with conditions that do not allow for conventional measurement of body weight. Therefore, it is recommended to utilize the length-based resuscitation (Broselow tape) (**Fig. 3**) to guide the selection of appropriate medication dosage and equipment size.

PEDIATRIC SHOCK—IDENTIFICATION AND MANAGEMENT

"Shock" is a life-threatening physiologic mismatch between oxygen or nutrient delivery and metabolic demand. Failure to meet cellular demand is usually a consequence of hypoxemia or hypoperfusion. It results in decreased energy production with a concomitant increase in lactic acid, disruption of cellular biochemical pathways, and, eventually, cell death.

Shock is a major worldwide contributor to morbidity and mortality in children, especially those under 5 years of age. In the developing countries, shock most commonly results from sepsis or hypovolemia and is complicated by a significantly higher mortality rate than children who present without shock.

In compensated shock, the body physiologic response allows for the maintenance of end-organ function and normal blood pressure. In uncompensated shock, inadequate tissue perfusion leads to hypotension and end-organ decline. If left untreated, this can progress to organ failure, cardiovascular collapse, and death.

Classification of Shock

Shock can be broadly classified into two categories—(1) distributive and (2) resistive. The major classes of shock are outlined below:

- *Hypovolemic shock* occurs when there is a significant decrease in intravascular blood volume. The two leading causes of reduced blood volume are—intravascular volume loss such as from gastrointestinal (e.g., vomiting and diarrhea secondary to gastroenteritis), skin (e.g., burns), or interstitial (third-spacing) causes. Hemorrhage—from traumatic or nontraumatic bleeding.
- *Distributive shock*: Four major causes of distributive shock are:
  i. Neurogenic shock—neurologic injury resulting in dysfunction of the sympathetic chain of the autonomic nervous system. A consequent parasympathetic-mediated peripheral vasodilation leads to hypotension. Classically, a neurogenic shock is associated with bradycardia and hypotension.
  ii. Anaphylactic shock—mast cell degranulation secondary to allergic trigger causes the release of vasodilatory cytokines
  iii. Drug-induced shock—secondary to vasodilatory effects (e.g., calcium channel blockers) or toxicity (e.g., cyanide toxicity)
  iv. Septic shock—secondary to the severe infectious state. Systemic inflammatory response, immune dysregulation, circulatory compromise, and end-organ deterioration results thereof.
- *Cardiogenic shock* is the inability of the heart to maintain sufficient cardiac output. Pediatric heart failure is often secondary to congenital disease or myocarditis.
- *Obstructive shock* refers to an impedance of blood flow in either the pulmonary or systemic circuit that results in reduced cardiac function. Examples, pericardial tamponade, tension pneumothorax, massive pulmonary embolism, cardiomyopathies, and congenital cardiac defects with outflow tract obstruction.

Recognition of Pediatric Shock

Prompt recognition and early treatment of shock are crucial in children as early intervention is associated with improved outcomes. Children often compensate for shock by increasing heart rate and systemic vascular resistance (delayed capillary refill time) to redirect blood flow toward vital organs.

Point-of-care ultrasonography (PoCUS) can augment the assessment of a shocked child (volume status, cardiac function, and locations of fluid loss in cases of shock secondary to trauma).

Management of Pediatric Shock

The following sections outline key principles of therapy for pediatric shock. Supplemental oxygen, attach cardiac monitor and pulse oximetry. Gain two large bore IV access.

Fluid Resuscitation

Current guidelines recommend isotonic crystalloid solutions as the initial fluid therapy of choice in pediatric shock treatment. At present, no significant difference exists between the use of lactated Ringer's solution and normal saline. Management should proceed with an initial IV bolus of fluid delivered rapidly (push) at 20 mL/kg, with the dose adjusted to 10 mL/kg when a cardiogenic shock is suspected. Additional boluses are given until the patient's perfusion status improves. Care taken to reassess the patient for signs of volume overload frequently (e.g., crackles on lung auscultation or appearance of B lines in lung ultrasound). Although shock may require fluid

up to 200 mL/kg, the shock that persists at 60 mL/kg of fluid therapy would require vasopressor and airway support in the form of endotracheal intubation to improve oxygen delivery and reduce the work of breathing.

Vasoactive Drugs

Initiate vasoactive medications in children with a fluid-refractory shock through an existing peripheral IV site rather than delay administration pending a central venous line placement. The vasoactive drug of choice varies depending on the clinical presentation. However, in general, initial therapy is recommended as below:

- *Cold shock* represents a shock state with decreased cardiac output and increased systemic vascular resistance. First-line vasoactive treatment is with epinephrine (IV infusion: 0.1–1.0 μg/kg/min), with dopamine as a second-line agent (IV infusion: 2–20 μg/kg/min).
- *Warm shock* is less commonly in children than in adults, is characterized by increased cardiac output and decreased systemic vascular resistance. First-line vasoactive therapy is with norepinephrine (IV/IO: 0.1–2.0 μg/kg/min), with dopamine as a second-line agent.

Antibiotics

When a shock is suspected to be secondary to sepsis, broad-spectrum antibiotics are recommended (as per local antibiotic guidelines) as soon as possible, preferably within the first hour of presentation. In a large, multicenter study of adult patients with sepsis, every hour of delay in antibiotic administration for patients in shock was associated with an increase in absolute mortality of 1.8%.

Steroids

A shock that persists despite fluid and vasoactive therapy could have underlying adrenal insufficiency. The use of stress-dose corticosteroids may prove beneficial. Use IV hydrocortisone in these scenarios, given at 50–100 mg/m^2/day (2–4 mg/kg/day), maximum 200 mg/day.

Endpoints of Resuscitation

Rapid recognition and early interventions in pediatric shock have been associated with significantly improved outcomes. Resuscitation protocols instituted by the American College of Critical Care Medicine (ACCM) and PALS are associated with a profoundly lower mortality rate (8% vs. 38%). Current consensus recommends resuscitation to target therapeutic endpoints as follows:

- Early resuscitation should target microcirculatory goals—correcting intravascular volume, mean arterial pressure (MAP), and cardiac output. Response to resuscitation can be followed to therapeutic endpoints by evaluating lactate levels (< 2 mmol/L), and central venous oxygen saturation ($ScvO_2$) <70%.
- Return to clinical baseline as an endpoint can be supported by using the following parameters: capillary refill <2 seconds, normal urine output, warm extremities, baseline blood pressure, mental status, and character of pulse.
- Clinicians are reminded that limitations exist when using the guidelines mentioned above and parameters. They are meant to guide resuscitative efforts but should not be regarded with a "one-size-fits-all" mindset. Management of pediatric shock is most effective when patients' individualized response to therapy guides it. Occasionally tachy- or bradyarrhythmias in children can result in significant symptoms including resultant shock. **Flowcharts 3** and **4** depict how to tackle symptomatic tachycardia and bradycardia.

CARDIOPULMONARY ARREST

The original pediatric Utsein guidelines of 1995 defined cardiac arrest as the "cessation of cardiac mechanical activity, determined by the inability to palpate a central pulse, unresponsiveness, and apnea." Pediatric arrest has been primarily described to occur as a consequence of progression from respiratory failure and shock (**Fig. 4**), contrasted to adult etiologies being mostly of a cardiac cause. However, recent literature suggests a rising significance and number of arrests secondary to a cardiac cause. Therefore, management of cardiopulmonary arrest is ideally designed to be comprehensive, emphasizing reversible causes, and incorporating interventions that will most likely improve outcomes.

Recognition of Cardiac Arrest

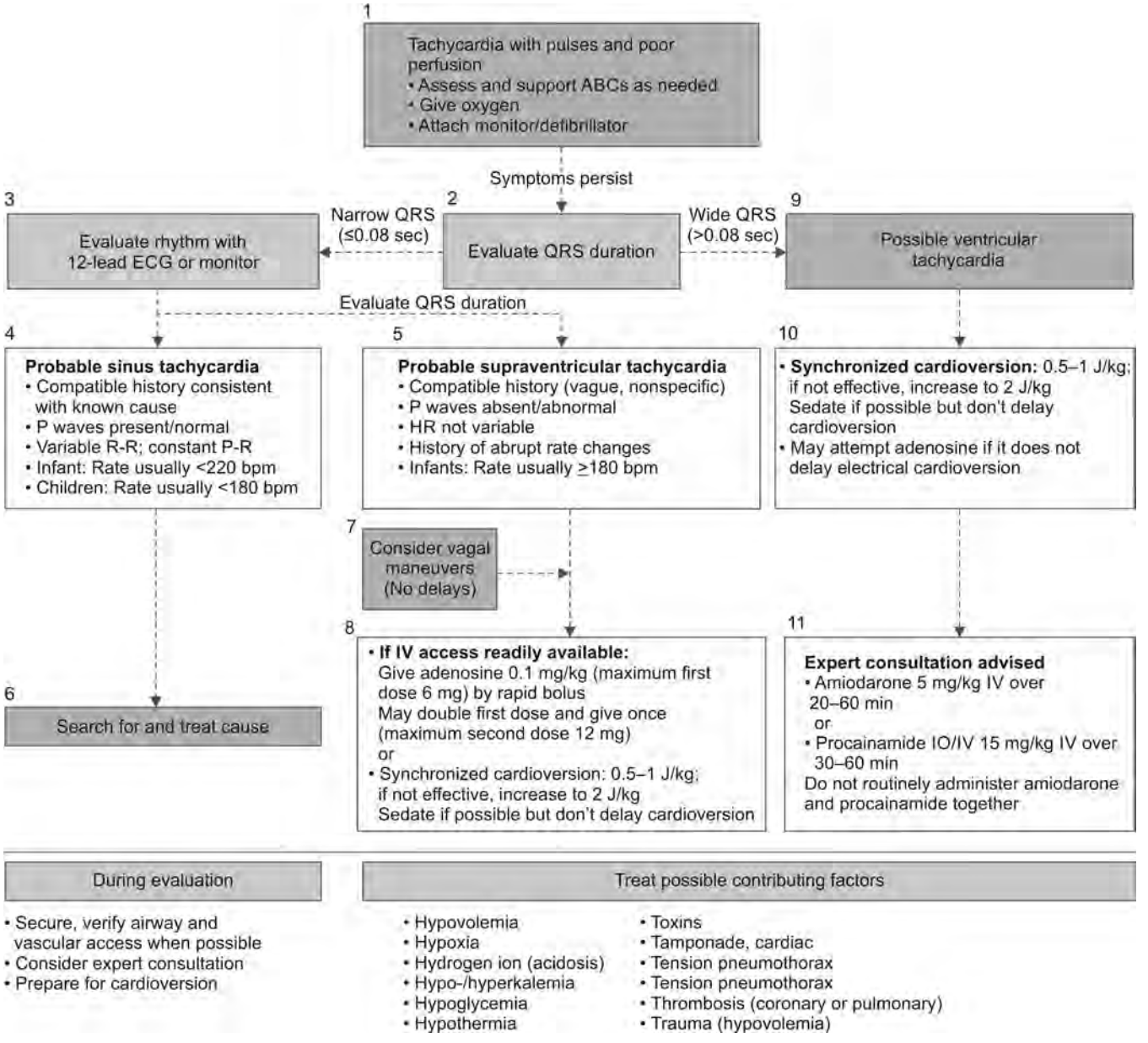
The PALS guidelines recommend assessing the unresponsive pediatric patient by first checking for normal breathing and a pulse. Breathing is ideally assessed by observation for any chest rise for a maximum of 10 seconds while simultaneously palpating for a pulse over the region of the brachial artery for infants and the carotid or femoral artery for children.

- *Respiratory arrest*: If breathing is absent or abnormal (e.g., gasping), but a pulse is present, management consists of providing 12–20 adequate "rescue breaths" per minute (approximately 1 breath every 3–5 sec) over 1 second with visible chest rise. Continue this with a pulse check every 2 minutes to check for progression to cardiac arrest.
- *Cardiac arrest*: Along with absent breathing, if no pulse or a pulse <60 beats/min is palpated, the patient is presumed to be in cardiac arrest, and cardiopulmonary resuscitation (CPR) is initiated after shouting for help and or activating the emergency response system. Start resuscitation using a compressions-airway-breathing (C-A-B) approach, while waiting for the code team to bring the defibrillator.

Compressions

The International Liaison Committee on Resuscitation (ILCOR) and the American Heart Association (AHA) have frequently stipulated the benefits of early, high-quality chest compressions in improving outcomes in cardiopulmonary resuscitation. To ensure compressions result in adequate cardiac output and coronary artery perfusion pressures, most guidelines recommend:

- Minimize interruptions between compressions for ventilation. Give two breaths after 30 compressions (single-rescuer CPR) or 15 compressions (2-person CPR). If possible, do not interrupt CPR for >10 seconds while doing any pulse, rhythm check, or shock delivery (Note: once an advanced airway is in place, chest compressions should be continuous).
- Maintain100–120 compressions per minute


1
Tachycardia with pulses and poor perfusion
• Assess and support ABCs as needed
• Give oxygen
• Attach monitor/defibrillator
Symptoms persist
2
Evaluate QRS duration
Narrow QRS (≤0.08 sec)
Wide QRS (>0.08 sec)
3
Evaluate rhythm with 12-lead ECG or monitor
9
Possible ventricular tachycardia
Evaluate QRS duration
4
Probable sinus tachycardia
• Compatible history consistent with known cause
• P waves present/normal
• Variable R-R; constant P-R
• Infant: Rate usually <220 bpm
• Children: Rate usually <180 bpm
5
Probable supraventricular tachycardia
• Compatible history (vague, nonspecific)
• P waves absent/abnormal
• HR not variable
• History of abrupt rate changes
• Infants: Rate usually ≥180 bpm
10
• Synchronized cardioversion: 0.5–1 J/kg; if not effective, increase to 2 J/kg
Sedate if possible but don't delay cardioversion
• May attempt adenosine if it does not delay electrical cardioversion
7
Consider vagal maneuvers (No delays)
8
• If IV access readily available:
Give adenosine 0.1 mg/kg (maximum first dose 6 mg) by rapid bolus
May double first dose and give once (maximum second dose 12 mg)
or
• Synchronized cardioversion: 0.5–1 J/kg; if not effective, increase to 2 J/kg
Sedate if possible but don't delay cardioversion
11
Expert consultation advised
• Amiodarone 5 mg/kg IV over 20–60 min
or
• Procainamide IO/IV 15 mg/kg IV over 30–60 min
Do not routinely administer amiodarone and procainamide together
6
Search for and treat cause
During evaluation
• Secure, verify airway and vascular access when possible
• Consider expert consultation
• Prepare for cardioversion
Treat possible contributing factors
• Hypovolemia
• Hypoxia
• Hydrogen ion (acidosis)
• Hypo-/hyperkalemia
• Hypoglycemia
• Hypothermia
• Toxins
• Tamponade, cardiac
• Tension pneumothorax
• Tension pneumothorax
• Thrombosis (coronary or pulmonary)
• Trauma (hypovolemia)

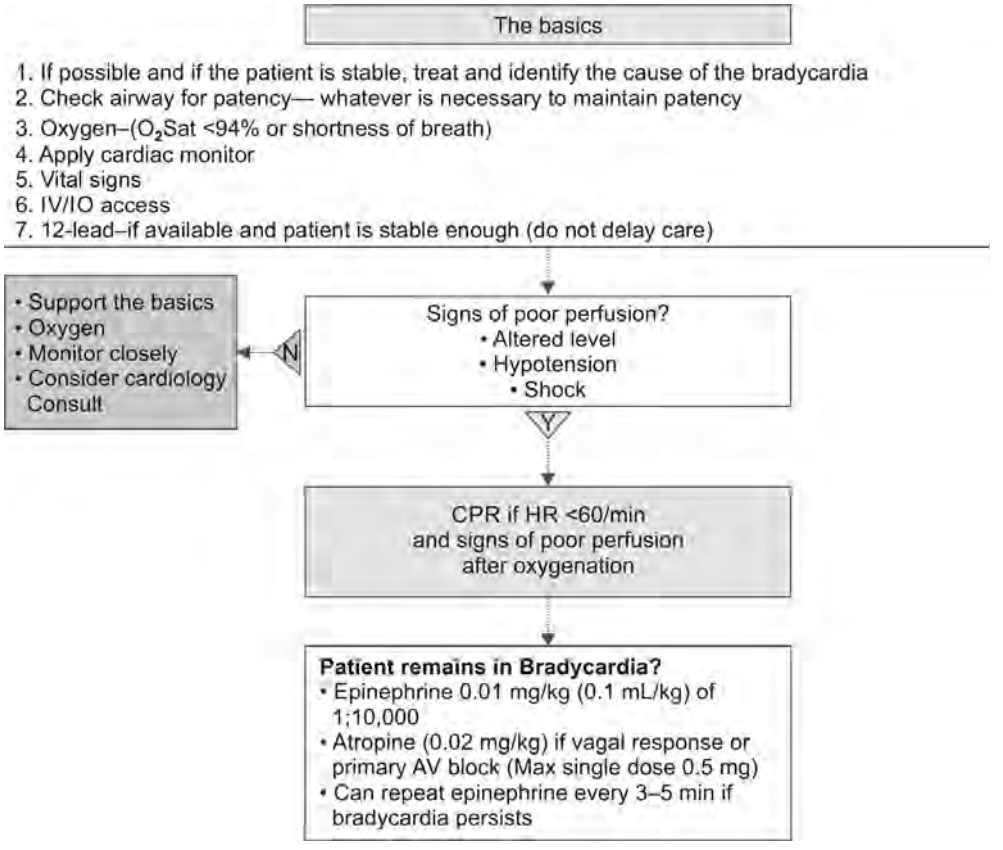
FLOWCHART 3: Pediatric tachycardia.

- Compression force should depress the chest to at least one-third of the anteroposterior diameter (approximately 4 cm deep in infants and 5 cm deep in children)
- Allow complete chest recoil at the end of each compression, allowing the heart to refill with blood
- In infants, if there is only one rescuer use the two-finger technique or the two-thumb-encircling hands technique with thumbs meeting over the lower half of the sternum as shown in **Figure 5A**. In children, the heel of one hand is placed over the lower half of the sternum, with the rescuers' elbows straight and their arm perpendicular to the child's chest. In older children or adolescents, both hands can be used with fingers interlocking **Figure 5B**.

Airway Management

Along with adequate compressions to promote blood flow in patients, an adequate airway is essential to provide sufficient oxygenation and ventilation for the child. Care must be taken to open the airway using the head tilt–chin lift and jaw thrust maneuvers described earlier, as well as ensures adequate seals for bag-valve-mask ventilation (BMV). Consider the following when managing the airway during pediatric resuscitation:

- *Avoid excessive ventilation*: Increased positive pressures from hyperventilation decrease venous return and result in lower cardiac output and reduced coronary perfusion pressures. Give each breath over 1 second and follow guidelines for the number of breaths given during resuscitation.
- Waveform capnography is useful in confirming endotracheal tube placement and predicting the return of spontaneous circulation (ROSC).
- An advanced airway, such as an endotracheal tube, allows for decreased subsequent interruptions during chest compressions. However, a systematic review from 2019 focused on comparing BMV versus endotracheal intubation use for out-of-hospital cardiac arrest (OHCA)


The basics
1. If possible and if the patient is stable, treat and identify the cause of the bradycardia
2. Check airway for patency— whatever is necessary to maintain patency
3. Oxygen–(O_2Sat <94% or shortness of breath)
4. Apply cardiac monitor
5. Vital signs
6. IV/IO access
7. 12-lead–if available and patient is stable enough (do not delay care)
Signs of poor perfusion?
• Altered level
• Hypotension
• Shock
N
• Support the basics
• Oxygen
• Monitor closely
• Consider cardiology Consult
Y
CPR if HR <60/min and signs of poor perfusion after oxygenation
Patient remains in Bradycardia?
• Epinephrine 0.01 mg/kg (0.1 mL/kg) of 1;10,000
• Atropine (0.02 mg/kg) if vagal response or primary AV block (Max single dose 0.5 mg)
• Can repeat epinephrine every 3–5 min if bradycardia persists

FLOWCHART 4: Pediatric bradycardia.

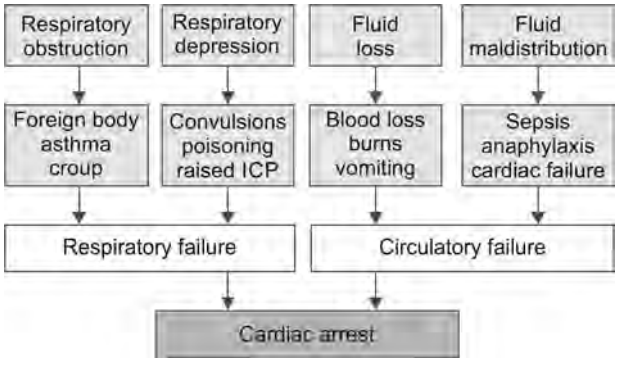


FIG. 4: Etiologies of cardiac arrest in children.

showed no significant difference in good neurological outcome or survival to hospital discharge between both groups. Therefore, it is reasonable to continue with BMV, at least during OHCA, rather than expedite the establishment of an advanced airway.

Defibrillation and Shockable Rhythms

Defibrillation in a pediatric arrest is not associated with improvements in survival outcomes similar to those seen in adults. However, early intervention remains an essential component in the management of shockable rhythms during pediatric resuscitation. Ventricular fibrillation is a chaotic irregular waveform which is never associated with cardiac output. Ventricular tachycardia (broad complex tachycardia) in the absence of a pulse is a shockable rhythm.

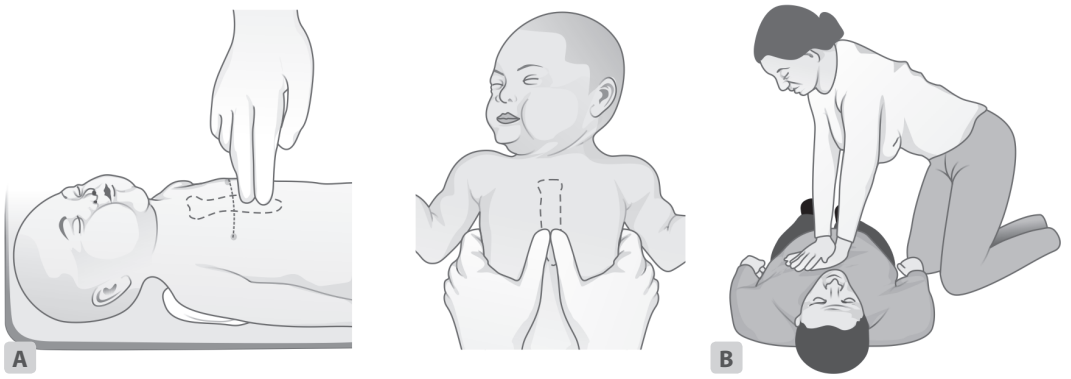
Initiate defibrillation as early as possible when an automated external defibrillator (AED) detects a shockable rhythm during CPR. In an in-hospital setting, attach the patient to a cardiac monitor. It allows the physician to identify a shockable rhythm upon CPR initiation or during pulse and rhythm checks between compressions.

Pulseless Electrical Activity and Asystole

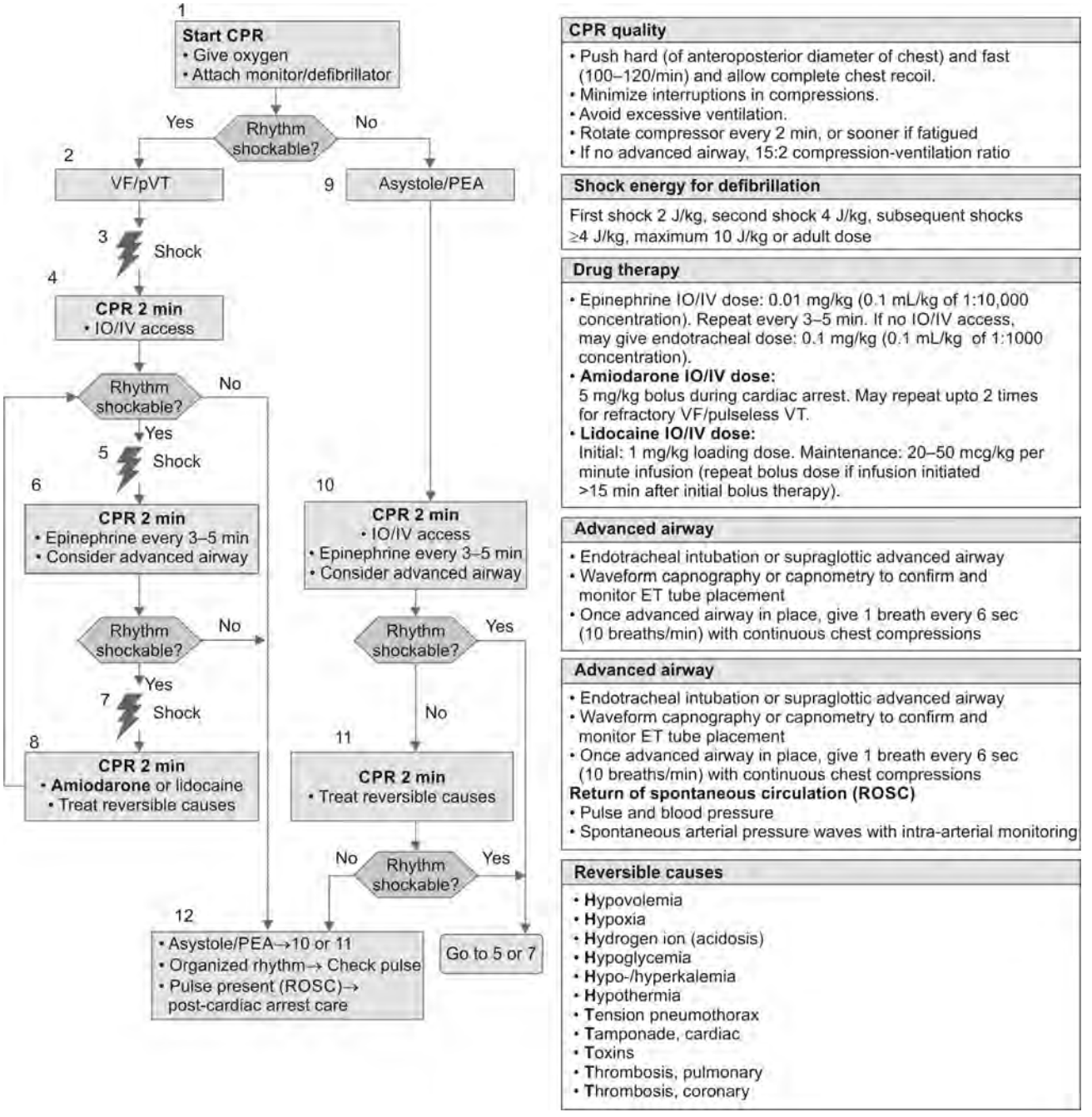
Nonshockable rhythms are managed primarily with compression cycles as described in **Flowchart 5**, with epinephrine administered at regular intervals to promote coronary and cerebral perfusion pressures. During resuscitation, it is important to review and address any potentially reversible causes, denoted by the H's and T's described in the PALS algorithm (**Flowchart 5**). Recognizable complexes in the absence of signs of life and a pulse are known as pulseless electrical activity. Asystole is most commonly seen in children after prolonged period of hypoxia and appears as a wavy line on a cardiac monitor. If a completely flat line appears on the cardiac monitor, check the equipment for any disconnection.

Postarrest Care

Following the successful ROSC, CPR is discontinued but resuscitation continues in the form of postarrest care. It is



FIGS. 5A AND B: (A) Chest compressions in infants; (B) chest compressions in adolescents.


1
Start CPR
• Give oxygen
• Attach monitor/defibrillator
Rhythm shockable?
Yes
No
2
VF/pVT
9
Asystole/PEA
3
Shock
4
CPR 2 min
• IO/IV access
Rhythm shockable?
No
Yes
5
Shock
6
CPR 2 min
• Epinephrine every 3–5 min
• Consider advanced airway
Rhythm shockable?
No
Yes
7
Shock
8
CPR 2 min
• Amiodarone or lidocaine
• Treat reversible causes
10
CPR 2 min
• IO/IV access
• Epinephrine every 3–5 min
• Consider advanced airway
Rhythm shockable?
Yes
No
11
CPR 2 min
• Treat reversible causes
No
Rhythm shockable?
Yes
12
• Asystole/PEA→10 or 11
• Organized rhythm→ Check pulse
• Pulse present (ROSC)→ post-cardiac arrest care
Go to 5 or 7
CPR quality
• Push hard (of anteroposterior diameter of chest) and fast (100–120/min) and allow complete chest recoil.
• Minimize interruptions in compressions.
• Avoid excessive ventilation.
• Rotate compressor every 2 min, or sooner if fatigued
• If no advanced airway, 15:2 compression-ventilation ratio
Shock energy for defibrillation
First shock 2 J/kg, second shock 4 J/kg, subsequent shocks ≥4 J/kg, maximum 10 J/kg or adult dose
Drug therapy
• Epinephrine IO/IV dose: 0.01 mg/kg (0.1 mL/kg of 1:10,000 concentration). Repeat every 3–5 min. If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of 1:1000 concentration).
• Amiodarone IO/IV dose:
5 mg/kg bolus during cardiac arrest. May repeat upto 2 times for refractory VF/pulseless VT.
• Lidocaine IO/IV dose:
Initial: 1 mg/kg loading dose. Maintenance: 20–50 mcg/kg per minute infusion (repeat bolus dose if infusion initiated >15 min after initial bolus therapy).
Advanced airway
• Endotracheal intubation or supraglottic advanced airway
• Waveform capnography or capnometry to confirm and monitor ET tube placement
• Once advanced airway in place, give 1 breath every 6 sec (10 breaths/min) with continuous chest compressions
Advanced airway
• Endotracheal intubation or supraglottic advanced airway
• Waveform capnography or capnometry to confirm and monitor ET tube placement
• Once advanced airway in place, give 1 breath every 6 sec (10 breaths/min) with continuous chest compressions
Return of spontaneous circulation (ROSC)
• Pulse and blood pressure
• Spontaneous arterial pressure waves with intra-arterial monitoring
Reversible causes
• Hypovolemia
• Hypoxia
• Hydrogen ion (acidosis)
• Hypoglycemia
• Hypo-/hyperkalemia
• Hypothermia
• Tension pneumothorax
• Tamponade, cardiac
• Toxins
• Thrombosis, pulmonary
• Thrombosis, coronary

(CPR: cardiopulmonary resuscitation; ET: endotracheal; IO: intraosseous; IV: intravenous; PEA: pulseless electrical activity; pVT: pulseless ventricular tachycardia; ROSC: return of spontaneous circulation; VF: ventricular fibrillation; VT: ventricular tachycardia)

FLOWCHART 5: Pediatric cardiac arrest algorithm—2015 American Heart Association update.

designed to treat the underlying pathologies in the patient, while systematically optimizing the following parameters:

- *Oxygenation*: Supplemental oxygen is titrated to achieve SpO_2 of 94–98% in order to avoid both hypoxemia and hyperoxemia in the resuscitated patient.
- *Ventilation*: $PaCO_2$ is maintained at 35–50 mm Hg to prevent hypo- and hypercapnia.
- *Circulatory support*: Primarily aimed at preventing hypotension. IV fluids are the mainstay along with vasopressor support as needed.
- *Temperature*: Evidence suggests no significant difference in neurologic outcome between therapeutic normothermia versus induced normothermia. However, there is a clear benefit to neurologic recovery in avoidance of hyperthermia. Therefore, guidelines recommend targeting temperatures between 32°C and 36° C with an emphasis on avoiding the emergence of fever during postarrest care.

In addition to the above, it is recommended to monitor blood glucose regularly and maintain modest euglycemia. Extracorporeal membrane oxygenation (ECMO) is feasible, especially in children with congenital heart disease.

OVERVIEW OF NEONATAL RESUSCITATION

Newborn or neonatal mortality contributes to an estimated total of 2.5 million deaths annually, with most of these deaths occurring in low-resource countries. Fortunately, organization, and implementation of standardized neonatal resuscitation protocols can be used to improve neonatal and perinatal outcomes in these settings.

Approximately 1 out of 10 newborns will require some form of resuscitation at birth. Less than 1% requires cardiac compressions and medications. A large number of cases are complicated by the presence of inappropriate oxygenation and or breathing at birth, termed birth asphyxia due to contractions that push the baby through the birth canal. Newborn babies are far more likely to need resuscitation due to respiratory cause rather than a cardiac one as before birth, the baby's lungs are filled with fluid. Therefore, all healthcare providers present during the delivery of infants have to be well-versed in strategies to recognize and manage situations requiring resuscitation of the neonate.

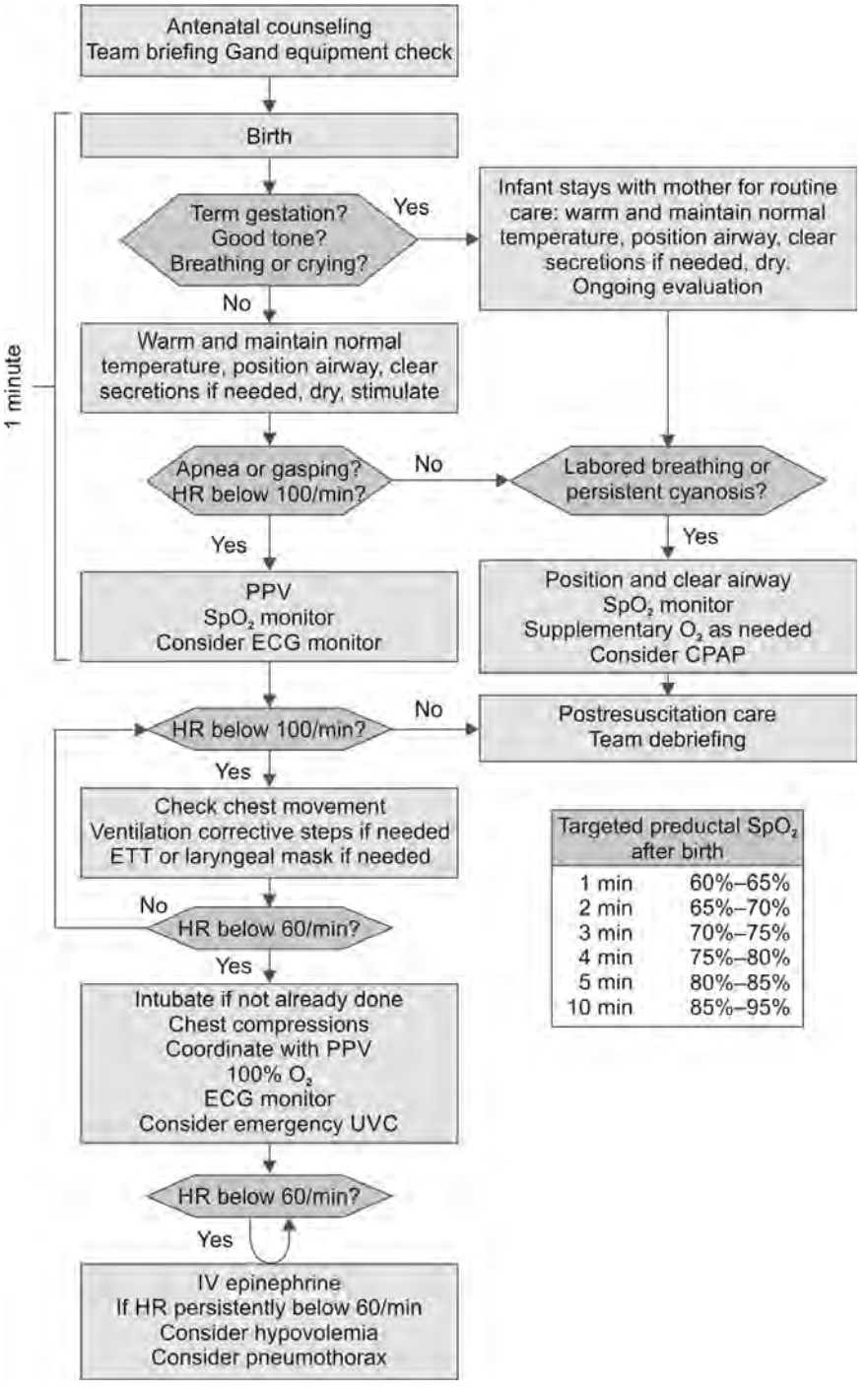
Prepare for delivery by anticipating perinatal risk and organizing the environment. Effective communication with immediate access to essential supplies and at least one person dedicated to the care of the newborn should be present in the delivery room. Care of the term infant upon delivery with good tone and normal breathing and or crying proceeds by drying the baby and placing them skin-to-skin with the mother. Observe breathing, activity, and color. Delayed cord clamping beyond 30 seconds is reasonable in these infants. Delayed cord clamping is associated with less need for transfusion, less necrotizing enterocolitis, and intraventricular hemorrhage (IVH) of any grade.

If, however, the infant is not of a term gestation or does not have an appropriate tone or breathing on delivery, they are placed in a radiant warmer, with interventions listed below in order of execution, alongside the regular assessment of the baby's heart rate (preferably using 3-lead ECG), respirations, and oxygen saturation:

FIG. 6: Optimal airway positioning of the newborn.

- Stabilize initially and prevent hypothermia by warming (wet babies lose heat rapidly), rub the baby dry to stimulate spontaneous breaths or crying, position to open airway [neutral position—place a folded towel under the shoulders (**Fig. 6**)]. Preterm babies may require a plastic wrap, cap, radiant warmer, adjusted room temperature, thermal mattress, and warm humidified gases to prevent hypothermia. Take extreme care not to overextend the neck as this may compromise the baby's soft airway. Clear secretions (blood, meconium, or other fluid) from mouth and nose by gentle suctioning as appropriate. Suctioning offers additional respiratory stimulation. In nonvigorous infants with meconium- stained amniotic fluid, routine intubation for tracheal suction is not recommended.
- If, despite the above, there is abnormal breathing or a heart rate below 100 beats/min (using a stethoscope is the most accurate method of assessing the heart rate), begin rescue breathing within 1 minute of an initial assessment. Use positive pressure ventilation (soft face mask and t-piece or self-inflating bag valve) and oxygenate using room air or supplemental oxygen with SpO_2 monitoring (titrate to achieve a preductal oxygen saturation approximating the interquartile range), possibly including positive end-expiratory pressure (PEEP) of 5 cm H_2O. The chest wall should be seen to rise. Continuous positive airway pressure may be considered in infants with persistent abnormal breathing but has not been shown to affect the need for intubation or mechanical ventilation significantly.
- If heart rate persists below 100, reposition the airway, and optimize ventilation and consider an advanced airway. The most sensitive indicator of a successful response to each step is an increase in heart rate. If low heart rate drops below 60 beats/min, initiate chest compressions using the two-finger or two-thumbs-encircling hands techniques with 3 compressions to every 1 breath. If chest compressions have been started, increase oxygen concentration to 100%. Coordinate compressions and ventilations to avoid simultaneous delivery.
- Seek expert help if not already requested. Persistent deterioration should prompt administration of IV or IO epinephrine at 0.01–0.03 mg/kg (or 0.05–0.1 mg/kg through the endotracheal tube), volume replacement (10 mL/kg of fluid or blood), investigation, and management of other possible causes of arrest, such as pneumothorax.

The neonatal resuscitation program (NRP) algorithm shown in **Flowchart 6** highlights the steps discussed above. Postresuscitative care should be conducted in an environment that allows for close monitoring and observation, emphasizing recognition and prevention of hypoglycemia, and a possible role for therapeutic hypothermia to improve neurologic outcomes in newborns > 36 weeks of gestation. If there is no improvement in the baby's condition after drugs are given, the outcome will be poor. A decision to stop resuscitation is painful, and prolonged attempts are unlikely to be successful. It is acceptable and appropriate for the baby's parents to witness the resuscitation attempts as it helps with the grieving process.



(CPAP: continuous positive airway pressure; ECG: electrocardiography; ETT: endotracheal tube; IV: intravenous; HR: heart rate; PPV: positive pressure ventilation; UVC: umbilical vein catheterization)

FLOWCHART 6: Neonatal resuscitation algorithm—2015 American Heart Association update.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Examination of Newborn

Nilu Sunil, Devendra Richhariya

INTRODUCTION

In today's modern world of high technology imaging and sophisticated laboratory examinations, we forget about the power of a thorough physical examination in detecting medical issues. In this chapter, we will discuss normal newborn examination, importance of knowing normal versus abnormal findings and discuss some common and not so common findings on the newborn examination.

Whenever the parent's perception that something is wrong with the newborn infants they may present to the emergency department for a various reason. The role of the emergency physician is important to recognize abnormality and, if no abnormality detected, address the concerns of the parent. It is very important to differentiate conditions that are self-limited or are variants without physiologic consequence from potential to worsen. Illness in the newborn is often subtle and early detection can be lifesaving. Therefore, the emergency physician should be familiar and comfortable with performing a newborn examination. Because of the time constraints in the emergency department, it may not be possible to complete physical examination, a systematic approach can allow a thorough examination in a matter of minutes (**Table 1**). Main focus should be on general wellbeing, heart lung, and abdomen. Complete neurological examination often not required and assessment of two to three of the primitive reflexes (such as the Moro reflex and sucking reflexes) and observing for spontaneous movement of the limbs will give a good sense of the neurological status of the child.

GENERAL EVALUATION

Before the start of a physical examination of a baby by simply watching a newborn and assessing the indicators of the wellness by a clinician is very important. General examination of a baby starts by observing the baby in the bassinet or in a parent's arms. Labored breathing and persistent crying are often the first indicators of signs of distress and impending problem. Generally during examination, newborn infant will often be soundly asleep, moaning or grunting during sleep may have underlying illness and should be evaluated. Baby

TABLE 1: Head-to-toe approach for normal newborn examination.

Head	• Shape • Fontanel • Lesions/swelling
Eyes	• Red reflex • Extraocular movement • Pupillary shape/size
Ears	• Positioning • Tags
Nose	Nasal patency
Mouth	• Palate • Dentition • Oral lesions
Neck	Swelling/cysts
Chest	• Asymmetric chest rise with respirations Retractions • Accessory respiratory muscle use
Lungs	• Symmetric air entry • Breath sounds
Heart	Murmur
Abdomen	• Hepatosplenomegaly • Cord vessels at birth
Genital	• Inguinal masses • Testicular/scrotal asymmetry • Genital hypertrophy/lesions • Rectal patency
Extremities	• Tenderness • Extremity use/range of motion • Additional digits/tags hip click
Neurology	• Tone • Suckling • Palmar/plantar • Moro

should be vigorous and alert and crying should be energetic and strong when awakened. Observe position of newborn, a newborn, full-term child will lie with his or her upper and lower extremities flexed inward thus showing good tone. Extremities observed in extended form from the body showing decreased tone in a premature or impaired child. Observe movement of the extremities and each limb should have spontaneous movement.

VITAL SIGNS

One of the most challenging parts of pediatric examination is recognizing normal versus abnormal vital signs because of variability in the ''normal'' ranges of values. In determination of significant abnormalities, other clinical indicators should be correlated with the vital signs. Temperature should always be included in the vital signs of newborn, temperatures >38°C are associated with increased risk of serious bacterial illness (sepsis, meningitis, urinary tract infection, enterocolitis, and osteomyelitis) in infants <2 months of age. Fever is a red flag for infection and detail work-up is required. Hyperthermia may be a manifestation of drug withdrawal, intracranial hemorrhage, or adrenal hemorrhage. Hypothermia may also be indicators of sepsis; but also associated with hypoglycemia, hypothyroidism, and hypoxia.

For evaluation of the newborn, height, weight, and head circumference (occipital frontal circumference or OFC) are critical very important and provide clues about potential problems or abnormalities. Assessment of weight is very important and the average weight of a term neonate at birth is 3.4 kg. Small or large for gestational age (SGA or LGA, respectively) of the infants can be determined by standardized growth charts, and are considered appropriate for gestational age (AGA) if they are within two standard deviations from the mean.

Physical characteristics of the neonate including skin creases, external genitalia, ears, breasts, and neuromuscular development are also taken in the account for estimation of gestational age. Further detailed evaluation of the child is required on the basis of LGA or SGA status for other possible anomalies. SGA is associated with serious congenital anomalies in infants. LGA infants may be associated with familial inheritance, large parents will often have large infants. Maternal weight gain during pregnancy (diabetes in the mother) is most common may translate into an LGA infant.

Head

The newborn head shows a great degree of variability in the ''normal'' examination, as well as a large number of findings that are due to molding in the vaginal canal and birth trauma. Normal variants and benign birth trauma finding should be differentiated from true pathological lesions. A brief review of anatomy reveals that the newborn skull ''neurocranium'' is composed of eight bones and facial skull is composed of 14 irregular bones, at birth each bone is separated by fibrous webs, known as suture lines. There are total of six fontanels in addition to the anterior and posterior fontanels, there are two pairs of lateral fontanels known as the sphenoidal or anterolateral fontanels and the mastoid or posterolateral fontanels. The four lateral fontanels generally fuse in infancy, posterior fontanel begins to close after the first few months and is generally not appreciable by 1 year of age. The anterior fontanel is generally closed by 18 months of age. Sutures are generally closed by age 12, but complete fusion continues until into the third decade. Head growth is primarily driven by brain growth, the neurocranium expands to allow more room. Brain growth is at a tremendous rate in utero and until during the first 3 years of life. At birth, the infant brain is about 40% of adult volume. By age 3, it has reached nearly 80% and by age 7 it is at 90% of adult size.

Eyes

A pediatrician often examines the red reflexes of the eye (for retinoblastoma), the red reflex can give much more information apart from tumors. A white reflex of eye (leukocoria), associated with many other conditions including cataracts, retinal detachment or dysplasia, papillary membranes, and vitreous opacities and requires referral to an ophthalmologist for further evaluation. In addition to examining for leukocoria, the clinician can look for colobomas, examine the pupillary reflex, and look for strabismus using the ophthalmoscope.

Ears

Cranial molding from birth can move the ears into various positions, so molding should be taken into account when examining the ears. One should examine the ears for their position, noting low-set ears, as this has been associated with several syndromes, and malformation of the auricle. Preauricular pits or skin tags are common, and often are hereditary and need no further work-up unless present with other anomalies. Hereditary preauricular pits can be associated with deafness, ear anomalies can be associated with genitourinary anomalies and this should be followed up with the physician as the infant grows. Additionally, as such a renal ultrasound is generally indicated in these patients.

Mouth

Several normal and benign findings such as natal teeth and Epstein's pearls are present in mouth of a normal child. Natal teeth are any teeth which erupt before 30 days of life (1 in every 3,000 births) and mostly involve mandibular central incisors. They are similar to normal teeth; lack a substantial root system often fall out on their own at some point. There is no need to remove them unless there is risk for aspiration of the tooth (loosen or come out of its own) or if the tooth prevents proper feeding. Epstein's pearls and Bohn nodules (yellowish or white and slightly raised) giving the appearance of a pearl are common findings in neonates. Bohn nodules are located on the alveolar ridges, and Epstein pearls are those located near the midpalate raphe at the junction of the hard and soft palates. They are remnants of embryonic development of the dental lamina and will resolve without treatment. Cleft lip and palate are most common anomaly of the head and neck in newborn. Surgical correction should be considered early in cases of poor nutritional intake and abnormal speech development. Surgery often produces very good cosmetic results also. Most clefts are quite obvious upon examination, can be identified visually, and the clinician is able to palpate the cleft using a finger to examine the upper palate of the infant.

Neck

One of the common (third most common) musculoskeletal anomalies of infants is congenital muscular torticollis. It follows behind clubfoot and dysplasia of the hip and can have an incidence upward of 1 in 250 live births. The exact cause is unknown; but commonly associated with breech and forceps deliveries. In approximately two-thirds of cases, a mass can be felt in the affected sternocleidomastoid muscle. Infants present as head flexed and the chin facing the direction opposite the affected muscle, contracture of the muscle can lead to plagiocephaly with abnormal placement of the eye and ear on the affected side. Physical therapy is generally therapeutic. In rare cases, surgical release of the sternocleidomastoid muscle is needed. If the torticollis is not corrected by age 1, plagiocephaly tends to be persistent. The neck should be examined for any pits or other anomalies such as branchial cleft anomalies, cysts, or sinuses. These branchial arch remnants will be found in the pinna of the ear, the preauricular area, or the lateral neck. When present, these anomalies may be associated with systemic syndromes such as Goldenhar syndrome, Pierre-Robin association, Treacher–Collins syndrome, and Hallermann–Streiff syndrome. A midline neck lesion may represent a thyroglossal duct cyst or cervical cleft.

SYSTEMIC EXAMINATION

Chest

Clavicle fractures are one of the most common chest birth injuries, with an incidence 0.2–3.5%. Clavicle fracture identified by crepitus in the clavicular region on palpation, radiograph confirms the fracture. Clavicular fractures heal well, even in the presence of significant angulation thus no further intervention is required. Assess for symmetry and equal chest excursion as well as adequacy of air exchange while examining the lungs of a newborn. Assess the indicators of respiratory distress while examination of the lungs, e.g., assessment of the respiratory rate, nasal flaring, grunting, or retractions. After cesarean section deliveries (in 0.3–0.5% of newborn) present with tachypnea, increased oxygen requirements, and a lack of hypercapnia on blood gas, the condition is called transient tachypnea of the newborn (TTN). Recovery is the rule, few infants may require ventilatory assistance for a short period of time. Respiratory distress typically will present a few hours after birth and resolves in 24–72 hours.

Cardiovascular

The cardiovascular exam can be difficult in a newborn because of their often rapid heart rate. To briefly review neonatal physiology of the heart, one must have a basic understanding of fetal cardiac physiology. Before birth, lungs are not used for oxygenation, pulmonary pressures are high and blood is returned to the systemic side of blood circulation after shunted through the foramen ovale and the ductus arteriosus. At the time of birth, many changes occur, such as decrease in pulmonary pressures to allow blood to flow through the lungs and closure of the foramen ovale. The ductus arteriosus typically closes 10–15 hours after birth. Full permanent fusion may take 3 weeks. Auscultation of the heart sounds of a neonate typically reveals a single S1 and a single, or very slightly split, S2 because of the continued relatively high pulmonary pressures. Once pulmonary pressures fully drop to their baseline in 4–6 weeks, the S2 becomes more physiologically split. Typically, S1 is louder near the apex of the heart and S2 is louder near the base. An S3 may be heard near the apex and is considered normal. S4 is never normal in a newborn. If a murmur is detected in the emergency department that is concerning for pathology, evaluation is warranted. This should include a chest X-ray and an electrocardiography (ECG) and echocardiography. If abnormalities are found, the neonate should be admitted for further evaluation. If no abnormalities are detected and the child appears well, follow-up with a pediatric cardiologist as an outpatient is reasonable.

Abdomen

In examining the abdomen, the clinician should assess for typical abdominal components, such as palpation for enlarged liver spleen or kidneys. Abdominal palpation is best accomplished using the flats of the fingers rather than the tips, as they are more sensitive to masses and so forth. The liver is often felt approximately 1 cm below the costal margin. This degree of extrusion is considered normal. As a general rule, spleen is only palpable when enlarged. An enlarged spleen with prolonged or severe jaundice should alert the clinician and should evaluate for Rh or ABO incompatibility or other red cell morphological defects such as spherocytosis and other hemolyzing states. While attempting to palpate for an enlarged spleen, one can also palpate for enlarged or cystic-feeling kidneys. The umbilical cord should be inspected to ensure the presence of a single umbilical vein and two umbilical arteries (higher incidence of severe renal anomalies and renal malformation in infants with single uterine artery). A scaphoid abdomen and respiratory distress at birth should raise concern for a congenital diaphragmatic hernia (CDH) (absence of a scaphoid abdomen does not rule out CDH). When the possibility of CDH exists, the infant should be intubated in an effort to prevent the swallowing of air that occurs with spontaneous breathing or with bag-valve mask ventilation. Air in the intestines will lead to worsening respiratory distress as the expanding intestines further compress the lungs and mediastinum. The differential diagnosis for hepatomegaly (a liver edge palpable beyond 3.5 cm below the costal margin is considered enlarged) in a neonate is quite extensive. First, true hepatomegaly is important to recognize. Palpation of the liver edge and percussion of liver span should be performed to ascertain the liver size. Start palpating the liver edges from the lower quadrants to ensure that extreme hepatomegaly is not missed. At 1 week of age, a normal liver span is 4.5–5.0 cm. An enlarged edge below the costal margin in the presence of a normal liver span may be caused by depression of the liver downward due to lung hyperinflation or other anatomical causes. Once hepatomegaly is confirmed, other important finding should be noted to ascertain underlying causes such as presence or absence of jaundice, splenomegaly, and other physical anomalies or systemic symptoms

Genitourinary Tract

Several anomalies can be found when evaluating the genitourinary tract. GU anomalies such as inguinal hernias, hydroceles, varicoceles, undescended testes, or signs of hypospadias and other urethral anomalies are found in both male and female newborns, thus a thorough examination is

important to identify any such findings that may exist. When an inguinal hernia (they can present as a bulge in the inguinal area or may have palpable bowel in the scrotum) is identified, light, constant pressure should be applied to the herniated bowel to reduce the bowel back into the abdomen. Sometime bowel may become nonreducible. This represents an incarcerated hernia and is a surgical emergency. Incarceration of an inguinal hernia may compromise blood flow to the intestines or the scrotal contents resulting in damage to the end organ. Female newborns are also susceptible to inguinal hernias although the male: female ratio is 6:1. Hydroceles are most commonly present at birth, although they rarely can arise later (resolve in 12–28 months duration). Transillumination can be used to aid in the diagnosis of a hydrocele as they tend to easily and uniformly light up, although bowel can occasionally transilluminate as well, making the distinguishing of the two difficult at times. Hydroceles do not extend into the inguinal canal. Varicoceles (almost always on left side) result from dilation of the pampiniform plexus and internal spermatic vein, they can be easily reducible or spontaneously with supine positioning. Any varicocele that does not reduce or is located on the right side should be evaluated by ultrasound, as failure to reduce is an indication of a possible blockage in venous drainage. This may be the result of an abdominal mass. At birth, full-term boys will experience an undescended testis (cryptorchidism) about 3–4% of the time. By age 1, only 0.3% persist. If one fails to locate a testis in the scrotum, examination of the inguinal canal area should be performed. True undescended testes cannot be manually drawn into the scrotum on examination. By 6 months of age, if testes have not descended down into the scrotum, will require intervention by surgical orchiopexy but hormonal treatment with human chorionic gonadotropin (hCG) can also be attempted. Undescended testes should be brought into the scrotum by intervention as this allows for better examination for malignancy (seminomas are most commonly seen) as they have a 4 to 10 times higher risk than descended testes. In girls, congenital adrenal hyperplasia (CAH) is the leading cause of ambiguous genitalia. During examination of the genitalia, the clinician should evaluate for clitoromegaly, micropenis, bifid scrotum, or fusion of the labia resulting in a scrotum-like appearance. Increased pigmentation of the skin can be seen with CAH because of increased adrenocorticotropic hormone (ACTH) concentrations in an attempt to stimulate cortisol production.

Extremities

All four extremities should be examined for any anomalies. Examine for presence/absence of any supernumerary digits in both hands and both feet. Polydactyly is an isolated finding mostly, but may be associated with other malformations. While spontaneous occurrences are frequent, a family history of polydactyly yields up to a 10-fold increase in occurrences. Polydactyly of the fingers is the second most common anomaly of the hand. Simple skin tag that can be removed by tying a suture at the base to a fully formed digit and more complex digits require surgical removal. Single palmar crease is associated with several syndromes, most notably Down syndrome. Talipes equinovarus (clubfoot) is a relatively common deformity (1 in 1,000 live births). Bilateral involvement occurs in 30–50% of cases. Male to female ratios are 2:1 Lknm. Clubfoot is a complex anomaly. It is composed of four main components: (1) The forefoot is inverted and adducted, (2) The heel and hindfoot are inverted, (3) Limitation of extension at the ankle and subtalar joint, and finally (4) Internal rotation of the leg. Inability to bring the foot fully to midline on physical examination. Progressive serial casting is attempted initially for correction, if needed, surgery is generally performed between 6 and 9 months.

Neurological

An extensive neurological examination can be quite time-consuming; however, all infants should receive at least a limited neurological examination including tone, primitive reflexes, and a gross assessment of muscular/sensory status and cranial nerves (CNs). Summary of primitive reflexes can be found in **Table 2**. A systematic neurological approach is helpful in older children, begin with a general assessment, followed by CNs, motor function, sensory function, and reflexes. A good assessment of neurological status can often be obtained simply by careful observation of the infant. Observe movements of the face for symmetry. Arms and legs should be to assessed for active movement. At birth, full-term infants show a flexed posture of the extremities and have the ability to raise their

TABLE 2: Common primitive reflexes.

Rooting reflex	Touch newborn on either side of cheek and baby turns toward stimulus
Walking reflex	Hold baby up in vertical position. As feet touch ground, baby makes walking motion
Tonic neck (fencing) reflex	Rotate baby's head leftward and the left arm stretches into extension and the right arm flexes up above head (opposite reaction if head is rotated rightward)
Moro reflex (startle reflex)	Hold supine infant by arms a few inches above bed and gently release infant back to elicit startle. Baby throws arms out in extension and baby grimaces
Hand-to-mouth (babkin) reflex	Stroke newborn's cheek or put finger in baby's palm and baby will bring his fist to mouth and suck a finger
Swimmer's (gallant) response	Hold baby prone while supporting belly with hand. Stroke along one side of spine and baby flexes entire torso toward the stroked side
Palmar	Stroke inner palm/sole and toes/fingers curl around ("grasp") examiner's finger
Plantar	Stroke outer sole (Babinski) and toes spread with great toe dorsiflexion
Doll's eyes	Give one forefinger to each hand (baby grasps both) and pull baby to sitting with each forefinger. Eyes open on coming to sitting (like a doll's)
Protective reflex	Soft cloth is placed over the baby's eyes and nose. Baby arches head, turns head side to side, and brings both hands to face to swipe cloth away
Crawling reflex	Newborn placed on abdomen and baby flexes legs under as if to crawl

heads in the vertical midline plane, although they may still be quite unsteady. Movements of the extremities should be generally smooth without a significant amount of jerking. The cry should be strong and vigorous. Often neurological problems will produce an altered cry such as a weak cry or a particularly high-pitched cry. CN assessment can begin with the examination of eyes. An infant's neurological system has developed enough by 28 weeks to produce a blink when a bright light is shone in the eyes (CN II and VII). The papillary reflex develops (CN II and III) between 28 and 32 weeks. CN V can be tested via corneal reflex or with light touch/pin prick to the trigeminal branch areas producing a withdrawal from the stimulus. Testing of CN II, III, IV, and VI can be performed by observing fixation and tracking of large objects by full term infants (dysconjugate gaze is not abnormal when a neonate is not fixing on an object). Facial asymmetry may be suggestive of facial nerve lesion. Eye blink on loud noises testing CN VIII. CN IX and X are tested by swallowing reflex. Fasciculations of the sternocleidomastoid muscle or tongue may represent a lesion involving CN XI or XII, respectively. Generally detailed CNs examination is not required unless there is suspicion of any abnormalities. Sensation testing is generally limited to light touch and pinprick testing. During the entire newborn examination, the clinician can be assessing the response of the baby to touch (infants commonly reacts to the stethoscope touching their chest). Motor examination can be assessed by observing spontaneous movement of the head and extremities, as well as muscular tone. Neonatal hypotonia is the most common abnormal neurological sign seen in neonates. It is associated with a wide array of disorders. Hypotonia can be divided into central and peripheral origins. Central hypotonia tends to be associated with other central nervous system (CNS) findings. Down syndrome and Prader-Willi syndromes are associated with hypotonia. Hypoglycemia, hypothyroidism, hypoxic-ischemic encephalopathy, infection, and metabolic disorders are the other important causes should be considered for hypotonia. Often, central causes of hypotonia become more classic of CNS lesions resulting in increased tone, increased reflexes, and so forth. Possible neck hyperextension in utero or during delivery gives rise to transection of the spinal cord should also be considered. Peripheral hypotonia presents without any specific central signs, e.g., spinal muscular atrophy, neonatal myasthenia gravis, and infantile botulism. Infant spinal muscular atrophy, also known as Werdnig-Hoffman syndrome or SMA type 1, can present with hypotonia at birth (in 60% of cases), weakness, poor suck, and absent reflexes. This is due to anterior horn cell degeneration. Neonatal myasthenia gravis occurs in infants born to mothers with myasthenia gravis. The acetylcholine receptor antibodies readily cross the placenta and can attach to the infant's receptors producing a myasthenic phenotype. Signs of bulbar weakness including a weak suck and cry, hypotonia, absence of a Moro reflex, and respiratory insufficiency can develop up to 72 hours after delivery. Treatment is with acetylcholinesterase inhibitors as in adults. Symptoms generally resolve by about 12 weeks of age as the maternal antibodies are cleared. The brachial plexus is formed from the C5-T1 nerve roots. Palsies involving this plexus are divided into three main types. Erb's palsy involves the C5, C6, and occasionally C7. Klumpke palsy involves C8 and T1. The third type involves the complete plexus. Erb's palsies present with the affected upper extremity in the classic ''waiter's tip'' position. Klumpke palsies yield a paralyzed hand with full function of the elbow and shoulder. This palsy is rare, comprising only 0.5% of all brachial plexus injuries. The range of resolution relates to the actual injury to the nerve roots. Mild cases generally are the result of the brachial plexus nerve roots being stretched, termed neurapraxia. In these cases, prognosis is excellent. The most severe cases result when the nerve root is avulsed from the spinal cord, known as axonotmesis. These cases have no chance for spontaneous resolution and surgical correction often does not yield good outcomes. Fortunately, 80–95% of cases (primarily Erb's palsies) will resolve spontaneously over the course of a few weeks to months. If, on physical examination, there is difficulty in determining if the infant does not move the area because of pain (as a result of a clavicular fracture, for example) or a palsy, the Moro reflex can be used. In cases of palsies, the Moro will result in asymmetric movement.

Skin

Newborn babies exhibit a plethora of skin findings. These findings are visible and cause of concern and alarming to parents and result in emergency department visits. Newborns often experience some degree of vasomotor instability that can present in several ways, including cutis marmorata, harlequin color changes, and acrocyanosis. Cutis marmorata is a condition resulting from uneven distribution of capillary blood flow presents as mottled appearance to the skin and often can be induced by cold exposure. Harlequin color changes are precipitated by turning the baby on the side commonly seen in low-birth-weight newborn and resolve during first few weeks. When this is done, the lower half of the baby becomes erythematous or dusky while the upper half becomes pale. Often there is a sharp demarcation between zones. This typically resolves within a few seconds after returning to the supine position but can persist for up to 20 minutes. Acrocyanosis is nonpathological condition (bluish color to the hands, feet sometimes lips) due to pooling of venous blood. This condition is exaggerated with cool temperatures and resolves with warming and resolves as vasomotor stability improves. Erythema toxicum (central flesh-colored papule with surrounding erythema at the base) is extremely common, affecting up to 50% of full-term infants. It typically presents in the first 2–3 days of life and typically resolves in 5–7 days. Biopsy is generally not needed but would show the presence of eosinophils. Its etiology is not well known at this point. Less common is neonatal pustular melanosis, which affects approximately 5% of black infants and <1% of white infants. The pustules are always present at birth or form within the first 24 hours of life. Following pustule formation, the pustules rupture leaving the classic collarettes of scaly skin and hyperpigmentation. 40% of newborn will have milia, most commonly found on the nose. They represent small cysts filled with keratinocytes and sebaceous debris. They may also be seen on other areas of the body.

Nevus simplex is a blanching macule that is typically pink or red in color found commonly on glabella and posterior neck. When located on the glabella, they are commonly referred to as angel kisses, and when located on the posterior neck, they are often termed stork bites but they may be found anywhere along the midline from the eyes to the nape of the neck and they fade with time, but not completely. Nevus simplex should be distinguished from a nevus flammeus or ''portwine stain.'' Port-

wine stains do not tend to resolve much spontaneously. Laser treatment can help reduce their appearance. In particular, a nevus flammeus that involves the ophthalmic and maxillary regions of the trigeminal nerve (unilaterally or bilaterally) may be associated with Sturge-Weber syndrome that can have CNS involvement and lead to seizures. Port-wine stains that involve the face and/or upper extremity with hypertrophy of the affected side may have a condition termed Klippel-Trenaunay. Dermal melanoses (Mongolian spots) are bluish black areas of hyperpigmentation often found on the buttocks, back, and shoulders. They are extremely common in darker skinned babies, fade with age. These spots can be confused with bruising and have resulted in evaluation for abuse in some cases. Hyperpigmented macule cafe´ au lait spot (light brown in color) is another common skin finding on examination of skin. A few cafe´ au lait macules are normal; however, the presence of many macules or a very large macule may indicate the presence of a systemic disease such as neurofibromatosis type 1 or McCune-Albright syndrome, respectively.

SUMMARY

Complete physical examination is highly reliable for screening of illness in infants despite the broad technologic advancements of medicine. It is important for the emergency physician to have a thorough understanding of abnormal findings but also the normal findings and their variants. The vast majority of infants are healthy and findings predictive of future health problems are subtle and infrequent. Yet, outcomes can be devastating. Therefore, it is critical for the physician to remain diligent during screening.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Crying Infant

Prabhat Maheshwari, Upasana Iyer

INTRODUCTION

Crying is a normal response to many stimuli in nonverbal children. It gives a clue to the child's physiological state ranging from normal needs of hunger and sleep to significant pathology. Healthy children cry for about 3 h/day on an average at 6 weeks of age with the peak occurrence between 3 PM and 11 PM. The cry is labeled as abnormal depending on the duration and its inconsolable nature. Excessive crying usually would present in concert with other manifestations of disease or distress such as fever, vomiting, rash, and trauma. However, it can be challenging for evaluation when it is the sole presentation. A systematic and appropriate history and physical examination coupled with a suspicion for a broad range of medical possibilities need to be considered for proper evaluation. Crying is one of the most common indications for seeking medical attention by parents in the first 3 months of life. The studies have reported a range of 0.25–13.6% of all annual emergency department (ED) visits for crying infant. Although most of the times, the etiology is benign and is self-limiting, excessive crying is associated with considerable parental anxiety and stress.

WHAT IS CRY?

A cry is a series of four movements that basically resembles a Valsalva maneuver. Crying has an effect on various organs of the body both immediately as well over the long run.

NORMAL AND EXCESSIVE CRYING

Crying in infant is a part of normal neurodevelopment. It follows a typical curve that peaks during 6th week of age with a mean duration of 110–118 min/day and declines to <1 h/day by 12 weeks of age. In the first week, following birth crying concentrates in late afternoon. Preterm neonates experience their peak at 6th week corrected age, thus have delayed peak. Due to specific age-related pattern, it has been thought to correlate with the development of circadian rhythm. Wessel's *''rule of threes''* states that crying in an otherwise healthy baby aged 2 weeks–4 months that occurs >3 h/day, >3 days in any week for at least 3 weeks may be called excessive crying. Based on above, infants are divided into three groups: (1) Contented, (2) Paroxysmal fussers, and (3) Seriously fussy. Infants meeting the above criteria are grouped as paroxysmal fussers and those not fitting the definition are grouped as contended. Seriously fussy infants are those whose paroxysmal fussing episodes continued for >3 weeks.

ETIOLOGY

An infant cries to shut out painful or disturbing stimuli, communicates hunger, thirst, boredom, fatigue, fussiness, injury, pain, indigestion, and displeasure. Organic diseases account for <5% of infants with excessive crying. The importance of distinguishing crying due to pathologic causes from benign causes needs to be emphasized. As the presentation is so nonspecific, the list of differential diagnosis is exhaustive. It is helpful to use a system-based approach while tacking such an infant. List of various etiologies is enlisted in a systematic approach in **Table 1**.

PATHOPHYSIOLOGY

The cry is one of the most potent distress signals the infant has to offers. It is designed to elicit a maternal response that will change the infant's physiologic condition or provide caregiving. Infant's cry activates the anterior cingulate area of a woman's brain, suggesting the involvement of neuroanatomic control in her response to an infant's cry. There are four phases of crying (**Fig. 1**)—(1) Inspiration (stress phase), (2) Inspiratory gap, (3) Pause, and (4) Expiration. Overall crying gives rise to various immediate and long-term effects (**Table 2**).

FEATURES OF CONCERN (RED FLAG SIGNS)

While evaluating a crying infant, it is important to look out for warning or red flag signs, which indicate toward life-threating condition and warrant urgent management. **Table 3** enlists various such signs.

PREHOSPITAL CARE

Most often the crying infant may present to the ED with their caregivers, but occasionally the ED can be called upon for dispatch of an ambulance. In the latter situation, the

TABLE 1: Etiologies of crying in infant.

System	*Causes*
Nonpathological	Lack of sleep, hunger, discomfort form soiled nappy, nappy rash, extreme temperature, sudden stimulation from light or sound, and parental variables
Head, eyes, ears, nose and throat	Trauma, corneal abrasion, foreign body, glaucoma, otitis media, oral thrush, stomatitis, and panniculitis
Cardiovascular	Congestive cardiac failure, supraventricular tachycardia, endocarditis/myocarditis, and myocardial infarction
Pulmonary	Upper respiratory tract infection, foreign body aspiration, pneumothorax, and pneumonia
Gastrointestinal	Constipation, anal fissure, hemorrhoids, bowel obstruction, intussusception, malrotation/midgut volvulus/ Hirschsprung's disease, milk protein allergy, GERD/esophagitis, celiac disease, appendicitis, and peritonitis
Genitourinary system	Testicular torsion, incarcerated inguinal hernia, balanitis/posthitis/ balanoposthitis, hydrocele, urinary retention, and urinary tract infection
Musculoskeletal	Fracture, osteomyelitis, arthritis, rickets, dactylitis, and vaso-occlusive crisis
Neurological	Raised intracranial pressure (hydrocephalus, mass, hemorrhage, and cerebral edema), meningitis/ encephalitis, and neonatal drug withdrawal
Dermatological	Insect bite, burns, cellulitis, atopic dermatitis, and mastocytosis
Metabolic	Hypoglycemia, electrolyte imbalance, inborn errors of metabolism, hyperthyroidism, toxic ingestion, and carbon monoxide poisoning
Others	Hunger, immunization, and abuses
Etiologic Mnemonic for crying Infant "IT CRIES" I—Infection, T—Trauma, C—Cardiac Disease, R—Reflux, Reaction to medicines, I—Intussusception, E—Eyes (corneal abrasion), S—Surgical emergency (strangulation, torsion, and hernia)	

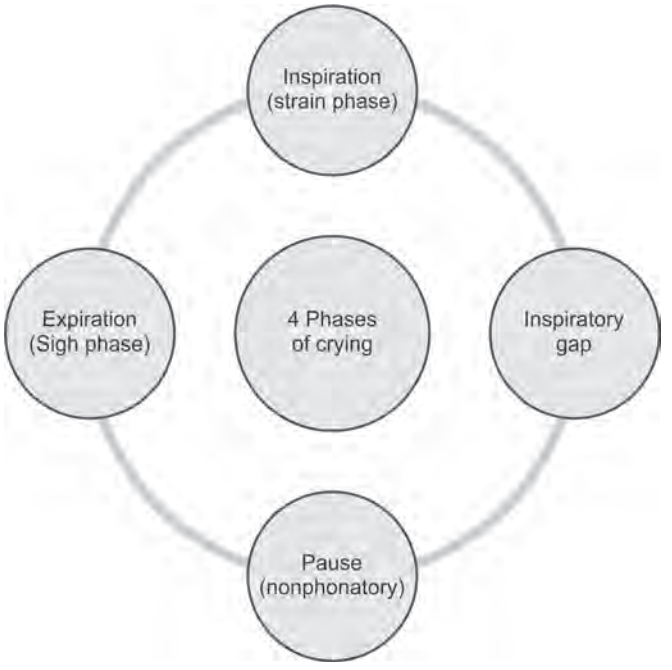


FIG. 1: Phases of crying.

TABLE 2: Sequelae of crying.

Immediate effect	*Long-term effect*
• Increase in heart rate: ○ Slight cry—170 bpm ○ Moderate cry—185 bpm ○ Hard cry—200 bpm ○ Prolonged cry—>200 bpm • Increase in systolic and diastolic blood pressure and fall in pulse pressure • Fall in arterial oxygen level • Fluctuations in cerebral blood flow and intracerebral pressure • Increase in cortisol level • Leukocytosis • Aerophagia and abdominal distension • Disruption of interaction with caregiver	• Hypoxic brain injury and intraventricular hemorrhage • Patent foremen ovale contributing to exertion and focus for stroke • Mother-infant distress syndrome

ED personnel should follow the standardized stabilization protocol while assessing these infants. Considering the heightened parental concern, appropriate assessment of airway, breathing, circulation, and necessary basic interventions such as oxygen administration, intravenous access, fluid administration, and bedside glucose testing should be initiated. The detailed information about the presenting episode from the caregivers and vital sign assessment can be done en route. Desist from providing false reassurances to caregivers and discouraging them from ED visit as there can be a possibility of serious underlying illness in these infants.

TABLE 3: Red flag signs in a crying infant.

Findings	*Possible causes*
Lethargy	Hydrocephalus, meningitis, sepsis, and subdural hematoma
Fever	Acute otitis media, appendicitis, bacteremia, endocarditis, meningitis, osteomyelitis, pneumonia, sepsis, urinary tract infection, and viral respiratory infection
Abdominal distension	Abdominal mass, hepatosplenomegaly, Hirschsprung's disease, intestinal malrotation with volvulus, and necrotizing enterocolitis

EVALUATION OF CRYING INFANTS IN EMERGENCY DEPARTMENT

A detailed history and a through physical examination are of utmost importance while evaluating a crying infant. Infants who continue to cry during the examination should be reevaluated during normal period.

History

Parents are excellent observers and should be asked for subtle signs and symptoms. The following points should be sought after while taking history from parents/caregivers—duration, frequency, intensity and periodicity of crying, aggravating and relieving factors, comorbid medical condition, recent vaccination, feeding and sleep behavior, sibling and family history infant-mother relationship, and maternal fatigue.

Determining the triggers for excessive crying in infants is like solving a puzzle. A comprehensive and detailed history is the key in the assessment of these patients. A good history has been reported as diagnostic in 20–86% of cases, either alone or in concurrence with examination findings.

Nevertheless all resuscitative measures must be performed prior to detailed history taking process. Relevant history to include duration, frequency, and intensity of crying episodes with aggravating and relieving factors and details of any prior evaluations in this respect. Assess for the different crying patterns to get clinical cues:

- High-pitched cry indicates infection of central nervous system.
- Continuous cry with grunting may indicate foreign body or respiratory infection.
- Crying with pulling of ears indicates otitis externa/media.
- Sporadic crying pattern with pallor and undrawn knees over abdomen may indicate intussusception.
- Paroxysmal crying in otherwise healthy infants of <4 months age usually during evening indicates infantile colic.

The points need to be specifically noted are as follows: Birth history, including birth weight, perinatal complications, and maternal substance use during pregnancy. Detailed feeding history, sleep behavior, bowel, and bladder patterns. History of past illnesses, medication use, vaccination. Comorbid medical conditions. Social history. Family history of any congenital or genetic disorders.

Physical Examination

Initial physical examination should aim to assess and identify general condition of the infant to determine if there exists a life-threatening condition associated with incessant crying.

All the vital parameters to be checked and recorded and a thorough whole-body inspection should be done. Studies have proven that physical examination either alone or in addition to history can contribute to diagnosis in >50% cases.

A complete head-to-toe examination to be systematically done. Important considerations while examining the infant are as follows:

- *Head and neck*:
  - Examine the eye for congestion/corneal abrasion; a study by Shope et al., in 2010 found that nearly 50% of infants presenting to primary care center had corneal abrasions.
  - Examine the external ear and perform otoscopic examination to rule out otitis media.
  - Oropharyngeal pathologies are not so common as a cause for crying but presence of trismus should raise a suspicion for peritonsillar abscess or deep neck space infection.
- *Nervous system*:
  - Persistent irritability and high-pitched cry points toward central nervous system cause such as meningitis or encephalitis. Appropriate history, clinical examination, and requisite investigations to be considered for ruling out these serious pathologies.
  - Evaluate for occult head injury especially in infants suspected to have nonaccidental injuries by relevant examination and imaging.
  - A bedside glucose measurement is a minimally invasive test to detect hypoglycemia as the cause for excessive crying.
- *Thorax*:
  - Clavicular fractures may occur during delivery when there is a history of difficult delivery, shoulder dystocia, or when the neonate is large for gestational age.
  - Presence of bony crepitus on palpation should raise a suspicion for rib fractures and also for nonaccidental trauma.
  - Examination of breast tissue for abscess/mastitis
  - Examine for cardiac arrhythmias. Infants with congenital heart diseases may also present with poor feeding, fussiness, irritability, and excessive crying.
- *Abdomen*:
  - Infantile colic affects around 10–30% of infants. It has been defined as episodic paroxysmal crying for >3 h/day for >3 days a week for up to 3 weeks in an otherwise healthy infant aged from 2 weeks to 4 months.
  - Many studies have proven that constipation is one of the common causes of crying infant, history and careful palpation of abdomen to be performed to rule out constipation. Rectal examination may be considered if mandated by clinical suspicion.
  - Paroxysmal crying episodes associated with intermittent flexing of lower extremities with or without bloody stools must raise a suspicion for intussusception.
  - Palpate for an abdominal mass in the right upper quadrant in a poorly feeding infant and history of nonbilious vomiting to rule out pyloric stenosis.
  - Urinary tract infection can also be the reason for excessive crying in an infant and careful evaluation regarding the same to be carried out.
  - Consider evaluation for midgut abnormalities including malrotation/volvulus in an ill looking infant.
  - Examine for inguinal hernia as there is around 60% risk of hernia becoming incarcerated in the first 6 months of life.
- *Extremities*:
  - Examine for joint swelling, tenderness, erythema, and any restriction of range of movement to rule out septic arthritis.
  - In infants of <1-year age have high index of suspicion for nonaccidental injury in cases of suspected or detected fractures.

- *Skin*:
  - Complete exposure of the infant and evaluation for bruises and ecchymosis. The most common sites are anterior tibia, knee, or forehead. However, bruises on face and trunk are rare and their presence should raise a concern for abuse.
  - Burn injuries in the patterned shape of hot objects (like cigarettes), bilateral glove and stocking pattern (suggestive of immersion injuries) should prompt an evaluation for infant abuse. Accidental scald injuries due to spill over of hot liquids tend to usually affect the face, neck, upper limbs, and anterior trunk and are usually asymmetrical and have irregular edge and burn depth.

Interpretation of Findings

Detailed observation of a crying infant gives clues into the underlying condition. For example, a continuous cry associated with grunt points to an underlying respiratory tract infection or foreign body. High-pitched incessant cry indicates a central nervous system etiology, screaming while pulling ears indicates acute otitis media and intermittent bout of crying with knee drawn up over abdomen is suggestive of intussusception.

INVESTIGATIONS

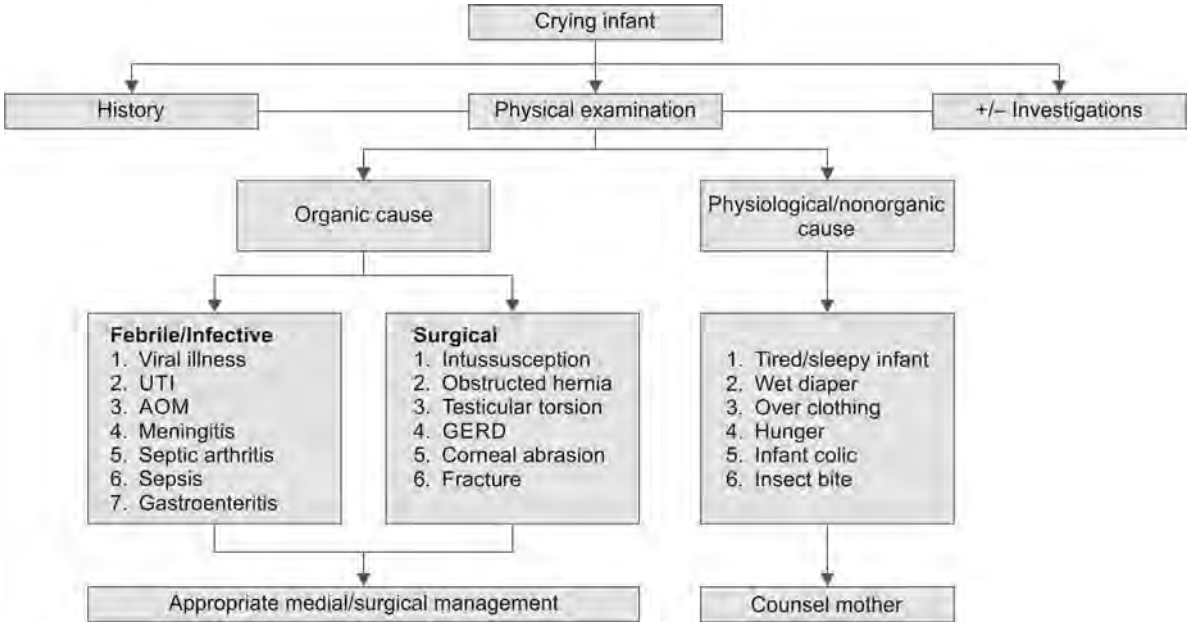
Role of investigations is very limited and may be useful in only about 3–5% cases where history and examinations are inconclusive. History and clinical assessment should guide decision making regarding investigations. A period of observation and follow-up is deemed desirable in cases where diagnosis has not been established. At times, negative results help in ruling out serious illness and can be reassuring before discharge. Investigations that can aid in diagnosis include corneal fluorescein staining for abrasions and USG abdomen for intussusception. Urine microscopic examination and culture, stool occult blood testing, and rectal examination have occasionally been of use in diagnosing an underlying condition in a crying infant. Testing for gastroesophageal reflux is not routinely done.

TREATMENT

Crying is a "common denominator" for a variety of illnesses and physiological disturbances. Management of a crying infant depends on the diagnosis. Ruling out apparent causes of crying such as hunger, sleepiness, and tiredness is the first step in treating an infant with persistent crying. Red flag signs should be sought after and managed accordingly. **Flowchart 1** provides a diagnostic approach.

Managing a crying infant is a two-part procedure, first, comprising of diagnosing and managing the underlying problem and secondly, counseling the mother regarding normal crying and sleep pattern and needs to timely address various clues. Among the benign causes, infant colic poses a challenging situation to both parents as well as to the clinician. Various pharmacological and nonpharmacological strategies have been tried with various successes.

- *Reassurance*—inform the parents the benign nature of the disease and its natural course.
- *Probiotics*—lactobacillus reuteri has been proposed to reduce colics in breastfed infants. Its role in formula fed infants is not well established.
- *Medications*—simethicone, though commonly used, its effectiveness has not been fully established. It is defoaming agent that is proposed to accelerate passage of flatus through intestinal tract. Dicyclomine and dicycloverine are anticholinergic medications thought to act by relieving spasms of intestinal smooth muscles. Owing to the large number of adverse effects these drugs are contraindicated in children <6 months of age. Proton pump inhibitors like omeprazole, act by relieving gastroesophageal reflux, though in various studies their efficacy was no better than that of placebo.



(AOM: acute otitis media; GERD: gastroesophageal reflux disease; UTI: urinary tract infection)

FLOWCHART 1: An approach to a crying infant.

BOX 1: Nonpharmacological interventions in a crying infant.

To prevent or minimize crying:
- Kangaroo care
- Swaddle holding
- Pacifier combined with sugar water
- Sugar water alone
- Sweet-tasting non-sucrose solution
- Heartbeat sounds
- Lullabies or mother's voice
- Rhythmic movement
- Reduction of external stimuli

When responding to a cry:
- Answer the cry as soon as possible
- Answer the cry consistently
- Answer the cry completely: touch, talk, and be in the infant's visual field

- *Diet*—colic prevalence is similar between breastfed and formula fed infants, hence mother should be encouraged to continue to breastfeeding. Maternal dietary modification may be considered in case of family history of atopy. Dietary counseling should be undertaken to ensure adequate nutrition. Formula fed infants might be considered for change of formula. Various nonpharmacological interventions have been studied in the management of a crying infant. **Box 1** enlists various such interventions.
- *REST* for parents includes *R*eassurance, *E*mpathy, *S*upport from the healthcare provider, and *T*ime out for the parents (e.g., rest and renewal). Such comforting measures do not work uniformly for everyone and hence parents should be guided to identify a unique, comforting technique that is suited to their child. Extreme cases may warrant mild sedation and temporary hospitalization. Professional support with reassurance and empathy from healthcare providers is crucial in dealing with these infants and parents.

SUMMARY

A crying infant is a frequent presentation to an emergency department. Each such infant needs to be thoroughly evaluated to look for warning or red flag signs, which might need urgent medical intervention. The role of detailed history from parents and a thorough physical examination cannot be emphasized more. Although infant colics are common, first episode of incessant cry should be dismissed off as colic without detailed evaluation. The general appearance of the baby can give clues to the underlying cause. Child abuse should be kept as a differential diagnosis while evaluating suck infants. Screening and diagnostic tests should be guided by history and examination. When a diagnosis of a benign cause such as colic is made, parents should be offered reassurance as well as insight into various pharmacological and nonpharmacologic methods available to comfort their child. As each child is different, they must be encouraged to seek the best possible intervention suited to their child. Approaching such a problem with an open-minded inquisitive manner is comforting to the parents as well the physician. In cases where history, physical examination, and initial testing do not prove conclusive, a period of observation must be considered in ED and the infant should be closely monitored and reexamined for crying pattern and any new manifestations such as fever and signs of acute abdominal conditions to guide additional testing and decide further disposition. There is no consensus on duration of the observation period in ED.

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164 CHAPTER

Immunization in Pregnant Women, Infant and Children

Ashok Mishra

INTRODUCTION AND BACKGROUND

Immunization is one of the most cost-effective public health interventions. Various foreign particles, e.g., proteins, virus, pathogens, parasitic worms, chemicals, and toxins are trying to gain access into the body. Our immune system readily separates them from natural healthy tissues, its cells and proteins. When this immune system is sensitized with the milder infective form of disease, this same immune system helps to protect the body from subsequent attack of disease causing agent. Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection or disease [World Health Organization (WHO)]. The most important elements of immune system are T-cells, B-cells, and the antibodies B-cells, while memory T-cells and memory B-cells are responsible for swift action at the time of second encounter with the disease causing agents. This whole process is known as active immunization. When readymade antibodies are inoculated into the body of a person without it is being produced by body itself, it is known as passive Immunization.

World Health Organization estimates that vaccination averts 2–3 million deaths per year (in all age groups), and up to 1.5 million children die each year due to diseases which could have been prevented by vaccination. During 2016, 116.5 million infants worldwide received three doses of diphtheria-tetanus-pertussis (DPT) vaccine, protecting them against infectious diseases that can cause serious illness and disability. There was 84% drop in measles deaths between 2000 and 2016 worldwide, due to measles vaccination. Polio cases have decreased by over 99% since 1988. Today, only three countries (Afghanistan, Nigeria, and Pakistan) remain polio-endemic, down from >125 in 1988. In 2016, an estimated 19.5 million infants worldwide were not reached with routine immunization services such as DTP3 vaccine. Around 60% of these children live in 10 countries—Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Iraq, Nigeria, Pakistan, and South Africa.

The Global Vaccine Action Plan (GVAP) was launched with a roadmap to prevent millions of deaths through more equitable access to vaccines by 2020. To date, progress toward the GVAP targets is off track. In May 2017, Ministers of Health from 194 countries endorsed a new resolution on strengthening immunization to achieve the goals of the GVAP ·vaccination is a miracle of modern medicine. In the past 50 years, it saved more lives worldwide than any other medical product or procedure. Modern medicine knows Edward Jenner as the father of immunology/vaccination, an English physician and scientist who was the pioneer of smallpox vaccine, the world's first vaccine and also coined the term vaccine and vaccination. But the story of vaccine does not begin here; rather Chinese were pioneer in variolation for smallpox as early as AD 1000.

HISTORICAL ASPECTS OF VACCINATION

Buddhist monks drank snake venom to confer immunity to snake bite and variolation (smearing of a skin tear with cowpox to confer immunity to smallpox) was practiced in 17th century China. The earliest documented examples of vaccination are from India and China in the 17th century, where vaccination with powdered scabs from people infected with smallpox was used to protect against the disease. The mention of inoculation in the *Sact'eya Grantham*, an *Ayurvedic text*, was noted by the French scholar Henri-Marie Husson in the journal Dictionnaire des sciences médicales. However, the fascinating story of vaccination goes back all the way to Ancient Greece.

Brief History of Vaccination

Prior to 1974 and Expanded Program on Immunization (EPI), child vaccination coverage for tuberculosis, diphtheria, pertussis, tetanus, polio, and measles was estimated to be <5%.

The WHO initiated the EPI in May 1974 with the objective to vaccinate children throughout the world. But the vaccination schedule for EPI was formulated by WHO in 1984 and included Bacillus Calmette–Guérin (BCG), DPT, oral polio vaccine (OPV), and measles. With the advent of newer vaccines, EPI was expanded and included HepB, *Haemophilus influenzae type B* (Hib), and Yellow Fever vaccine in endemic areas. Subsequently in 1999 Global Alliance for Vaccines and Immunization (GAVI) was created to increase the access of

EPI in the farthest and poorest countries. Inspired from WHO, India launched the EPI in 1978 which was expanded in 1985 as Universal Immunization Program (UPI) which became part of Child Survival and Safe Motherhood in 1992. UIP then became important component of National Reproductive and Child Health Program in 1997, currently UIP is part of NHM since 2005. At present, 12 vaccine preventable diseases are covered under UIP, i.e., TB, diphtheria, pertussis, tetanus, polio, measles, hepatitis B, diarrhea, Japanese encephalitis, rubella, pneumonia (Hib), and pneumococcal diseases (pneumococcal pneumonia and meningitis). Hepatitis B and pneumococcal diseases were added to the UIP in 2007 and 2017, respectively. Inactivated poliovirus vaccine (IPV), rotavirus vaccine (RVV), Measles-Rubella (MR), and JE were the addition in the UIP program recently. To strengthen routine immunization planning and delivery mechanism, the Ministry of Health and Family Welfare (MoHFW), Government of India (GOI) launched its flagship program "Mission Indradhanush" in December 2014 to achieve >90% full immunization coverage in the country.

VACCINATION IN PREGNANCY

Fetal development and its fate depend on mother's health and wellbeing. Her contracting the disease affects the fetus in womb. Hence, proper immunization of "to be mother" plays a significant role in preventing untoward incidents during pregnancy and at term. Vaccinated mother passes disease protecting antibodies to fetus having immature adaptive immune system, which then protects both mother and fetus from vaccine preventable diseases during pregnancy and later life as "to be born baby" is highly susceptible for various disease-causing agents.

Live virus poses a threat to developing fetus in womb hence it is generally contraindicated for giving live vaccines to women planning conception within 4 weeks (in preconception phase) and already pregnant women. Toxoids, killed/inactivated bacteria, or virus vaccines have not shown any untoward incidents to both mother and fetus hence it is very important to vaccinate a mother if she is at high risk of being exposed to vaccine preventable disease or if infection poses a great threat to the lives of fetus or mother or both.

It is very imperative to assess the risk versus the protective benefits provided by the vaccination in each situation, regardless of its being live or inactivated vaccine. UIP by government of India recommends two doses of tetanus toxoid (TT) to all pregnant women at an interval of 4 weeks as soon as pregnancy is detected.

All live attenuated vaccines are not routinely recommended for immunization schedule. Vaccines which are contraindicated in pregnant women are human papillomavirus (HPV), measles, mumps, rubella, varicella, oral typhoid vaccine, live attenuated JE vaccine, and zoster vaccine. Others not recommended in routine immunization schedule can be given in exceptional circumstances where benefits of vaccination surpass the associated risk.

BC 429	• The Greek historian *Thucydides* observed that those who survived the smallpox plague in Athens did not become reinfected with the disease.
AD1554	• Some 8,000 children died in Goa, India, from a smallpox epidemic most likely introduced by the Portuguese.
1718	• Variolation in Turkey–Lady Mary Wortley Montagu (1689–1762) had her son variolated in Constantinople by Dr Charles Maitland, April 1718.
1721	• Lady Mary Montagu brought the practice of variolation to England, where she had Dr Charles Maitland variolate her 2-year-old daughter.
1796	• On May 14, 1796, Edward Jenner inoculated 8-year-old James Phipps with matter from a cowpox sore on the hand of milkmaid Sarah Nelmes and form the basis of vaccination.
1813	• US Vaccine Agency established signed by James Madison.
1853	• The United Kingdom Vaccination Act of 1853 made smallpox vaccination mandatory in the first three months of an infant's life.
1881-85	• Louis Pasteur presented the success of rabies vaccine and successfully used them on 350 people later, only one died as vaccination was started late. Anthrax vaccine was developed by Louis Pasteur in 1881.
1923	• Diphtheria toxoid vaccine developed.
1926-27	• Pertussis, BCG vaccination.
1936	• Oral polio vaccine.

Vaccination for Pregnant Women as per National Immunization Schedule

Tetanus Toxoid Vaccine

Exotoxin produced by *Clostridium tetani* causes tetanus which is an acute, often fatal disease. This is due to low levels of antitetanus antibody in neonates transferred passively from mother.

Tetanus toxoid vaccine was first produced in 1924 and used extensively for the first time among soldiers during World War II. Since then, immunization program using TTs has been highly successful in preventing maternal and neonatal tetanus (MNT) as well as injury-associated tetanus.

World Health Organization estimates that there were 59,000 neonatal tetanus deaths in 2008, a 92% reduction from the late 1980s and an indicator of how widely maternal TT immunization is being used. It is estimated that at least 100 million doses of TT vaccine were given to pregnant women in 2011 (compared with 64 million women between 1995 and 2004).

A WHO position paper on tetanus, published in 2006, suggested that three doses of DTP vaccine should be given in infancy, with boosters in childhood and adolescence and a sixth dose at first pregnancy as tetanus diphtheria and acellular pertussis (TdaP). If a good immunization history is not available, pregnant women should receive two doses of vaccine 4 weeks apart and at least 2 weeks (preferably 4 weeks) before delivery.

Optimal timing for TdaP/TT administration is between 27 and 36 weeks of gestation although TdaP/TT may be given at any time during pregnancy.

A search of the vaccine adverse event reporting system (VAERS) database for 2005–2010 did not identify any concerns about maternal, infant, and fetal outcomes following vaccination with a reduced amount of diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine (DTaP).

Recently, vaccination with TdaP combined with IPV has been recommended for pregnant women in the United Kingdom.

The American Congress of Obstetricians and Gynecologists also recommends giving diphtheria toxoid, TT, and acellular pertussis vaccine to pregnant women.

Vaccination for Pregnant Women under Special Circumstances

Influenza Vaccine

Pregnant women are at increased risk of influenza disease. Its severe complications included small for gestational age and preterm birth for fetus, both are at increased risk of mortality. Pregnant women with underlying medical conditions develop increased incidence of seasonal influenza disease with severity. Benefits associated with influenza vaccination particularly in second and third trimester with transplacental transfer of protective antibodies providing indirect protection against illness in mothers and their infants have outnumbered the risk factors. These benefits have made many countries all over the world to incorporate influenza vaccines in their national immunization schedule and policies. A single dose of 0.5mL IM is to be given.

Though live attenuated influenza vaccine (LAIV) is not recommended for use during pregnancy.

Japanese Encephalitis Vaccine

Japanese encephalitis vaccine should not be routinely administered during pregnancy. Pregnant women who must travel to an endemic area during the transmission season where risk of JE is high and if staying for >30 days should be vaccinated. Vaccination should be considered, if she is visiting a rural area with extensive outdoor activities and even if staying for <30 days, as the theoretical risks of immunization are outweighed by the risk of infection to the mother and developing fetus. Dose is 1 mL SC on 0, 7, and 30 days. Booster doses of 1.0 mL may be administered after 2 years.

Hepatitis A Vaccine

Not routinely recommended for immunization in pregnant lady. Hepatitis A vaccine (HAV) is produced from inactivated HAV; the theoretical risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who might be at high risk for exposure to HAV. Live vaccine is contraindicated in pregnancy.

Hepatitis B Vaccine

Pregnant women who are identified as being at risk for hepatitis B vaccine (HBV) infection during pregnancy [e.g., having more than one sex partner during the previous 6 months, been evaluated or treated for an sexually transmitted disease (STD), recent or current injection drug use, or having had a HBsAg-positive sex partner] should be vaccinated. Dose of vaccination is 1 mL IM at 0, 1, and 6 months interval.

Meningococcal Vaccines

Meningococcal conjugate vaccines may be given to pregnant women who are at increased risk, e.g., complement component deficiency, e.g., C5-C9, properdin, factor H, factor D, etc., or functional or anatomic asplenia (including sickle cell anemia), HIV, etc. Two primary doses of meningococcal conjugate vaccines are required with booster doses every 5 years.

Serogroup B meningococcal vaccines should only be given to pregnant or breastfeeding women who are at increased risk for serogroup B meningococcal disease, if the benefits of receiving the vaccine outweigh the risk. Dose is 0.5 mL IM.

Haemophilus Influenzae Type B

Pregnant women with certain high-risk conditions, for example, lack of a functioning spleen, need vaccination with Hib. It is safe to receive this at any time during pregnancy though not routinely recommended in immunization schedule.

Pneumococcal Polysaccharide Vaccine-23

Pneumococcal polysaccharide vaccine (PPSV) can be given in pregnant women if she is having high risk of getting pneumococcal infection/disease, i.e., DM, chronic lung disease, chronic cardiovascular diseases, cochlear implants, immunocompromising conditions, and functional or anatomic asplenia (e.g., sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, splenic dysfunction, or splenectomy).

Rabies Vaccine

If a pregnant lady gets exposed to category two or three bites by a wild animal/rabid dog or untraceable dog/cat, she should get five doses of ARV IM on 0, 3, 7, 14, and 28 days with or without rabies immunoglobulin as per schedule without delay. If the risk of exposure to rabies is substantial, pre-exposure prophylaxis also might be indicated during pregnancy on 0, 3, and 21 days or 0, 7, and 21 days.

As an alternative to intramuscular (IM) regimen intradermal (ID) route can be used. Dose is 0.1 mL ID on both shoulders on 0, 3, 7, and 28 days.

Yellow Fever Vaccine

Vaccines are live attenuated viral vaccines from the 17D lineage. As far as possible, it should be avoided in pregnant women. Pregnant women should be advised against going to the rural areas of yellow fever endemic areas (and to urban areas of West African countries as well). However, where travel to an at-risk country is unavoidable, such women should be vaccinated. Yellow fever vaccines are given as a single dose (0.5 mL) injected either subcutaneously or intramuscularly.

VACCINATION IN CHILDREN

Every year vaccination prevents 2.5 million deaths globally. All the children immunized against vaccine preventable diseases can thrive and have better chances of survival with full potential. Hence immunization is, and should be recognized as, a core component of the human right to health. As part of a comprehensive package of interventions for disease prevention and control, vaccines, and immunization is an essential investment in a country's—indeed, in the world's—future. Now is the time for showing commitment to achieving the full potential of immunization. The vision for the decade of vaccines (2011–2020) is of a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases. The mission of the decade of vaccines is to extend, by 2020 and beyond, the full benefit of immunization to all people, regardless of where they are born, who they are or where they live. Vaccines routinely recommended for children as per National Immunization Schedule from birth onward are summarized in **Table 1**. Some vaccines are recommended in special situation which are also summarized in **Table 2**.

TABLE 1: National Immunization Schedule for children and pregnant women endorsed by IAPSM.

Vaccine	*Dose /site*	*Schedule for children*	*Schedule for pregnant women*
TT	0.5 mL, IM	At 10 years and 16 years as boosters	First dose as soon as pregnancy is diagnosed. Second dose, 4 weeks later. Only one booster if present pregnancy is within 3 years of the previous pregnancy with full immunization
BCG	0.05 mL or 0.1 mL, ID	As soon as possible after birth till 1 month of age. If missed can be given till 1 year of age	
Hepatitis B	0.5 mL, IM	Birth dose within 24 h. Then as pentavalent vaccine at 6, 10, and 14 weeks	
bOPV	Two drops orally	• At birth as zero dose, then 6, 10, and 14 weeks.16–24 months as booster • Also, as a part of pulse polio campaign	
Pentavalent vaccine	0.5 mL, IM	At 6, 10, and 14 weeks	
Fractional IPV	0.1 mL, ID	At 6 and 14 weeks	
Rotavirus	Five drops orally	At 6, 10, and 14 weeks	
Measles	0.5 mL, SC	First dose at 9–12 months and second dose at 16–24 months	
Vitamin A	1 lakh IU (1 mL) 2 lakh IU (2 mL)	• First dose At 9–12 months • Second dose at 16–24 months then repeated every 6 months till 5 years of age	
DPT	0.5 mL, IM	At 16–24 months, and at 5 years of age, can be given up to 7 years	
Pneumococcal conjugate vaccine	0.5 mL, IM	6 and 14 weeks then booster at 9 months	
JE live attenuated vaccine	0.5 mL, SC	2 doses at 9–12 months then 16–24 months of age (in selected endemic states)	

Pentavalent vaccine contains diphtheria toxoid, pertussis, tetanus toxoid, hepatitis B, and H. influenzae type B

(BCG: Bacillus Calmette–Guérin; bOPV: bivalent oral polio vaccine; ID: intradermal; IAPSM: Indian Association of Preventive and Social Medicine; IM: intramuscular; IPV: inactivated poliovirus vaccine; JE: Japanese encephalitis; SC: subcutaneous; TT: tetanus toxoid)

TABLE 2: Other vaccines recommended under special circumstances.

Vaccine	*Dose*	*Recommended in children in special situation*	*Recommended in pregnant women in special situation*
TdaP	0.5 mL, IM		Ideally at 27 and 36 weeks of pregnancy. But can be given at any time in pregnancy
HepB	0.5 mL, IM	0, 1, and 6 months if not received earlier	Pregnant women with increased risk can get 1 mL IM at 0, 1, and 6 months
Mumps	0.5 mL, IM	12–18 months then 2nd at 2–6 years of age	
Rubella	0.5 mL, IM, SC	12–15 months as single dose	
Pneumococcal polysaccharide vaccine	0.5 mL, IM, SC		Can be given as single dose
Japanese encephalitis (JE) (inactivated Vero cell)	0.5 mL, SC	2 doses 4 weeks apart	All should be vaccinated if travelling to high risk areas. 1.0 mL SC, on 0, 7, and 30 days
Inactivated influenza vaccine	0.5 mL, IM		Single dose in pregnant women. 0.5 mL, IM
Hepatitis A—Inactivated	0.5 mL, IM	>1 year age children then 2nd at an interval of 6/12 months	Single dose 0.5 mL, IM
Hepatitis A—live	0.5 mL, SC	Single dose	
Meningococcal conjugate vaccine (quadrivalent)	0.5 mL, IM	High-risk children • >2 years as 0.5 mL, single IM dose • 9–23 months should get two doses 3 months apart	High-risk pregnant women should get two primary doses with booster every 5 years depending on the conditions
Meningococcal polysaccharide	• 0.5 mL, IM • Not recommended in <2 years children	High risk >2 years old, booster after 3–5 years later	High-risk pregnant women should get a dose with booster every 5 years
Haemophilus influenzae type b (Hib)	0.5 mL, IM	>1 year of age, only single dose	High-risk pregnant women should get single dose
Typhoid vaccine (live attenuated Ty21a) Ty21a also as an oral capsule	• 0.5 mL, IM • Enteric-coated capsule	• >6 months as a single dose • Two doses on alternate days (oral capsule)	
Typhoid vaccine unconjugated Vi polysaccharide (ViPS)	0.5 mL, IM, SC	>2 years as a single dose	
Cholera vaccine	Oral vaccine	2–5 years, three doses, 1–6 weeks apart. >5 years, two doses, 1–6 weeks apart recommended	High-risk pregnant women. Two doses, 1–6 weeks apart to help prevent spread
Varicella vaccine	0.5 mL, SC	Preferably starting at 12–18 months of age. Two doses 4–12 weeks apart	
Rabies vaccine	0.5/1 mL, IM	Depending on exposure/risk 0, 3, 7, 14, and 28 days of schedule	Depending on exposure/risk 0, 3, 7, 14, and 28 days of schedule
Human papillomavirus vaccine	0.5 mL, IM	• 9–14 years age—0, 6 month or 0, 1–2, 6 months • 15–26 years age should get 0, 2, and 6 months	
Yellow fever vaccine	0.5 mL IM, SC	9–12 months of age	

*All vaccines which are recommended in special circumstances must be given after consultation with qualified doctor.

(IM: intramuscular; SC: subcutaneous)

Vaccination for Children as per National Immunization Schedule

Bacillus Calmette–Guérin Vaccine

Bacillus Calmette–Guérin vaccine is a suspension of a live attenuated strain of mycobacterium. Reconstituted vaccine contains 8–32 × 10^6 colony forming units per mL and monosodium glutamate 1.5% w/v. BCG vaccination probably has little effect on preventing infection per se, or reactivation among those already infected with TB. However, there is strong evidence that BCG vaccination in infancy provides >70% protection against severe disseminated forms of TB disease in young children, including military TB and tubercular meningitis. BCG vaccine should be stored at +2 to +8°C, not to be frozen and should be protected from light. Reconstituted vaccine is very unstable and must be stored at +2 to +8°C and used within one working session preferably of 4 hours. Diluent of BCG vaccine is normal saline. Dose is 0.05 mL for infants <1 month, 0.1 mL for >1 month till 1 year by intradermal route, using 26–27-gauge needle as a single dose on left deltoid region only. Generally, within 2–3 weeks of vaccination a small red papule forms and eventually ulcerates, it heals subsequently. Moderate-to-late preterm infants (gestational age >31 weeks) and low birth weight infants (<2,500 g) who are healthy and clinically stable can receive BCG vaccination at birth, or at the latest, upon discharge. Infants born to mothers treated with disease modifying anti-rheumatic drugs (DMARDs) [e.g., tumor necrosis factor-alpha (TNF-α) blocking monoclonal antibodies] in the third trimester of pregnancy frequently have detectable antibodies for several months and they should not be vaccinated. Infants exposed to immunosuppressive treatment in utero or via breastfeeding should not receive BCG.

Precaution can be taken for neonates who are medically unstable or born to mothers who are HIV positive and HIV status of infant is not ascertained yet, till then it should be avoided.

Hepatitis B Vaccine

About 0.5 mL monodose vial or prefilled syringe of HBV contains 10 μg HBsAg protein, adsorbed onto 0.25 mg aluminum as aluminum hydroxide and it may contain yeast proteins also. Hepatitis B is given at birth along with OPV and BCG, as birth dose of hepatitis B, followed by three doses of a hepatitis B containing combination vaccine (e.g., pentavalent) at 6th, 10th, and 14th week of life. As per UIP, birth dose is to be given within 24 hours of birth only, if missed need not be given later, only three doses at 6th, 10th, and 14th week can be given. For older children <20 years, if hepatitis B is missed earlier, a three-dose schedule of pediatric formulation can be given at 0, 1st, and 6th month interval. For those >20 years, 1 mL IM dose can be given at 0, 1st, and 6th month.

Oral Polio Vaccine

Two drops of zero dose bivalent OPV (bOPV) is to be given to infant at birth or as soon as possible within 15 days followed by bOPV at 6th, 10th, and 14th week along with other vaccines. To ensure early protection, a schedule of two fractional intradermal doses of IPV administered at 6 and 14 weeks is added in the National Immunization Schedule. Site is right upper arm. There was a planned global switch from trivalent OPV (tOPV) to bOPV in April 2016. A booster dose is given at 16–24 months of age.

Government of India launched the Pulse Polio Abhiyan in 1995 as an immunization campaign by vaccinating all children under 5 years of age till poliomyelitis is eliminated from India. Since almost all the cases of polio come under 5 years, the upper age limit for vaccination in the campaign is 5 years for bOPV. The age range of polio might go up in well-immunized communities, due to the retardation of circulation of the causative wild polioviruses. The WHO recommends to monitor all cases of acute flaccid paralysis in children up to 15 years and to investigate them for poliovirus etiology.

Pneumococcal Vaccine

The vaccine contains 0.02% polysorbate 80 (P80), 0.125 mg of aluminum as aluminum phosphate (AlPO4) adjuvant, 5 mL of succinate buffer, and no thiomersal preservative. Except for the addition of six serotypes, P80, and succinate buffer, the formulation of PCV13 is the same as that of PCV7. Dose is 0.5 mL IM on anterolateral aspect of mid-thigh at 6th and 14th week followed by booster dose at 9 months of age or alternately as three primary doses 4/8 weeks apart.

Pentavalent Vaccine

It contains combination of five vaccines, i.e., diphtheria toxoid, pertussis, TT, Hib, and HepB vaccine. In 2000, before widespread introduction of Hib vaccine in resource-poor countries, Hib caused 8.13 million cases of serious disease in children aged 1–59 months with 371,000 deaths.

When Hib is given to a child >12 months of age for the first time (who has not received pentavalent vaccine), only one dose is recommended. Hib vaccine is not required for healthy children after 5 years of age.

Pentavalent vaccine is given in a dose of 0.5 mL IM on anterolateral aspect of mid-thigh at 6th, 10th, and 14th week of age. The need for early infant vaccination with DTP-containing vaccine, i.e., pentavalent vaccine is principally to ensure rapid protection against pertussis, because severe disease and death from pertussis are almost entirely limited to the first weeks and months of life. Despite high vaccination coverage (in 2014, 86% coverage with three doses of a pertussis containing vaccine), pertussis remains endemic in all countries and continues to be a public health concern. Pertussis containing vaccine (DPT, pentavalent vaccine, etc.) should be started as soon as 6 weeks of age and WHO recommends that primary series of immunization should ideally be completed by 6 months. It provides protection for at least 6 years. Only acellular pertussis containing vaccines should be used for vaccination of persons aged ≥7 years.

Pentavalent vaccine is a freeze sensitive vaccine, and should be stored and transported at +2 to +8°C in ice-lined refrigerators and vaccine carriers with conditioned ice packs.

From 2011–2015, India had the largest number of reported cases of diphtheria (18,350 cases) followed by Indonesia and Madagascar (3,203 and 1,633 cases, respectively). The first dose of vaccine should be given as early as 6 weeks of age, and the third dose should be completed by 6 months of age, i.e., 4 week interval between doses. DPT is given at 16–24 months of age as first booster and at 5–7 years as second booster dose.

Tetanus can be protected for life if at least six doses (three primary plus three booster doses) are provided to all people through routine childhood immunization schedules. WHO recommends three TT booster doses, ideally with at least 4 years between booster doses. These should be given at: 12–23 months of age; 4–7 years of age; and 9–15 years of age.

In National Immunization Schedule, TT is given as pentavalent vaccine at 6, 10, and 14 weeks, then as DPT vaccine at 16–24 months and at 5–7 years of age. Then TT is given at 10 and 16 years of age. Pentavalent vaccine is not given beyond 1 year of age.

Rotavirus Vaccine

Rotaviruses (RVs) are globally the leading cause of severe, dehydrating diarrhea in young children. Two RVVs are available. RV1 originates from a human strain, whereas RV5 contains five reassortants developed from RVs of human and bovine origin. It is a live, oral, and attenuated RVV. National Immunization Program recommends three doses at 6th, 10th, 14th week. Five drops are given orally along with pentavalent vaccine and OPV. Healthy children aged over 2 years are not considered necessary. Precautions for use of rotavirus vaccination include a history of intussusceptions or intestinal malformations, chronic gastrointestinal disease, and severe acute illness. Vaccination should be postponed when the child has ongoing acute gastroenteritis or fever with moderate-to-severe illness.

Measles Vaccine

Measles is one of the most contagious diseases of humans, and in the absence of vaccination, about 95% of individuals would be infected with measles virus by 15 years of age. In 2000, measles was the fifth leading cause of childhood morbidity and mortality worldwide. There were estimated 770,000 deaths, with more than half of these occurring in Africa. In 2015, there were estimated 134,200 measles deaths globally, representing a 79% decline since 2000. All six WHO regions have measles elimination goals before or by 2020, and the GVAP, endorsed by the WHO, has a goal to eliminate measles in five of the six WHO Regions by 2020.

Measles vaccination is a cost-effective measure in preventing morbidity and mortality with measles. Dose recommended is 0.5 mL SC at 9–12 months of age and booster to be given at 16–24 months of age. Vaccinating infants before or at the age of 6 months often fails to induce seroconversion due to the immaturity of the immune system as well as the presence of neutralizing maternal antibodies. WHO recommends vaccination of infants from 6 months during a measles outbreak/epidemic, here the risk of measles among infants <9 months is high; infants travelling to countries experiencing measles outbreaks; infants known to be HIV infected or exposed. Measles administered before 9 months of age should be considered a supplementary dose and recorded as "measles 0 (Zero) dose, these infants should be immunized at recommended age as per schedule. Diluent for measles vaccine is double distilled water and reconstituted vaccine should be used within 2 hours to prevent toxic shock syndrome due to contamination with *Staphylococcus aureus*.

Vaccination for Children under Special Circumstances (Table 2)

Mumps Vaccine

The initial dose is recommended between the age of 12 and 18 months of age. The second dose is then typically given between 2 and 6 years of age. Usage after exposure in those not already immune may be useful. Combined vaccine in the form of MR, MMR, and MMRV can be given with minimum 4 weeks interval between two doses.

Rubella Vaccine

Usually a mild self-limited illness, rubella during early pregnancy may result in miscarriage, fetal death, or congenital defects known as congenital rubella syndrome (CRS). Before introduction of rubella vaccine, the incidence of CRS varied from 0.1 to 0.2 per 1000 live births during endemic periods and from 0.8 to 4 per 1,000 live births during rubella epidemics.

Most rubella vaccines are based on the live, attenuated RA 27/3 strain. Up to 95–100% of susceptible persons aged ≥12 months develop rubella antibodies after a single dose of the vaccine. Dose schedule is 0.5 mL, SC or IM at 12–15 months of age.

Japanese Encephalitis Vaccine

Japanese encephalitis virus is the leading cause of viral encephalitis in Asia, currently and estimated three billion people live in the 24 countries mainly in the WHO South East Asia and Western Pacific Regions, considered at risk of JE. It is estimated that 67,900 severe clinical cases of JE occur annually despite widespread availability of vaccine with approximately 13,600-20,400 deaths.

Japanese encephalitis vaccines fall into four classes:

1. Inactivated mouse brain derived vaccines
2. Inactivated Vero cell-derived alum-adjuvanted vaccine (SA14-14-2 strain) requires two intramuscular doses at 4-week intervals, starting at ≥6 months of age in endemic settings. The dose is 0.5 mL, IM.
3. Live attenuated vaccines with single dose of 0.5 mL SC at ≥8 months of age
4. Live recombinant (Chimeric) vaccines single dose at ≥9 months of age, a single booster dose can be given 12–24 months later for those <18 years of age as booster for adults are not recommended as of now.

In our national immunization schedule, two doses of live attenuated JE vaccine (SA-14-14-2) are given at 9–12 months and at 16–24 months of age in high endemic areas, e.g., in selected endemic districts of UP, Bihar, Assam, Karnataka, and West Bengal. Diluent used for JE vaccine is phosphate buffer.

Yellow Fever Vaccine

Vaccines are live attenuated viral vaccines from the 17D lineage. Yellow fever vaccines are given as a single dose (0.5 mL) injected either subcutaneously or intramuscularly at age 9–12 months at the same time as the measles vaccine. All unvaccinated travelers aged >9 months and asymptomatic HIV infected persons with CD4 T-cell counts ≥ 200 cells/mm should

get yellow fever vaccine. Yellow fever vaccine is contraindicated in children aged <6 months. It is not recommended for those aged 6–8 months, except during epidemics.

Typhoid Vaccine

Typhoid fever is an acute generalized infection, caused by a highly virulent and invasive enteric bacterium, *Salmonella typhi*. Global estimates of typhoid fever burden range between 11 and 21 million cases and approximately 128,000 to 161,000 deaths annually. The majority of cases occurs in South/South-East Asia and sub-Saharan Africa.

Currently three types of typhoid vaccines are licensed for use: (1) Typhoid conjugate vaccine (TCV); (2) Unconjugated Vi polysaccharide (ViPS); and (3) Live attenuated Ty21a vaccines. The second and third types have been recommended by WHO since 2008 for the control of typhoid in endemic and epidemic settings. Typbar-TCV was first licensed in India in 2013 for intramuscular administration of a single dose (0.5 mL) in children aged 6 months and older. Each vaccine dose comprises 25 μg of purified Vi-capsular polysaccharide conjugated to TT. ViPS is licensed for use in individuals aged 2 years and older, to be administered subcutaneously or intramuscularly as a single dose of 0.5 mL. But booster dose may be given after 3 years.

The Ty21a vaccine is currently only available as enteric-coated capsules for oral administration on alternate days in a three-dose regimen (or a four-dose regimen in Canada and the USA).

Cholera Vaccine

Cholera is a rapidly dehydrating diarrheal disease caused by ingestion of toxin producing strains of serogroup O1, or less commonly, serogroup O139, of the bacterium *Vibrio cholera*. Approximately 1.3 billion people are at risk of cholera in endemic countries. An estimated 2.86 million cholera cases (uncertainty range 1.3–4.0 m) occur annually in endemic countries. Among these cases, there are an estimated 95,000 deaths. About half of the cholera cases and deaths are estimated to occur in children ≤5 years of age. WC vaccines (Shanchol, Euvichol, and mORCVAX) [killed modified whole cell bivalent (O1 and O139) vaccine without the B subunit], two doses should be given 14 days apart to individuals ≥1 year of age.

For WC-rBS vaccine (Dukoral) [killed whole cell monovalent (O1) vaccines], three doses should be given to children 2–5 years of age, and two doses to children aged ≥6 years and adults, with an interval of 1–6 weeks between doses in both groups.

Rabies Vaccine

If a child gets exposed to category two or three bites by a wild animal/rabid dog or untraceable dog/cat, he/she should get five doses of ARV IM on 0, 3, 7, 14, and 28 days with or without rabies immunoglobulin as per schedule without delay. If the risk of exposure to rabies is substantial, preexposure prophylaxis also might be indicated on 0, 3, and 21 days or 0, 7, and 21 days

As an alternative to IM regimen ID route can be used. Dose is 0.1 mL ID on both shoulders on 0, 3, 7, and 28 days.

Human Papillomavirus Vaccine

Persistent infection by oncogenic HPV types is a prerequisite for the development of cervical cancer, which each year hits about 528,000 women and causes 266,000 deaths worldwide. The viral types 16 and 18 HPV are the most common types in invasive cervical cancer, accounting for about 70% of all cervical cancers. In total, 85% of cervical cancer cases occur in the less developed regions and mortality rates vary as much as 18-fold between industrialized and developing countries. Other manifestations of HPV infection include vaginal, vulvar, penile, Oropharyngeal, and anal cancers. In addition, HPV types 6 and 11 cause anogenital warts and recurrent respiratory papillomatosis. HPV is mainly transmitted sexually. Recommended target population for the prevention of cervical cancer is females aged 9–14 years, prior to becoming sexually active.

Three prophylactic HPV vaccines are in use directed against high-risk HPV types. The quadrivalent vaccine (e.g., Gardasil) was first licensed in 2006. It contains noninfectious protein antigens for HPV 6, 11, 16, and 18. The bivalent vaccine was licensed in 2007 and contains noninfectious protein antigens for HPV 16 and 18. The monovalent vaccine (e.g., Gardasil 9) licensed in 2014 contains noninfectious protein antigens for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Dose is 0.5 mL, IM. Two-dose schedule for 9–14 years old children are 0 and 6–12 months. Three-dose schedules for 9–14 years are 0, 2, and 6 months. For >15 years old, three-dose schedule is recommended at 0, 2, and 6 months interval.

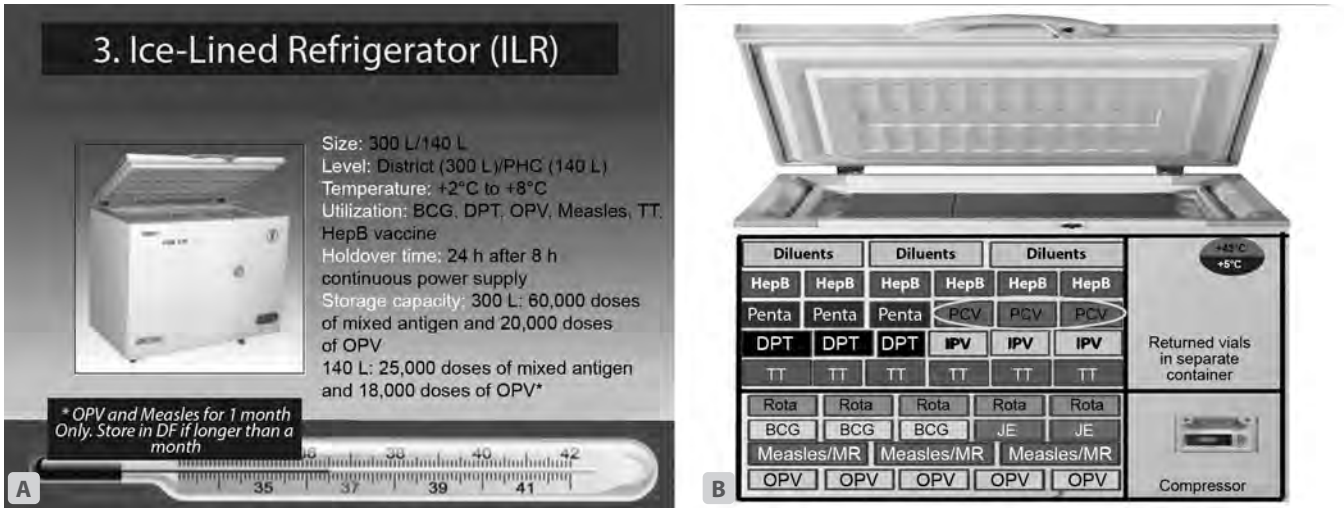
Varicella Vaccine

Varicella (chickenpox) is an acute, highly contagious disease with worldwide distribution caused by the varicella zoster virus (VZV). In temperate climates, most cases occur before the age of 10 years. Based on conservative estimates, the global annual varicella disease burden would include 4.2 million severe complications leading to hospitalization and 4,200 deaths. In the prevaccine era in high-income developed countries, case fatality rates for varicella were approximately 3 per 100,000 cases.

Two doses of varicella vaccine are recommended and should be administered at 12–18 months of age as 0.5 mL SC dose 3 months apart till 12 years of age. For >12 years, two doses of 0.5 mL each can be given as subcutaneous (SC) injection 4 weeks apart.

COLD CHAIN

Vaccines are sensitive biological products. Some vaccines are sensitive to freezing, some to heat, and others to light. Vaccine potency, meaning its ability to adequately protect the vaccinated patient, can diminish when the vaccine is exposed to inappropriate temperatures. Once lost, vaccine potency cannot be regained if it is lost anytime between manufacturing site and administration site. The storage and transportation of vaccine from the site of manufacturing to the site of utilization under optimum temperature (+2 to +8°C) are known as cold chain and equipment used is ice-lined refrigerator (**Figs. 1A** and **B**).


3. Ice-Lined Refrigerator (ILR)
Size: 300 L/140 L
Level: District (300 L)/PHC (140 L)
Temperature: +2°C to +8°C
Utilization: BCG, DPT, OPV, Measles, TT, HepB vaccine
Holdover time: 24 h after 8 h continuous power supply
Storage capacity: 300 L: 60,000 doses of mixed antigen and 20,000 doses of OPV
140 L: 25,000 doses of mixed antigen and 18,000 doses of OPV*
* OPV and Measles for 1 month Only. Store in DF if longer than a month
35 37 39 41
A
Diluents Diluents Diluents
HepB HepB HepB HepB HepB HepB
Penta Penta Penta PCV PCV PCV
DPT DPT DPT IPV IPV IPV
TT TT TT TT TT TT
Rota Rota Rota Rota Rota
BCG BCG BCG JE JE
Measles/MR Measles/MR Measles/MR
OPV OPV OPV OPV OPV
+43°C +5°C
Returned vials in separate container
Compressor
B

(BCG: bacillus Calmette–Guérin; DPT: diphtheria-tetanus-pertussis; IPV: inactivated poliovirus vaccine; TT: tetanus toxoid; OPV: oral polio vaccine)

FIGS. 1A and B: (A) Ice-lined refrigerator specifications; (B) arrangement of vaccine in ice-lined refrigerator.

Freeze sensitive vaccines are—cholera DTP, hepatitis B, Hib, IPV (hexavalent), pentavalent, HPV, IPV, influenza, pneumococcal, rotavirus (liquid and Freeze-dried), Tetanus, DT, and Td.

Vaccines that are as sensitive to light as they are to heat include BCG, measles, measles-rubella, measles-mumps-rubella, and rubella. These vaccines are often supplied in dark glass vials.

A vaccine vial monitor (VVM) is a label containing a heat sensitive material which is placed on a vaccine vial to register cumulative heat exposure over time.

ADVERSE EVENT FOLLOWING IMMUNIZATION

Immunization is among the most cost-effective public health interventions. It has led to the global eradication of smallpox as well as the elimination of poliomyelitis in regions of the world. Immunization currently averts an estimated 2–3 million deaths from diphtheria, tetanus, pertussis (whooping cough), and measles every year in all age groups. Unlike drugs, the expectations from vaccinations are much higher and problems arising from the vaccine or vaccination are less acceptable to the general public. Allegations that vaccines/vaccination cause adverse events must be dealt with rapidly and effectively as it can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence long after proof is generated that the adverse event was not caused by vaccine (e.g., autism and MMR, encephalopathy, and pertussis).

Adverse event following immunization (AEFI)—this is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. The adverse event may be any unfavorable or unintended sign, an abnormal laboratory finding, a symptom, or a disease. All vaccines should be given under medical supervision after consultation with a qualified medical practitioner. Before starting any immunization session, kindly ensure the availability of emergency tray (**Fig. 2**) with all necessary drugs and equipment.

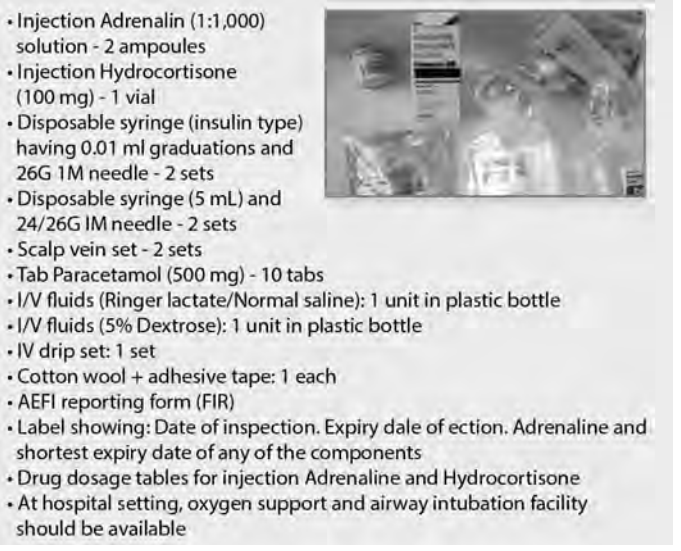

• Injection Adrenalin (1:1,000) solution - 2 ampoules
• Injection Hydrocortisone (100 mg) - 1 vial
• Disposable syringe (insulin type) having 0.01 ml graduations and 26G 1M needle - 2 sets
• Disposable syringe (5 mL) and 24/26G IM needle - 2 sets
• Scalp vein set - 2 sets
• Tab Paracetamol (500 mg) - 10 tabs
• I/V fluids (Ringer lactate/Normal saline): 1 unit in plastic bottle
• I/V fluids (5% Dextrose): 1 unit in plastic bottle
• IV drip set: 1 set
• Cotton wool + adhesive tape: 1 each
• AEFI reporting form (FIR)
• Label showing: Date of inspection. Expiry dale of ection. Adrenaline and shortest expiry date of any of the components
• Drug dosage tables for injection Adrenaline and Hydrocortisone
• At hospital setting, oxygen support and airway intubation facility should be available

FIG. 2: Contents of AEFI treatment kit.

SUMMARY

Immunization is a proven, time tested, and effective tool for controlling and eradicating disease. A successful immunization program is very much important for India because country contributes to one-fifth of global under-five mortality and most number of deaths due to vaccine preventable diseases. There is a significant progress which has been achieved in India with wider use of vaccines, resulting in prevention of several diseases. Successful immunization strategy for the country goes beyond vaccine coverage in that self-reliance in vaccine production, creating epidemiological database for infectious diseases and developing surveillance system are also integral parts of the system. National Immunization schedule for pregnant women, infants, and children are summarized in **Table 3**.

TABLE 3: National Immunization Schedule for pregnant women, infants, and children.

Vaccine	*When to give*	*Dose*	*Route*	*Site*
For pregnant women				
TT-1	Early in pregnancy	0.5 mL	Intramuscular	Upper arm
TT-2	4 weeks after TT-1*	0.5 mL	Intramuscular	Upper arm
TT-Booster	If received 2 TT doses in a pregnancy within the last 3 years*	0.5 mL	Intramuscular	Upper arm
For infants				
BCG	At birth or as early as possible till 1 year of age	0.1 mL (0.05 mL until 1 month age)	Intradermal	Left upper arm
Hepatitis B—Birth dose	At birth or as early as possible within 24 hours	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
OPV-0	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV-1, 2, and 3	At 6 weeks, 10 weeks, and 14 weeks (OPV can be given till 5 years of age)	2 drops	Oral	Oral
Pentavalent 1, 2, and 3	At 6 weeks, 10 weeks, and 14 weeks (can be given till 1 year of age)	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
Rotavirus#	At 6 weeks, 10 weeks, and 14 weeks (can be given till 1 year of age)	5 drops	Oral	Oral
IPV	Two fractional dose at 6 and 14 weeks of age	0.1 mL	Intradermal two fractional doses	Intradermal: Right upper arm
Measles/MR 1st Dose$	9 completed months–12 months, (can be given till 5 years of age)	0.5 mL	Subcutaneous	Right upper arm
JE-1**	9 completed months–12 months	0.5 mL	Subcutaneous	Left upper arm
Vitamin A (1st dose)	At 9 completed months with measles-Rubella	1 mL (1 lakh IU)	Oral	Oral
For children				
DPT booster 1	16–24 months	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
Measles/MR 2nd dose$	16–24 months	0.5 mL	Subcutaneous	Right upper arm
OPV Booster	16–24 months	2 drops	Oral	Oral
JE-2	16–24 months	0.5 mL	Subcutaneous	Left upper arm
Vitamin A*** (2nd to 9th dose)	16–18 months. Then one dose every 6 months up to the age of 5 years	2 mL (2 lakh IU)	Oral	Oral
DPT Booster-2	5–6 years	0.5 mL	Intramuscular	Upper arm
TT	10 years and 16 years	0.5 mL	Intramuscular	Upper arm

* Give TT-2 or booster doses before 36 weeks of pregnancy. However, give these even if >36 weeks have passed. Give TT to a woman in labor, if she has not previously received TT.

** JE vaccine is introduced in select endemic districts after the campaign.

*** The 2nd to 9th doses of vitamin A can be administered to children 1–5 years old during biannual rounds in collaboration with ICDS.

Phased introduction, at present in Andhra Pradesh, Haryana, Himachal Pradesh, and Orissa from 2016 and expanded in Madhya Pradesh, Assam, Rajasthan, and Tripura in February 2017, and planned in Tamil Nadu and Uttar Pradesh in 2017.

$ Phased introduction, at present in five states namely Karnataka, Tamil Nadu, Goa, Lakshadweep, and Puducherry (As of February 2017).

(BCG: Bacillus Calmette–Guérin; DPT: diphtheria, pertussis, and tetanus; IPV: inactivated poliovirus vaccine; JE: Japanese encephalitis; MR: Measles–Rubella; OPV: oral polio vaccine; TT: tetanus toxoids)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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165 CHAPTER

Pediatric Fever and Other Life-threatening Infections

Faiz Ahmad, Devendra Richhariya

INTRODUCTION

Fever is one of the most common presenting complaints in children brought to the emergency department. It is defined as a rectal temperature > 38°C (100.4°F). Rectal temperature most closely represents the core temperature in ambulatory setting and is more accurate than oral, axillary, tympanic, and temporal artery thermometry. A patient with a fever measured rectally at home should undergo the same evaluation as if this measurement were obtained in ED. In most children it's due to viral infection but in some it may be due to serious bacterial infection (SBI) such as urinary tract infection (UTI), pneumonia, bacteremia, meningitis, bacterial gastroenteritis, osteomyelitis, septic arthritis, retropharyngeal/parapharyngeal abscess, or intra-abdominal abscess. On rare occasion, a child may have sepsis without fever or even with hypothermia, especially in noticeably young children. Other than infection, fever could also be due to poisoning (aspirin, phenothiazines), collagen vascular disease, vasculitis (Kawasaki disease), familial Mediterranean fever, or malignancy to name a few.

Traditionally, febrile young children are divided into three general groups—(1) neonates (birth to 28 days old), (2) young infants (1 month to 2–3 months of age), and (3) older infants or toddlers (2–3 months of age and older).

ETIOLOGY

One of the most common presenting complaints in pediatric age-group is fever, which is associated with several illnesses. All types of fever can be divided into four main groups based on the etiology, i.e., (1) infectious, (2) inflammatory, (3) neoplastic, and (4) miscellaneous. Common causes of fever in pediatric age-group are shown in **Figure 1**. Each of them shows certain characteristics, which can provide us clue about the underlying etiology. Such as fever related to viral infections is typically associated with a slow declining fever with relatively shorter duration, which may be up to 1 week. Whereas in a bacterial infection, fever gets subsided promptly after administration of proper antibiotics. Usually the pathogens are eliminated once the antimicrobial therapy is employed, but still fever may persist for few more days as a result of tissue injury and related inflammatory changes. Cause of very high-grade fever, i.e., higher than 105.8 is usually associated with noninfectious cause, and most importantly due to central nervous system dysfunction. Types of fever are summarized below:

- *Intermittent fever*: Fever with exaggerated circadian rhythm, period of normal temperature
- *Septic or hectic fever*: Fever with wide fluctuations throughout
- *Sustained fever*: There is a persistent temperature with variations not > 0.9°F per day.
- *Remittent fever*: Persistence of fever and variations of > 0.9°F per day
- *Relapsing fever*: Febrile period is separated by interval of normal temperature
- *Biphasic fever* indicates a single illness with two distinct periods, characteristically seen in poliomyelitis, enteroviral infection, leptospirosis, and dengue fever.

Causes of prolonged fever, lasting for > 14 days has different etiology, however, infectious cause still remains the most common, below are the other etiologies of prolonged fever:

- Infectious—tuberculosis, human immunodeficiency virus (HIV), chronic fungal infection, and liver abscess
- Inflammatory diseases—rheumatoid arthritis, systemic lupus erythematous, Kawasaki disease, Behçet disease, and polyarteritis nodosa
- Malignancies—lymphomas, leukemia, neuroblastoma, and Wilms tumor
- Hematological and immune deficiency—spherocytosis, hemolytic anemia, Langerhans cell histiocytosis, disorders of phagocytosis, and T or B cell
- Other causes—drug fever, anhidrotic ectodermal dysplasia

PATHOPHYSIOLOGY OF FEVER

Body temperature is regulated by thermosensitive neurons which are located in the anterior hypothalamus, which responds to any change in temperature of blood and also through the warm and cold receptor located at skin and muscle. To maintain the temperature either the blood flow is redirected to or from the cutaneous vascular bed, regulating the extracellular fluid volume and also by increasing or decreasing the sweating. There are *three main mechanisms* for producing fever—(1) in response to the pyrogens, (2) production of heat is in excess to the loss, and (3) defective mechanism of heat loss.

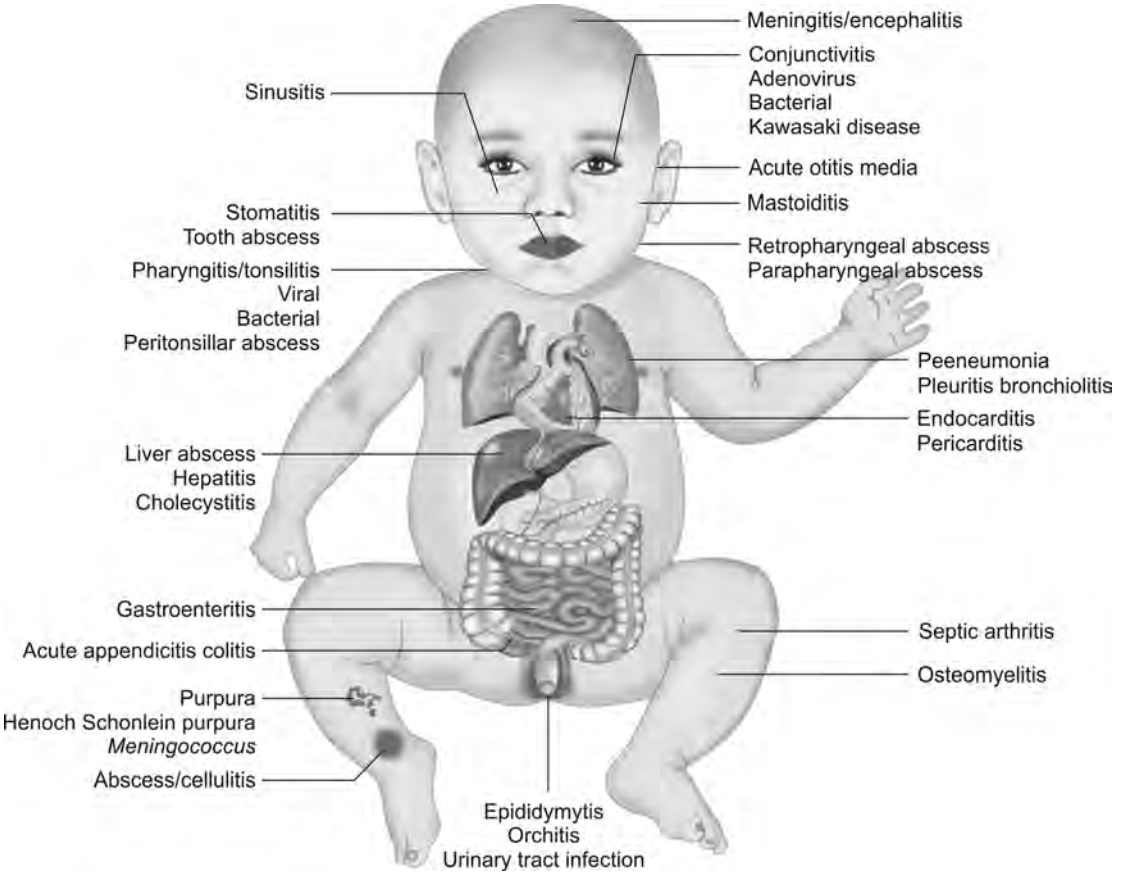

FIG. 1: Causes of fever in pediatric age-group.

The pyrogens play a big role in inducing fever, by raising the hypothalamus temperature set point. These pyrogens may be endogenous and exogenous. Endogenous pyrogens are mainly cytokines such as interleukins 1 and 6 (IL-1 and IL-6), tumor necrosis factor-α (TNF-α), and interferons β and γ. Other endogenous pyrogen includes leukemia inhibitory factor-M (LIF), ciliary neurotrophic factor (CNTF) and oncostatin-M. In cases of febrile illnesses, higher levels of IL-6 have been seen, and also the IL 6 with TNF contributes in clinical pyrexia. Prostaglandin E2 is the ultimate pyrogen in the whole cascade, which in turn attaches to the prostaglandin receptor site located on the hypothalamus and produces a net temperature set point.

Many exotoxins such as drugs, malignancies, and inflammatory diseases can also produce fever by production of endogenous pyrogens. Among all exogenous pyrogens, endotoxins are one of substances which can directly alter the thermoregulation center in hypothalamus, and stimulate endogenous pyrogens as well.

Another mechanism in which the heat production is in excess to the release, for example in case of salicylate poisoning and, malignant hyperthermia. The third mechanism, where the loss of heat is defective, is seen in cases of ectodermal dysplasia and victims of severe heat exposure.

CLINICAL PRESENTATION

Unlike in adults, adolescent and elder children, young infants and younger children have certain differences in clinical presentations, as they may become irritable and show fatigue, without any other apparent symptoms. Fever in children makes them very much uncomfortable. Fever can present in wide range of symptoms in children from no symptoms at all to extreme malaise. They may be having facial flushing appearance, experience shivering, and complain of feeling hot or even cold. Various other symptoms may be manifested such as loss of appetite, and some clinical features may be typical for specific diseases and can be used to point out the etiology, for example any sick child with fever and petechial rashes, raise suspicion toward meningococcemia or acute bacterial endocarditis.

Changes in the heart rate from baseline, is the most prominent clinical finding, and most of the patients have fever associated with tachycardia (increase in heart rate by 10, for each raise in temperature of 1.8°F). Disproportionately increase in heart rate is commonly seen in noninfectious conditions, or in infections in which toxins play role in clinical manifestation. In children of age-group 6–60 months (5 years), children may present with episodes of febrile convulsions.

FEATURES OF CONCERN—RED FLAGS

Parent concerns or physician instincts to evaluate further

- Inconsolable cry, change in crying pattern
- Rapid breathing or shortening of breaths with any duration of onset
- Findings such as decreased breath sounds, or crackles on respiratory examinations
- Poor peripheral circulation, hypotension, and appearing cyanosed on examination

- Fever associated with rash
- Seizures during the febrile illness
- Fever with meningeal irritation signs, neck stiffness, or photophobia
- Child presenting with cyanosis, breathlessness
- Poor hydration status and decreased skin turgor
- Drowsiness or lethargic or in altered consciousness
- Fever with chills and rigor, or bleeding manifestations

HISTORY AND PHYSICAL EXAMINATION

Fever could be from infectious or noninfectious causes. Fever in young children is accepted as a rectal temperature of 38.0°C (100.4°F) or higher. In younger children, hyperpyrexia (temperature 40°C) may be associated with increased rates of SBI. The duration of fever does not predict whether a child has occult bacteremia. Similarly, response to antipyretics does not distinguish between bacterial and viral infections. Although bundling a young child may increase the skin temperature, this does not increase the core temperature. Teething does not cause fever. It is important to look for additional signs and symptoms, underlying medical conditions, sick contacts, recent immunizations, and immunization status.

Yale Observation Score (YOS) is an objective scoring system based on child's alertness, playfulness, interaction with the environment, color, state of hydration, quality of cry, and whether the child is consolable or not. In young infant (<8 weeks), YOS cannot be relied upon to determine the risk of SBI. In this age-group, a history of poor feeding, lethargy, irritability, moaning, increased sleepiness or difficulty in breathing, seizure, or cyanotic episode is overly concerning for SBI. An infant with UTI may only have a low-grade fever with vomiting or diarrhea.

In young infant, physical examination may reveal mottled skin, pallor, bulging fontanel, weak cry, grunting, tachypnea, tachycardia, and lethargy. Meningeal signs may not be present even in meningitis.

In children above 8 weeks of age, clinical impression is more reliable. A child with sepsis is usually not interested in surrounding and does not smile. Parents often report a change in child's behavior. Localizing signs are more reliable in older children (toddlers), like in case of meningitis the presence of nuchal rigidity and positive Kernig's or Brudzinski's signs.

There are three common criteria (Boston criteria, Rochester criteria, and Philadelphia criteria) commonly used to determine if the patient is at low risk or high risk for SBI. These risk stratification rules are derived for febrile young infants and are not helpful in neonates. They all have following components in common for a patient to be in low-risk category:

- Patient must appear well
- No signs of focal infection on examination
- Peripheral white blood cell (WBC) count within a specific range
- No evidence of UTI on rapid urine testing

Boston Criteria

It is designed for febrile children from 1 to 3 months of age with a temperature of 38.0°C or more. Patients meet the low-risk criteria if they appear well, and had no ear, soft tissue, bone, or joint infection on examination. Laboratory evaluation must have a peripheral WBC count of ≤20,000/mm^3, microscopic UA showing ≤10 WBC/hpf or urine dipstick negative for leukocyte esterase, and cerebrospinal fluid (CSF) with ≤10 WBC/hpf and a normal chest X-ray (CXR) if that is performed. 5.4% children (27 out of 503) in the original study were later found to have SBI (UTI, bacterial gastroenteritis, and occult bacteremia).

Rochester Criteria

It is designed for febrile children < 60 days old. Patients are at low risk for SBI if they appear well, have been previously healthy, have no evidence of ear infection, skin, soft tissue, bone, or joint infection. Additionally, these patients must have normal peripheral WBC count (5,000–15,000/mm^3), normal absolute band counts (≤1500/mm^3), UA ≤10 WBC/hpf of centrifuged urine and patients with diarrhea should have ≤5 WBC/hpf on stool smear. Lumbar puncture is not a required component of the Rochester criteria. The Rochester criteria, in the original study, had a negative predictive value of 98.9%.

Philadelphia Criteria

It is designed for patients between 29 and 56 days of age with temperature ≥38.2°C. Patients are at low risk of SBI, if they appear well (defined by an infant observation score of ≤10), have a peripheral WBC count ≤15,000/mm^3, a band to neutrophil ratio ≤0.2, UA with <10 WBC/hpf, few or no bacteria on a centrifuged urine sample, CSF with <8 WBC/mm^3, a gram-negative stain, negative result on CXR (obtained on all patients), and stool negative for blood and few or no WBC on microscopy (ordered on patients with diarrhea). The low-risk patients were not treated with antibiotics. Of the 747 enrolled patients, in the original study, 65 (8.7%) had SBI and all of them were identified using these screening criteria. In another follow-up study of 422 febrile children (temp ≥38°C rectally), 43 (10%) had SBI and all of them were identified as high risk for SBI using the Philadelphia criteria.

Even though there is an imperfect correlation between physical examination findings and serious bacterial illness, ill-appearing children are more likely than well-appearing children to have SBI. Similarly, patients with septic shock presenting with abnormal mental status, weak peripheral pulses, cool extremities, delayed capillary refill with or without hypotension need aggressive resuscitation, and empiric antibiotic therapy. Children with clinically recognizable viral conditions (e.g., croup, chickenpox, and stomatitis) have lower rates of bacteremia than children with no obvious source of infection.

DIAGNOSIS AND MANAGEMENT

Birth to 8 Weeks of Age

Full sepsis evaluation including complete blood count (CBC) with differential count, blood culture, urine culture, urinalysis (catheterized or suprapubic aspiration), and lumbar puncture (cell count, glucose, protein, Gram's stain, and culture) should be performed. CXR is indicated if there are respiratory signs and symptoms. Stool study is indicated if there is diarrhea. All cultures, including lumbar puncture, should be obtained before starting antibiotics unless the infant is in respiratory distress or shock. Any patient who appears ill or toxic (inconsolable, lethargic, or tachypneic has poor perfusion or grunting) should be admitted and treated for sepsis while entertaining other diagnosis such as congenital heart disease or metabolic conditions.

Febrile young infants (age 0–90 days) have a 12.5–12.6% prevalence of SBI if they were tested negative for RSV, whereas the prevalence is 1.15–7.0% in those positive for RSV. And most of these SBIs are UTIs. Similarly in febrile young infants (age 0–90 days) have a 13.3–17.5% prevalence of SBI if they tested negative for influenza, whereas the prevalence is 2.5–2.65% in those positive for influenza. And similar to patients with RSV, most of these SBIs are UTIs.

The incidence of neonatal herpes simplex virus (HSV) infections is approximately 1 per 3,200 deliveries in the United States. These neonates with HSV infections usually present within the first 2 weeks of life, and only a small number of infected children have fever. Risk factors for neonatal HSV infection include primary maternal HSV infection (especially in those neonates delivered vaginally); prolonged rupture of membranes at delivery; use of fetal scalp monitoring electrodes; eye, skin, or oral lesions; and seizures.

Both the C-reactive protein and procalcitonin performed better than the peripheral WBC count in detecting SBIs, with procalcitonin having a higher sensitivity [83%, 95% confidence interval (CI) 70–91%] than the C-reactive protein (74%, 95% CI 49–67%) and peripheral WBC count (58%, 95% CI 49–67%).
Infants with following criteria are at low risk for sepsis:

- Well appearing
- No focal signs of infection on examination
- No known immunodeficiency/VP shunt or other comorbidity
- White blood cell 5,000–15,000/mm^3
- Erythrocyte sedimentation rate (ESR) < 30 mm/H, CRP <1 or a band to neutrophil ratio <0.2
- Urinalysis with ≤10 WBC per high-power field and no bacteria
- Cerebrospinal fluid shows <8 WBC/mm^3 and no bacteria on Gram stain
- Stool is heme negative and ≤5 WBC per high-power field.
- Normal CXR

Under 4 weeks (28 days) of age:

- Admit all patients
- IV ampicillin (<1 week: 100 mg/kg/day, div q 12 h; >1 week: 200 mg/kg/day, div q 6 h)
- IV cefotaxime (< 1 week: 100 mg/kg/day, div q 12 h; 1–4 weeks: 150 mg/kg/day, div q 8 h)
- Gentamicin 2.5 mg/kg IV can be used instead of cefotaxime
- In case of suspected meningitis increase the dose of cefotaxime to 200 mg/kg/day div q 6 h
- Ceftriaxone is not recommended for this age-group because of the concern of inducing unconjugated hyperbilirubinemia.
- IV acyclovir if HSV infection is suspected; high-dose acyclovir (20 mg/kg IV) improves outcomes in patients.

4–8 weeks of age:

- Infants who meet the low-risk criteria for sepsis may be managed as outpatients with close follow-up without antibiotics.
- Additional antibiotics should be considered in some circumstances (e.g., ampicillin or vancomycin for suspected infection by *Listeria*, gram-positive cocci, or *Enterococcus*).
- Empiric antibiotic therapy before discharge of low-risk patients should be considered if a lumbar puncture is performed. Ceftriaxone, 50 mg/kg IV or IM can be given before discharge.
- Infants who appear ill or do not meet low-risk criteria for sepsis should be admitted to the hospital and treated with IV ceftriaxone (100 mg/kg/day div q 12 h); can be given IM if IV access is difficult

8 Weeks–6 Months of Age

Clinical impression is more reliable in this age-group. If there is no definite source of fever, partial sepsis work-up with blood and urine studies should suffice. CXR should be done if patient has respiratory symptoms or there is focal finding on physical examination. Treat focal infections such as UTI, pneumonia, and otitis media with appropriate antibiotic. Infants under 3 months of age with UTI or suspected bacterial pneumonia should be admitted to the hospital for antibiotic therapy.

ANTIPYRETICS

Antipyresis includes use of both pharmacological and nonpharmacological approach. However, use of antipyretics may help to manage the child overall, but it does not appear to play any role in occurrence of febrile seizures.

Nonpharmacological Antipyresis

- *Environmental modification*: Keeping the room temperature cooler (21–22°C) in order to enhance the heat loss by convection and minimal clothing can be helpful in bring the body temperature lower.
- *Hydration*: Due to raised body temperature there is an increase in metabolism and increase in insensible water losses, i.e., for each 1°C of increase in temperature above 37.2°C, insensible water loss increases by 7 mL/kg. Hence increasing fluid intake is recommended in febrile patients.
- *Hydrotherapy or sponging*: Tepid water sponging helps to lower the temperature by evaporation, conduction, and convection. It lowers the temperature gradually, but it doesn't lower the thermoregulatory set point, and also soon it limits the further body cooling by inducing vasoconstriction and shivering. Hence the hydrotherapy should always be accompanied by pharmacological therapy.

Pharmacological Antipyresis

Antipyretic agents act upon the arachidonic acid pathway. The main action is to competitively bind on COX enzymes catalytic site competing with arachidonic acid, hence inhibiting production on prostaglandin 2.

- *Paracetamol*: It is recommended in dose of 10–15 mg/kg, at 4–6 hourly intervals (maximum 60 mg/kg/day). Antipyretic effect takes 30–60 min to initiate. Paracetamol helps in reduction of body temperature by 1–2°F within 2 hours of administration. Greater the initial temperature, greater the fall of temperature after the drug intake.
- *Ibuprofen*: This drug can be used at dose of 10 mg/kg, as a first-line antipyretic. No great differences have been shown in safety and efficacy as compared to paracetamol. Although combination of these two can be more effective, but not recommended routinely in children because of associated improper drug dosages.
- *Mefenamic acid*: This is an effective antipyretic, mainly in controlling the high-grade fever at the dose of 6–7 mg/kg/dose (20 mg/kg/day is maximum). Commonly practiced as

to give 1 dose of mefenamic acid for high temperature and then subsequently to follow with paracetamol.

Care to be taken in prescribing antipyretics, regarding the need of pharmacological agents, personal experience, clinical data on safety and efficacy, ~duration of effect, cost, adverse effects and patient's clinical condition. Paracetamol is safest antipyretic in children in therapeutic dosage, but also is associated with most serious cause of hepatotoxicity in children. Ibuprofen is also known for overdose and is relatively difficult to manage as compared to paracetamol. Aspirin should be avoided in children, due to its adverse effects, like Reye syndrome, other side effects like blunting of immune response, increased risk of gastritis, and gastrointestinal bleeding.

URINARY TRACT INFECTION

Urinary tract infection is a common source of fever in young children and, if untreated, can lead to renal damage. Despite the high disease prevalence, this diagnosis is often missed. In young children, symptoms are often nonspecific, and fever may be the only symptom of UTI.

Risk factors for UTI include uncircumcised status, young age, female sex (girls are at higher risk for UTIs than boys in all age categories except for young uncircumcised boys), and nonblack race. Urine testing is generally indicated in girls younger than 2 years with at least 1 risk factor for UTI (history of UTI, temperature >39°C, fever without other apparent source, ill appearance, suprapubic tenderness, fever >24 hours, or nonblack race). Circumcised boys between 3 months and 2 years of age without suprapubic tenderness or with no >1 risk factor for UTI (temperature 39°C, fever without other apparent source, fever >24 hours, or nonblack race) have a probability of UTI of ≤2%. Increased risk of UTI in uncircumcised males persists until at least 12 months of age.

Urine dipstick (positive for either leukocyte esterase or nitrites) has a sensitivity of 88%. It is important to remember that no rapid screening test detects all UTIs, therefore, urine cultures should be ordered for all of these patients.

OCCULT BACTEREMIA

Haemophilus influenzae type b (Hib) and *Streptococcus (diplococcus) pneumoniae* used to be two most common organisms responsible for bacteremia in young children. But since the introduction of Hib and pneumococcal conjugate vaccine covering 13 serotypes (PCV 13), the incidence of bacteremia from these two organisms has significantly decreased after administration of at least 2 doses (2 months and 4 months).

The third most common cause of bacteremia is *E. coli*. *E. coli* bacteremia is the most common in children 3–6 months of age but also seen in children up to 12 months of age. And most of these children have concomitant *E. coli* UTI.

Salmonella bacteremia is seen in about 0.1% of all children 3–36 months old who have temperatures ≥39.0°C. Most patients with *Salmonella* bacteremia have diarrhea but about 5% have primary bacteremia.

Neisseria meningitidis is an infrequent cause of bacteremia and risk factors include sick contact with patients with meningococcal disease, periods of meningococcal outbreaks, and presence of fever and petechiae.

PNEUMONIA

Occult pneumonia in most young children is viral and does not require antibiotic treatment. In case of bacterial pneumonia, high-dose amoxicillin is the first-line agent (90 mg/kg divided into 2 daily doses), because this agent is effective against *Streptococcus pneumoniae*. Mycoplasma pneumonia is uncommon in this age-group but if suspected, azithromycin or other macrolide antibiotics can be used. Oseltamivir should be started if influenza is thought to be either the primary infectious cause or if there is concern for influenza coinfection in someone with suspected bacterial pneumonia.

Children with community-acquired pneumonia require admission if they have respiratory distress with or without hypoxia, poor feeding or an inability to take oral medications, infants 3–6 months of age, documented or suspected infection by a pathogen with increased virulence (e.g., methicillin-resistant *Staphylococcus aureus*), and in cases where follow-up or close home observation cannot be ensured. Vancomycin or clindamycin should be also given to those patients with suspected methicillin-resistant *S. aureus* pneumonia.

6–36 months of age:

- Due to widespread use of pneumococcal vaccine, the risk of occult bacteremia is <1–2% in a child with a temperature of ≥39.5°C (103°F)
- If the blood culture is positive of *Streptococcus pneumoniae* and the patient is still febrile or afebrile <24 hours—repeat the blood culture.
- If the patient is ill-appearing or still febrile, complete the sepsis work-up and admit and treat with IV penicillin G (100,000 units/kg/day div q6h).
- If there is a concern for resistant strain of *S. pneumoniae* based on local antibiogram administer third-generation cephalosporin (ceftriaxone or cefotaxime) and vancomycin (10–15 mg/kg q8h).
- If the patient with *S. pneumoniae* bacteremia has been afebrile for >24 hours and is well appearing, treat as outpatient with oral penicillin (50 mg/kg/day div QID) for 7 days.
- In children treated as outpatient, parents should be given specific instructions to control the temperature (acetaminophen 15 mg/kg orally/rectally q4h) and bring the child back to the hospital for irritability, decreased oral intake or lethargy.
- Ensure follow-up within 24–48 hours.

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION IN CHILDREN

Coronavirus disease 2019 (COVID-19) is a global health crisis and caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical characteristics, disease progression, and outcome in children and young adults appear significantly milder compared to older individuals. Coronaviruses are a family of enveloped, single-stranded, zoonotic RNA viruses which can rapidly mutate and recombine, leading to novel viruses that can spread from animals to humans. SARS-CoV-2 is transmitted via inhalation of respiratory droplets of an infected person and touching surfaces contaminated with the virus.

Pathogenesis

The SARS-CoV-2 virus utilizes angiotensin converting enzyme-2 (ACE-2) receptors as its cell surface receptor. ACE2 is expressed highly by ciliated epithelial cells in the human lungs and this receptor allows the virus to attach to the cell. The ACE2 receptor is also expressed in the intestines, potentially accounting for the gastrointestinal symptoms that commonly occur in the early stage of the illness. Severe COVID-19 disease is characterized by three phases: (1) The first being the viral phase; (2) The second being the cytokine storm; and (3) The third encompassing acute respiratory distress syndrome (ARDS), impaired cardiac function and death.

The cytokine storm associated with severe COVID-19 disease is similar to that of secondary hemophagocytic lymphohistiocytosis (HLH), which is a rare complication of other viral infections and characterized by fulminant and fatal hypercytokinemia with multiorgan failure. In severe infection, lower peripheral lymphocyte counts (CD4 and CD8 T cells), higher interleukin (IL) levels (IL-6 and IL-10), decreased interferon-gamma expression in CD4+ T cells and higher D-dimer and fibrin degradation products (FDP) levels, leading to increased thrombosis and multiorgan injury have been observed. Patients with severe infection may also have abnormal coagulation parameters, perhaps related to high expression of ACE2 receptors in vascular endothelial cells.

Transmission

Most likely children are secondary cases and acquire the infection after exposure to a COVID-19 positive adult, although there are no large studies at present to confirm this. Intra-family transmission may be important. An as yet unquantified proportion of children with COVID-19 is asymptomatic and may contribute to transmission. Multiple reports have demonstrated that children and young adults have a milder form of the disease compared to adults. The possible reasons for lower number and milder infections in children and young adults include healthier respiratory tracts, home isolation, lower exposure to virions, and minimal exposure to pollution and cigarette smoke.

Clinical Features

Children of all ages can be infected with SARS-CoV-2 (COVID-19) with more cases reported in younger children and infants. There is no age or sex preponderance and the median age of infection is 6.7 years (range: newborn to 15 years). The incubation period of COVID-19 in children has been reported as 2 days (range: 2–10 days). The most common symptoms described at onset in children are fever (50%) and mild cough (38%). Fever is present in about 40% of children. Other clinical features include sore throat, rhinorrhea, sneezing, myalgia, fatigue, diarrhea, and vomiting. Children may have more upper respiratory symptoms than lower respiratory symptoms, and appear to recover in 1–2 weeks. The Ministry of Health and Family Welfare (MOHFW) in their updated guidelines (as of 18 June, 2021) has categorized patients into three groups—those with mild, moderate, and severe illness.

Diagnosis and Investigations

Reverse transcription polymerase chain reaction (RT-PCR) testing of nose and throat swab for detection of SARS-CoV-2 nucleic acid has been recommended as the confirmatory test for COVID-19. On the basis of confirmatory RT-PCR and the antibody test, clinical assessment, hospital treatment or home isolation measures are provided to the patient. Contact tracing measures are also instituted per protocol. If signs for severe infection are present, recommendation to monitor the lymphocyte count and CRP, and procalcitonin levels to detect potential bacterial co-infection. Chest X-ray findings in children are usually nonspecific. In view of the high-radiation exposure, children with mild disease should not routinely need computed tomography (CT) chest. When CT is performed, ground glass opacities are seen in one-third of patients. Peripheral distribution of lung lesions has been noted, with multilobar involvement. Consolidation and surrounding halo sign are considered typical of pediatric patients. However, chest CT alone cannot accurately diagnose COVID-19 due to similar radiological presentations with other infections. Patients admitted with severe infection are known to have elevated plasma levels of elevated ferritin and IL-2, IL-7, IL-10, granulocyte colony stimulating factor (GCSF), interferon-gamma-inducible protein 10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-alpha (MIP-1α), and tumor necrosis factor (TNF) alpha. These cytokines are produced by inflammatory macrophages which have been implicated in the cytokine storm.

Management of Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (Coronavirus Disease 2019)

Immediate infection prevention control (IPC) measures must be instituted upon suspicion of COVID-19 infection. Standard precautions such as hand hygiene, use of personal protective equipment (PPE), safe waste management, and cleaning and disinfection of equipment must be followed as per the guidelines issued by the MOHFW. For the few children who will require admission to a healthcare facility, the cornerstone of management is supportive therapy including adequate nutrition and calorie intake, fluid and electrolyte management, and oxygen supplementation. Emergency physician must communicate with parents regularly and alleviating anxiety is an important part of management. Classification of severity, investigations, and management of SARS-CoV-2 infection in children are summarized in **Table 1**.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN RELATED TO COVID-19

Multisystem inflammatory syndrome in children (MIS-C) is a new entity in children characterized by unremitting fever >38°C and epidemiological linkage with SARS-CoV-2.

WHO Diagnostic criteria of MIS-C:Children and adolescents 0–18 years of age with fever ≥3 days and any two of the following features:

- Rash or bilateral nonpurulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands, or feet)
- Hypotension or shock
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-pro BNP)

- Evidence of coagulopathy (PT, PTT, and elevated D-dimers)
- Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)
- And raised inflammatory markers such as ESR (>40 mm), C-reactive protein (>5 mg/L), or procalcitonin
- And no other possible microbial cause of inflammation, e.g., bacterial sepsis, staphylococcal or streptococcal shock syndromes.
- And evidence of recent COVID-19 infection (RT-PCR, antigen test, or serology positive), or likely contact with COVID-19 infected patient.

Following conditions must be excluded before making a diagnosis of MIS-C:

- Tropical infections (malaria, dengue, scrub typhus, and enteric fever)
- Toxic shock syndrome (staphylococcal or streptococcal)
- Bacterial sepsis

Multisystem inflammatory syndrome in children with Kawasaki disease (KD) phenotype is presented with fever, conjunctival redness, oropharyngeal findings (red and/or cracked lips, strawberry tongue), rash, swollen and/or erythematous hands and feet and cervical lymphadenopathy.

Investigations

Group 1 tests: May be done at COVID Care Center: CBC, complete metabolic profile (LFT/KFT/blood gas/glucose), CRP and/or ESR, SARS-CoV-2 serology and/or RT-PCR, blood culture. If: 1. CRP > 5 mg/L and/or ESR > 40 mm/h; 2. At least one of these: Absolute leukocyte count < 1,000 µL, Na < 135 mEq/L, neutrophilia, hypoalbuminemia follow group 2 tests.

Group 2 tests: Cardiac (ECG, echocardiogram, BNP, troponin T); inflammatory markers (procalcitonin, ferritin, PT, PTT, D-dimer, fibrinogen, LDH, triglyceride, cytokine panel); blood smear; SARS-CoV-2 serology.

TABLE 1: Clinical features of SARS-CoV-2 (COVID-19) in children.

Common symptoms: Fever, sore throat/throat irritation, diarrhea, cough, body ache/headache, anorexia/nausea/vomiting, rhinorrhea, malaise/weakness, loss of sense of smell and/or taste

Differentiating features	***Asymptomatic***	***Mild***	***Moderate***	***Severe***
Respiratory rate/min	Normal with age	Normal with age	Rapid respiration (age based): • <2 months: ≥60 breaths/min • 2–12 months: ≥50 breaths/min • 1–5 years: ≥40 breaths/min • >5 years: ≥30 breaths/min	Rapid respiration (age based): • <2 months: ≥60 breaths/min • 2–12 months: ≥50 breaths/min • 1–5 years: ≥40 breaths/min • >5 years: ≥30 breaths/min
SpO_2 on room air	≥94%	≥94%	≥90%	<90%
Grunting/severe chest retraction	–	–	–	±
Lethargy somnolence	–	–	–	±
Seizures	–	–	–	±
Where to treat	Home isolation (teleconsultation SOS)	Home isolation (tele consultation SOS) or COVID Care Centre	Admit COVID-19 hospital	Admit in HDU/ICU of COVID-19 hospital
Investigations	No investigation needed	No investigation needed	• *Baseline*: CBC including ESR, blood glucose chest X-ray • CT chest is not indicated in diagnosis or management of COVID-19 infection in children. Consider CT chest only if no improvement in respiratory status	• *Baseline*: CBC including ESR, blood glucose, CRP, LFT, KFT, serum ferritin, D-Dimer • Chest X-ray • CT chest is not indicated in diagnosis or management of COVID-19 infection in children. Consider CT chest only, if no improvement in respiratory status

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Differentiating features	***Asymptomatic***	***Mild***	***Moderate***	***Severe***
Mainstay of treatment	Infants and younger children to stay under immediate care of parents/guardians: • No specific medication required for COVID-19 infection • Continue medications for other conditions, if any • Promote COVID appropriate behavior (mask, strict hand hygiene, physical distancing); please see guide for using mask • Fluids and feeds: ensure oral fluids to maintain hydration and give a nutritious diet • Advise older children and family to stay connected and engage in positive talks through phone, videocalls, etc. • Parent/caregivers to contact the doctor in case of appearance of symptoms	• For fever, give paracetamol 10–15 mg/kg/dose; may repeat every 4–6 h • For cough, give throat soothing agents and warm saline gargles in older children and adolescents • Fluids and feeds: ensure oral fluids to maintain hydration and give a nutritious diet • No other COVID-19 specific medication needed • Antimicrobials are not indicated • Maintain monitoring chart including counting of respiratory rate 2–3 times a day, look for chest indrawing, cold extremities, urine output, oxygen saturation, fluid intake, activity level, especially for young children • Promote COVID appropriate behavior (mask, strict hand hygiene, physical distancing); please see guide for using mask • Advise older children and family to stay connected and engage in positive talks through phone, videocalls, etc. • Parents/caregivers to contact the doctor in case of deterioration of symptoms	*Initiate oxygen if SpO_2 is 38°C (or 100.4°F)*: Paracetamol 10–15 mg/kg/dose; may repeat every 4–6 h • Antimicrobials to be administered if there is evidence/strong suspicion of superadded bacterial infection; please see antimicrobial use guide • Supportive care for comorbid conditions, if any Remdesivir (an emergency use authorization drug) is NOT recommended in children. There is lack of sufficient evidence on safety and efficacy with respect to remdesivir in children below 18 years of age	• Initiate immediate oxygen therapy and maintain target SpO_2 94–96% • Maintain fluid and electrolyte balance • Corticosteroid therapy to be initiated • Anticoagulants may also be indicated • In case of (ARDS) or shock develops, initiate necessary management; see ARDS and shock guide • Antimicrobials to be administered if there is evidence/strong suspicion of superadded bacterial infection; see antimicrobial use guide • May need organ support in case of organ dysfunction, e.g., renal replacement therapy Remdesivir (an emergency use authorization drug) is NOT recommended in children. There is lack of sufficient evidence on safety and efficacy with respect to remdesivir in children below 18 years of age
Management of ARDS	ARDS may be classified based on Pediatric Acute Lung Injury Consensus Conference (PALICC) definition into mild, moderate, and severe. • Mild ARDS: High flow nasal oxygen (start with 0.5 L/kg/min to begin with and increase to 2 L/kg/min with monitoring) or noninvasive ventilation (BiPAP or CPAP) may be given • Moderate–Severe ARDS: Lung protective mechanical ventilation may be initiated; low tidal volume (4–8 mL/kg); plateau pressure <28–30 cmH_2O; MAP <18–20 cmH_2O; driving pressure <15 cmH_2O; PEEP: 6–10 cmH_2O (or higher if severe ARDS); FiO_2 < 60%; Sedation + analgesia ± neuromuscular blockers; cuffed ETT, inline suction, and heat and moisture exchange filters (HMEF) • Avoid frequent disconnection of ventilator circuit, nebulization, or metered dose inhaler • Restrict fluids; calculate fluid overload percentage, keeping it <10% • Prone position may be considered in hypoxemic children, if they are able to tolerate it • Daily assessment for weaning and early extubation; enteral nutrition within 24 h, achieve full feeds by 48 hours • Transfusion trigger Hb <7 g, if stable oxygenation and hemodynamic and <10 g/dL if refractory hypoxemia or shock			
Management of shock	• Consider crystalloid fluid bolus 10–20 mL/kg cautiously over 30–60 min with early vasoactive support (epinephrine) • Start antimicrobials within the first hour, after taking blood cultures, according to hospital antibiogram or treatment guidelines • Consider inotropes (milrinone or dobutamine) if poor perfusion and myocardial dysfunction persists despite fluid boluses, vasoactive drugs, and achievement of target mean arterial pressure • Hydrocortisone may be added if there is fluid refractory catecholamine resistant shock (avoid if already on dexamethasone or methylprednisolone) • Once stabilized, restrict IV fluids to avoid fluid overload • Initiate enteral nutrition—sooner the better • Transfusion trigger Hb <7 g/dL if stable oxygenation and hemodynamic, and <10 g/dL if refractory hypoxemia or shock			

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Antimicrobial use	COVID-19 is a viral infection, and antimicrobials have no role in the management of uncomplicated. • Asymptomatic and mild cases: antimicrobials are not recommended for therapy or prophylaxis. • Moderate and severe cases: antimicrobials should not be prescribed unless there is clinical suspicion of a superadded infection. • Septic shock: empirical antimicrobials (according to body weight) are frequently added to cover all likely pathogens based on clinical judgment, patient host factors, local epidemiology, and antimicrobial policy of the hospital.
Use of steroid and anticoagulation	*Steroids*: • Steroids are not indicated and are harmful in asymptomatic and mild cases of COVID-19 • Indicated only in hospitalized severe and critically ill COVID-19 cases • Steroids should be used at the right time, in right dose, and for the right duration • Indications and recommended dose of corticosteroids—may be used in rapidly progressive moderate and all severe cases: ○ Dexamethasone 0.15 mg/kg, maximum dose 6 mg once a day, or ○ Methylprednisolone 0.75 mg/kg, maximum dose 30 mg once a day • Continue for 5–7 days and taper, up to 14 days, depending on clinical assessment on daily basis • Avoid steroids in first 3–5 days since onset of symptoms as it prolongs viral shedding *Anticoagulants*: • Not indicated routinely • All hospitalized children should be monitored for thrombosis; on suspicion, confirm by appropriate investigations and start on low molecular weight heparin in therapeutic doses for period of 12 weeks with monitoring • Predisposing risk factors for development of thrombosis—personal history of venous thrombotic events (VTE), family history of first-degree relative with VTE, presence of central venous line, decreased mobility from baseline, burns, active malignancy, estrogen therapy, flare of inflammatory disease, morbid obesity, severe dehydration, recent surgery or trauma • Prophylactic anticoagulant is indicated in following circumstances: (a) Strong personal or family history of VTE, or (b) An indwelling central venous line and two or more additional risk factors, or (c) Four or more risk factors • The decision to administer prophylactic anticoagulation must be balanced with the child's bleeding risk • Children already on anticoagulation therapy may continue same unless they develop active bleeding • Dose of low molecular weight heparin (enoxaparin), if indicated in severe cases: ○ Prophylactic dose 0.5 mg/kg twice daily, till child is discharged from hospital ○ Therapeutic dose 1 mg/kg twice daily
Guideline for using mask in children	• Masks are not recommended for children aged 5 years and under • Children aged 6–11 years may wear a mask depending on the ability of child to use a mask safely and appropriately under direct supervision of parents/guardians • Children aged 12 years and over should wear a mask under the same conditions as adults • Ensure hands are kept clean with soap and water, or an alcohol-based hand rub, while handling masks
Infection prevention and control	Every COVID care facility should have a multidisciplinary hospital infection control committee; key components of infection control strategy are: • Standard precautions • Droplet precautions • Airborne precautions • Contact precautions and hand hygiene • Physical distancing • Cough etiquette/respiratory hygiene • Well-ventilated rooms • Monitor healthcare associated infections • Train all healthcare workers to develop IPC skills • Environment cleaning, disinfection, and sanitation • Cleaning/disinfection of frequently touched surfaces/equipment • Cleaning and disinfection of linen • Safe management of biomedical waste • Triple layer mask to be worn by patient, as per guidance below • Masks for caregivers (home/hospital)

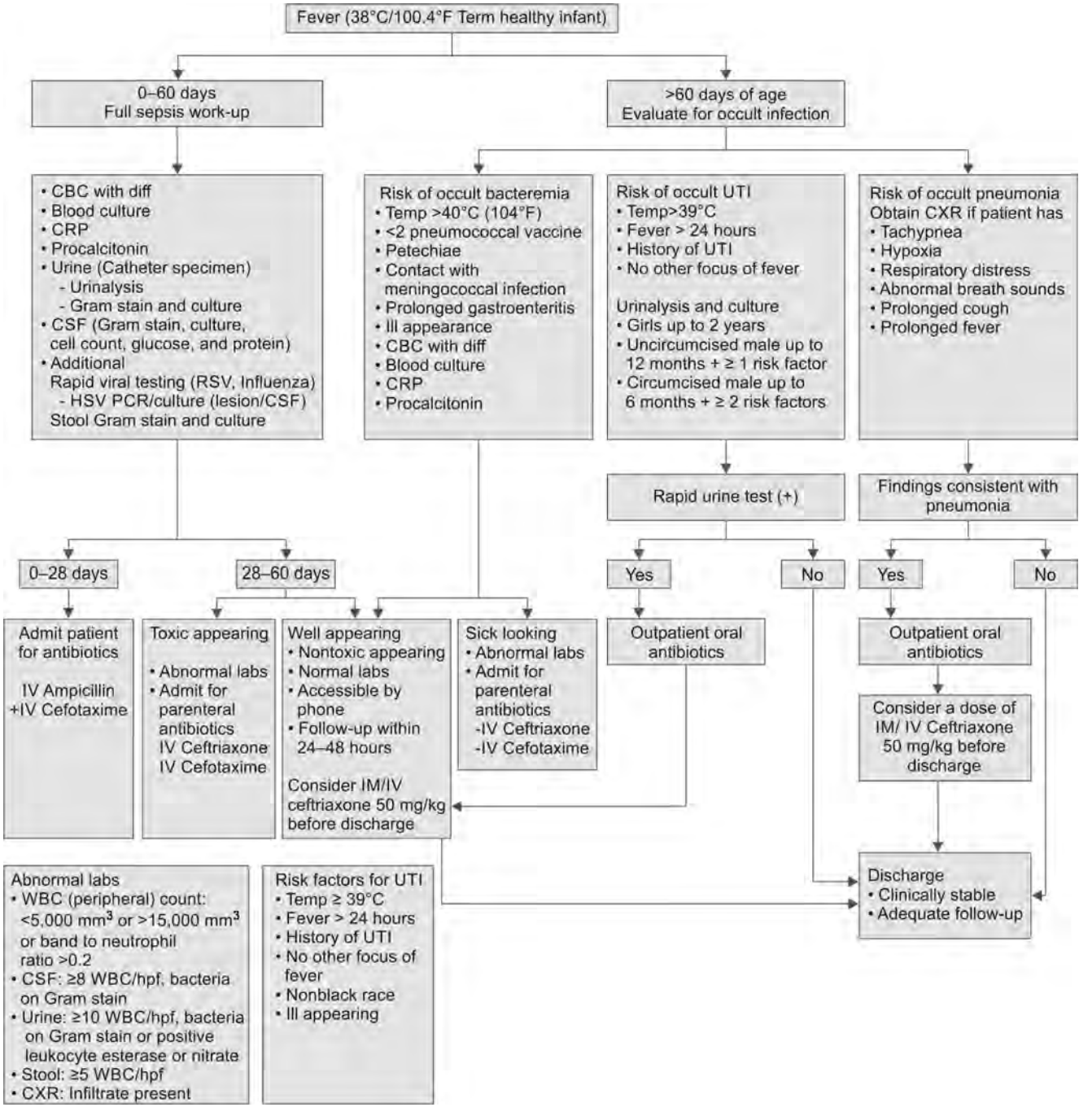
(ARDS: acute respiratory distress syndrome; BiPAP: bi-level positive airway pressure; CBC: complete blood count; COVID-19: coronavirus disease 2019; CPAP: continuous positive airway pressure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; KFT: kidney function test; LFT: liver function test; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: oxygen saturation)

Carry out investigations to rule out common tropical infections include malaria, dengue, enteric fever, rickettsial illness (scrub typhus), etc.

Guidelines for Management of Multisystem Inflammatory Syndrome in Children Related to Coronavirus Disease 2019

Appropriate supportive care is needed preferably in ICU for treatment of cardiac dysfunction, coronary involvement, shock, or multiorgan failure. Methyl prednisolone (MPS), intravenous immunoglobulin (IVIG) antiplatelet, and heparin are the mainstay of treatment.

- Intravenous immunoglobulin to be given slower (over up to 48 hours) in children with cardiac failure/fluid overload
- Taper steroids over 2–3 weeks with clinical and CRP monitoring
- Aspirin 3–5 mg/kg/day, maximum 75 mg/day in all children for 4–6 weeks (with platelet count >80,000/μL) for at least 4–6 weeks or longer for those with coronary aneurysms
- Low molecular weight heparin (enoxaparin) 1 mg/kg/dose twice daily subcutaneously in >2 months (0.75 mg/kg/dose in <2 months) if patient has thrombosis or giant aneurysm



(CXR: chest radiography; CRP: C-reactive protein)

FLOWCHART 1: Fever without apparent source in children 0–24 months of age.

with absolute coronary diameter ≥8 mm or Z score ≥ 10 or LVEF < 30%

- For children with cardiac involvement, repeat ECG 48 hourly and repeat ECHO at 7–14 days and between 4 and 6 weeks, and after 1 year if initial ECHO was abnormal. Therapy for MIS-C with or without shock is discussed as below.

MIS-C without shock: IV methylprednisolone 1–2 mg/kg/day, if symptoms persist for 48–72 hours of treatment, or if early worsening, treat as per the phenotype to which evolution occurs.

MIS-C with shock or multiorgan failure: IVIG 2 g/kg over 12–16 hours (maximum 100 g), and IV methylprednisolone 2 mg/kg/day, and empirical antimicrobials as per hospital antibiogram. If symptoms persist for 48–72 hours of treatment, or if early worsening, increase IV MPS to 10 mg/kg/day (maximum 1 g) consult specialist/expert for biological.

MIS-C with Kawasaki phenotype: IVIG 2 g/kg over 12–16 hours (maximum 100 g), and IV methylprednisolone 1–2 mg/kg/day. If symptoms persist for 48–72 hours of treatment, or if early worsening, consult specialist/expert for biologicals. Use biologicals only after expert consultation and at tertiary care only.

SUMMARY

Fever is one of the most common presenting complaints in children brought to the emergency department. Serious bacterial infection such as UTI, pneumonia, bacteremia, meningitis, bacterial gastroenteritis, osteomyelitis, septic arthritis, retropharyngeal/parapharyngeal abscess, or intra-abdominal abscess are required to diagnose and manage in early stage. Unlike in adults, adolescent and elder children, young infants and younger children have certain differences in clinical presentations, as they may become irritable and show fatigue, without any other apparent symptoms. Fever in children makes them very much uncomfortable. Observation score is used for evaluation and assessment of child with fever. Various risk stratification scores are helpful in SBI. Child should be admitted if indicated for antibacterial therapy. Evaluation and management of SBIs in children are summarized in **Flowchart 1**.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Pediatric Abdominal Pain

Thiagrajan Jaiganesh, Faiz Ahmad

INTRODUCTION

Abdominal pain in pediatric age group continues to be a frustrating presenting symptom. Diagnosis and treatment of a child with abdominal pain is time consuming—time for listening, counseling, and education. A majority of pediatric patients who evaluated for abdominal pain do not have features of classic organic disease and fall into a functional category. Abdominal pain may develop due to disorders in multiple organ systems, including the pulmonary, gastrointestinal, urologic, and gynecologic systems. Infectious, neoplastic, metabolic, and anatomic mechanisms may give rise to the presenting symptom of abdominal pain (**Box 1**).

BOX 1: Potential causes of abdominal pain in the pediatric patient.

- ***Functional*:** IBS, functional abdominal pain, functional constipation, cyclic vomiting syndrome
- ***Gynecological*:** Ovarian cyst, ovarian torsion, and testicular torsion
- **Pulmonology:** Pneumonia
- **Infectious:** *Viral*: Enterovirus, adenovirus; *Bacterial*: ***Salmonella, Shigella, Campylobacter, Yersinia, E. coli;*** *Parasites*: ***Giardia, Entamoeba histolytica***
- ***Intestinal*:** Gastroesophageal reflux (esophagitis), gastritis ulcer (duodenal/peptic), cholelithiasis, cholecystitis, choledochal cyst, pancreatitis (acute and chronic), pancreatic pseudocyst, hepatitis, inflammatory bowel disease (Crohn/ulcerative colitis), eosinophilic disease (esophagitis and gastroenteritis), and carbohydrate malabsorption (lactose intolerance)
- ***Metabolic*:** Diabetes mellitus
- ***Neoplastic*:** Porphyria tumors
- ***Structural/Surgical*:** Malrotation, intussusception, polyp, foreign body, Meckel's diverticulum volvulus, and trauma
- ***Urologic*:** Urinary tract infection, nephrolithiasis, urinary pelvic junction obstruction

(IBS: irritable bowel syndrome)

Acute abdominal pain is one of the most common pediatric complaints, and it is a diagnostic challenge for emergency physician due to the variety of underlying causes. Acute abdominal pain is mostly a self-limiting, benign condition, such as in gastroenteritis, constipation, or viral illness. However, the challenge for the emergency physician is to identify potentially life-threatening conditions that require urgent evaluation and treatment, such as appendicitis, intussusception, volvulus, or adhesion. Around 1% of pediatric population presenting with acute abdominal pain require surgical intervention. But major concern for emergency physician is not to miss serious organic etiology and accurate and timely diagnosis is the key for preventing significant morbidity and mortality.

Chronic abdominal pain remains one of the most common problems seen by pediatrician and pediatric gastroenterologists. Abdominal pain is best understood with biopsychosocial model of disease, i.e., multifactorial nature of abdominal pain, including genetic, environmental, social, and psychological components. History and physical examination remain the most important steps for evaluation of alarming symptoms, which may guide emergency physician for more specific testing (**Box 2**). Treatment plans can be individualized on the basis of history, physical examination, and investigations.

EVALUATION OF ACUTE ABDOMINAL PAIN IN CHILDREN

In children, acute abdominal pain can be the harbinger of acute appendicitis or a presentation of Hirschsprung's disease or can be presentation of a child with pneumonia or a life-threatening illness requiring urgent surgical intervention. Therefore, it is very important to differentiate the cause of the acute abdominal pain in children. This chapter addresses the common causes, red flags, evaluation, and treatment guidelines for a pediatric acute abdomen in the emergency room.

Etiology

A wide spectrum of medical and surgical causes of acute abdomen in children. Out of which, only 6% require surgical intervention. In the emergency room, it is a diagnostic challenge

BOX 2: Red flags signs suggestive of higher risk in children with chronic abdominal pain.

- Involuntary weight loss
- Deceleration of linear growth
- Gastrointestinal blood loss
- Significant vomiting (bilious emesis and protracted vomiting)
- Dysphagia
- Odynophagia
- Chronic severe diarrhea
- Night-time stooling
- Pain awakening the child at night
- Persistent right upper or right lower quadrant pain
- Unexplained fever
- Abnormal physical findings (clubbing, localized tenderness, mass, hepatomegaly, splenomegaly, perianal abnormalities, and erythema nodosum)
- Abnormal laboratory testing (elevated C-reactive protein/erythrocyte sedimentation rate, and occult blood in stool)
- Family history of inflammatory bowel disease

to accurately gather all the key signs in a child with severe pain. The most common causes of acute abdominal pain in children are gastroenteritis, mesenteric adenitis, acute appendicitis, colic, obstructed inguinal hernia, ovarian/testicular torsions, intestinal obstruction, and constipation. Various causes of acute abdominal pain are listed in **Table 1**.

TABLE 1: Causes of acute abdominal pain in children.

Hemodynamically stable (medical causes)	• Gastroenteritis • Constipation • Early stage of acute appendicitis • Hemolytic uremic syndrome • Acute pneumonia
• *Hemodynamically unstable (surgical causes)* • *Sick looking, severe pain, and signs of shock*	• Perforated bowel or appendicitis • Intestinal obstruction (volvulus, bands) • Intussusception >24 hours • Ovarian/testicular torsion • Obstructed and strangulated hernia • Trauma

Pathophysiology

Essentially, abdominal pain can have three origins. It is more commonly visceral pain or parietal pain and rarely it is referred pain. Visceral pain occurs when noxious stimuli affect bowel. Tension, stretching, and ischemia stimulate visceral pain fibers. Tissue congestion and inflammation tend to sensitize nerve endings and lower the threshold for stimuli. Visceral pain fibers are bilateral and unmyelinated and enter the spinal cord at multiple levels, visceral pain usually is dull, poorly localized, and felt in the midline. Pain from foregut structures (e.g., lower esophagus and stomach) generally is felt in the epigastrium. Midgut structures (e.g., small intestine) cause periumbilical pain, and hindgut structures (e.g., large intestine) cause lower abdominal pain (**Fig. 1**).

Parietal pain originates from noxious stimulation of the parietal peritoneum. Pain due to ischemia, inflammation, or stretching of the peritoneum is transmitted through myelinated afferent fibers to specific dorsal root ganglia on the same side and at the same dermatomal level as the origin of the pain. Parietal pain usually is sharp, intense, discrete, and localized, and coughing or movement can aggravate it. Referred pain has many of the characteristics of parietal pain but is felt in remote areas supplied by the same dermatome as the diseased organ. It results from shared central pathways for afferent neurons from different sites. A classic example is a patient with pneumonia who presents with abdominal pain because the T9 dermatome distribution is shared by the lung and the abdomen. Pain due to laparoscopic surgeries can be felt in the left shoulder.

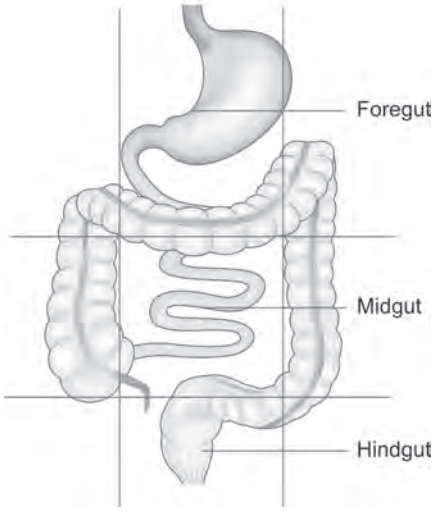


FIG. 1: *Pathophysiology*: Possible site of origin of acute abdominal pain in children.

Clinical Presentation

The challenge for the clinician is to identify patients with abdominal pain who may have the following: serious, potentially life-threatening conditions, such as an acute abdomen from appendicitis or bowel obstruction (as can occur from volvulus, intussusception, or adhesions); acute manifestations of inflammatory bowel disease (IBD), pancreatitis, hepatitis, myocarditis, or intra-abdominal mass. Extra-abdominal infections that require specific treatment (such as streptococcal pharyngitis, urinary tract infection, or pneumonia), this is very important to note serious life-threatening signs (red flags) in the early stage (**Table 2**). If these red flag signs are noted, urgent surgical consult should be obtained and rapid radiological confirmation of the diagnosis is needed before surgical intervention.

Evaluation

Assess general condition, vitals, and hydration status:

- *History taking*: It is extremely vital to get an accurate history, although it can sometimes be hearsay in children. The clues we can obtain by simple questioning are, length of current illness, similar episodes in the past, periodicity,

colicky nature of pain, and aggravating factors. Which came first, pain or vomiting? For example, in surgical causes of acute abdomen, the pain comes before the vomiting, but vice versa in medical causes. Nature of vomiting, whether bilious, also carries significance, as it indicates intestinal obstruction.

TABLE 2: Red flags: Acute onset abdominal pain.

Red flags	*Interpretation*
Acute abdomen with septic shock (hypotension, lethargy, and tachycardia)	In generalized abdominal sepsis
Bilious vomiting with scaphoid abdomen	Malrotation with volvulus
"Red currant jelly" stools	Classical in intussusception
Generalized guarding/ peritonism	Bowel perforation
Irreducible groin swelling	Obstructed inguinal hernia's
Testis pulled up into upper scrotum/inguinal region, firm, and tender	Testicular torsion
Abdominal distension, tenderness with shock (H/o blunt trauma abdomen)	Internal hemorrhage due to solid organ/bowel injury secondary to trauma
Feculent vomitus/ obstipation	Intestinal obstruction
Palpable tender abdominal mass	Appendicular mass/abscess
Inability to walk due to abdominal pain	Appendicular/psoas abscess
Hematemesis	Bowel gangrene/portal hypertension
Incessant cry	Bowel strangulation/ischemia/ obstruction

- *Physical examination:* The examiner's technique should be gentle and patient, with both the parent and the child. The examination should end in the area of interest while trying to engage the child in conversation or distraction. A per rectal examination is a must, as it adds diagnostically relevant information regarding the stool, melena, hematochezia, and sphincter tone. Evaluation should be completed by examining the genitalia, testes, and spine of the child. **Table 3** describes the differential diagnosis of acute abdominal pain in children.

Investigations

X-ray abdomen is a good diagnostic tool in children with abdominal pain, signs such as football sign or Rigler's sign (pneumoperitoneum), multiple air fluid levels indicating bowel obstruction, or the pneumatosis intestinalis [intramural air in necrotizing enterocolitis (NEC)], paucity of bowel gas in volvulus, paucity of rectal gas in Hirschsprung's disease, all are good diagnostic markers of specific disease. X-ray can be used in adjunction with oral contrast also when feasible to confirm certain diagnosis. Ultrasound abdomen is the standard investigation for the common appendicitis, mesenteric adenitis and intussusception seen in the pediatric emergency room every day. A finding of a nonperistaltic blind ending dilated >6 mm in the region of the right iliac fossa is diagnostic of appendicitis. In intussusception, the pseudo kidney sign or target sign is the classical finding. When Doppler is added to the USG, malrotation and volvulus can also be picked up, if we see the whirlpool sign. Important modalities of investigation are listed in **Table 4**.

Treatment

Treatment should be aimed at the underlying cause of the acute abdomen once the diagnosis is made, till the resuscitative measure should be carried out, e.g., intravenous fluids should be started for dehydrated children according to the metabolic

TABLE 3: Differential diagnosis of acute abdomen with regards to the age.

	0–1 years	*2–5 years*	*6–10 years*	*11–15 years*
Medical causes	Infantile colic	Gastroenteritis	Gastroenteritis	Gastroenteritis
	Gastroenteritis	Lower lobe pneumonia	Constipation	Pancreatitis
	Constipation	Urinary tract infection	Mesenteric lymphadenitis	Constipation
	Urinary tract infection	Henoch–Schönlein purpura	Urinary tract infection	Mittelschmerz
		Constipation	Pneumonia	Pelvic inflammatory disease
		Mesenteric adenitis	Inflammatory bowel disease	Inflammatory bowel disease
		Sickle cell crisis		
Surgical causes	Intussusception	Intussusception	Appendicitis	Appendicitis
	Obstructed inguinal hernia	Appendicitis	Trauma	Ovarian/testicular torsion
	Midgut volvulus	Trauma	Testicular torsion	Trauma
	Hirschsprung's disease	Volvulus	Cholecystitis	Hollow viscus perforation
		Ovarian/testicular torsion	Ovarian/testicular torsion	Intestinal obstruction
		Obstructed inguinal hernia	Intestinal obstruction	
		Intestinal obstruction	Hollow viscus perforation	

TABLE 4: Important investigations helpful in acute abdominal pain in children.

Modality	*Radiological sign*	*Interpretation*
X-ray abdomen	Football sign/Rigler's sign	Pneumoperitoneum/bowel perforation
	Multiple air fluid levels	Intestinal obstruction
	Paucity of bowel gas	Midgut volvulus
	Paucity of rectal gas	Hirschsprung's disease
	Pneumatosis intestinalis	Necrotizing enterocolitis
USG abdomen	Nonperistaltic blind ending dilated bowel loop >6 mm in the RIF	Appendicitis
	Pseudo kidney sign/target sign	Intussusception
USG abdomen with color Doppler	Whirlpool sign	Midgut volvulus

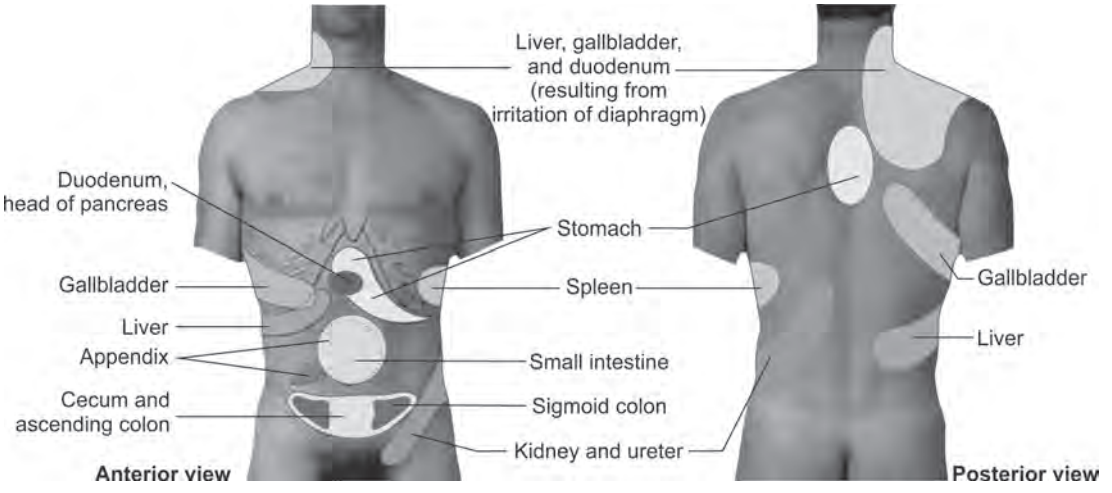


FIG. 2: Possible site of origin of chronic abdominal pain in children.

deficit. Urine output assessment can be done by catheterizing the bladder. Nasogastric decompression is advisable in children with bilious or feculent vomiting to prevent aspiration of vomitus. Analgesics can be avoided in some situations till the diagnosis is clear, as nature of tenderness can guide the physician. Occasionally, an irritable infant may not allow optimal examination unless sedated with oral/nasal/IV sedatives.

EVALUATION OF CHRONIC OR RECURRENT ABDOMINAL PAIN IN CHILDREN

Chronic abdominal pain is defined as at least three episodes of pain over at least 3 months interfering with a child's normal function. In clinical practice, abdominal pain that is >2 months in duration is considered chronic abdominal pain. The term "chronic abdominal pain" encompasses "recurrent abdominal pain" classically defined by four criteria: (1) ≥3 episodes of abdominal pain; (2) pain sufficiently severe to affect activities; (3) episodes occur over a period of ≥3 months, and (4) no known organic cause. The prevalence of recurrent abdominal pain in children ranges from 9 to 15%. Chronic abdominal pain in children could result in poor social and education development while placing a significant burden on local healthcare resources. Therefore, our aim is summarizing a variety of childhood disorders that could lead to chronic abdominal pain and provide some diagnostic and treatment strategies (**Fig. 2**). The two main categories of causes of chronic abdominal pain in children are organic and functional disorder (**Table 5**).

Pathophysiology

The pathophysiology of functional abdominal pain is likely due to the involvement of the enteric nervous system (ENS), also known as "gut brain". Pain receptors in the abdomen respond to mechanical or chemical stimuli. Stretch is the major mechanical stimulus involved in visceral pain which is induced by distension, contraction, traction, compression, and torsion.

Clinical Presentation

The clinical presentation could be varied, but one should pay attention to the "*red flags*" as they may indicate an organic cause. Organic pathology is identified in approximately 1 in 10 children who present with chronic and or recurrent abdominal pain. The signs and symptoms that can suggest underlying organic pathology are—nocturnal or chronic diarrhea, deceleration of linear growth, delayed puberty, dysphagia, family history of inflammatory bowel, celiac or peptic ulcer disease, gastrointestinal blood loss, genitourinary tract symptoms, involuntary weight loss, pain that wakes the

TABLE 5: Chronic causes of abdominal pain in pediatric age.		
Organic disorders	Gastrointestinal	Celiac disease, chemical gastritis, constipation, eosinophilic esophagitis, erosive esophagitis, gallbladder disease, gastroenteritis/colitis, GERD, *Helicobacter pylori* infection, hiatal hernia, inflammatory bowel disease irritable bowel syndrome, pancreatitis, and peptic ulcer
	Genitourinary	Imperforate hymen, menstrual cramps, mittelschmerz, ovarian cyst, endometriosis, pelvic inflammatory disease, recurrent UTI, testicular pain, ureteropelvic junction obstruction, and urolithiasis
	Metabolic	Adrenal crisis, diabetic ketoacidosis, porphyria
	Musculoskeletal	Anterior cutaneous nerve entrapment
	Neurologic	Spinal tumor and transverse myelitis
	Other	Familial mediterranean fever, lead poisoning, lymphoma, peritoneal, abscess/tumor, pneumonia, sickle cell disease, polyarteritis nodosa/vasculitis, IgE-mediated food allergy
Functional disorders	Functional dyspepsia	Dyspepsia is pain or discomfort in the epigastric region. Children with dyspepsia and alarm findings should be evaluated for an organic disorder (e.g., peptic ulcer disease)
	Irritable bowel syndrome (IBS)	It is characterized by chronic abdominal pain and altered bowel habits (diarrhea or constipation) in the absence of any alarm findings
	Abdominal migraine	It is characterized by recurrent episodes of abdominal pain for at least 6 months, usually in the midline or poorly localized, moderate to severe in intensity and is associated with at least two more features including anorexia, nausea, vomiting, headache, photophobia, and pallor. A family history of a migraine headache is common

child from sleep, persistent right upper or lower quadrant pain, significant vomiting, and recurrent unexplained fevers.

Evaluation

The initial evaluation of chronic abdominal pain includes history, physical examination, and stool guaiac for occult blood to determine, if the child has any "*red flags*" that can help in distinguishing organic from functional abdominal pain and direct the need for additional evaluation:

- *History*: It is important to ask specifically about the alarm findings: unexplained fever or weight loss, painful swallowing or difficulty swallowing, vomiting—bilious, protracted, projectile, or worrisome, diarrhea—severe and chronic (lasting >2 weeks and >20 mL/kg/day), bloody or nocturnal, back pain, urinary symptoms, family history of IBD, celiac disease, or peptic ulcer disease, and skin changes (e.g., hives, eczema, and rash).
- Asking the patient/family to keep the pain diary regarding the time of the day the pain started, pain location and severity, pain duration, triggering factors, and interventions if any and if they were helpful.
- *Physical examination*: A thorough physical examination may help in the diagnosis of chronic abdominal pain. General appearance and level of discomfort may indicate the severity of abdominal pain. Alarm findings on examination include—deceleration in linear growth, anemia, oral ulcers or perianal skin tag, fissure or fistula, localized abdominal pain, suprapubic tenderness, or costovertebral angle tenderness, delayed puberty, hepatosplenomegaly, guaiac-positive stool, joint swelling or tenderness, and hypertension.
- *Carnett sign:* It helps to differentiate visceral from abdominal wall pain. With the child in a supine position, ask him or her to cross the arms and sit halfway forward. A focal tenderness that increases and or remains the same during abdominal wall contraction (i.e., positive Carnett sign) suggests pain originating in the abdominal wall (e.g., hematoma, hernia, muscular pain, and anterior cutaneous nerve entrapment syndrome).
- *Psoas sign*: Pain on hyperextension of the hip is suggestive of inflammation of psoas muscle (e.g., psoas abscess). Delayed puberty may be a clue to organic disease (e.g., IBD); absence of menarche despite sexual maturity may be a clue to hematocolpos.

Investigations

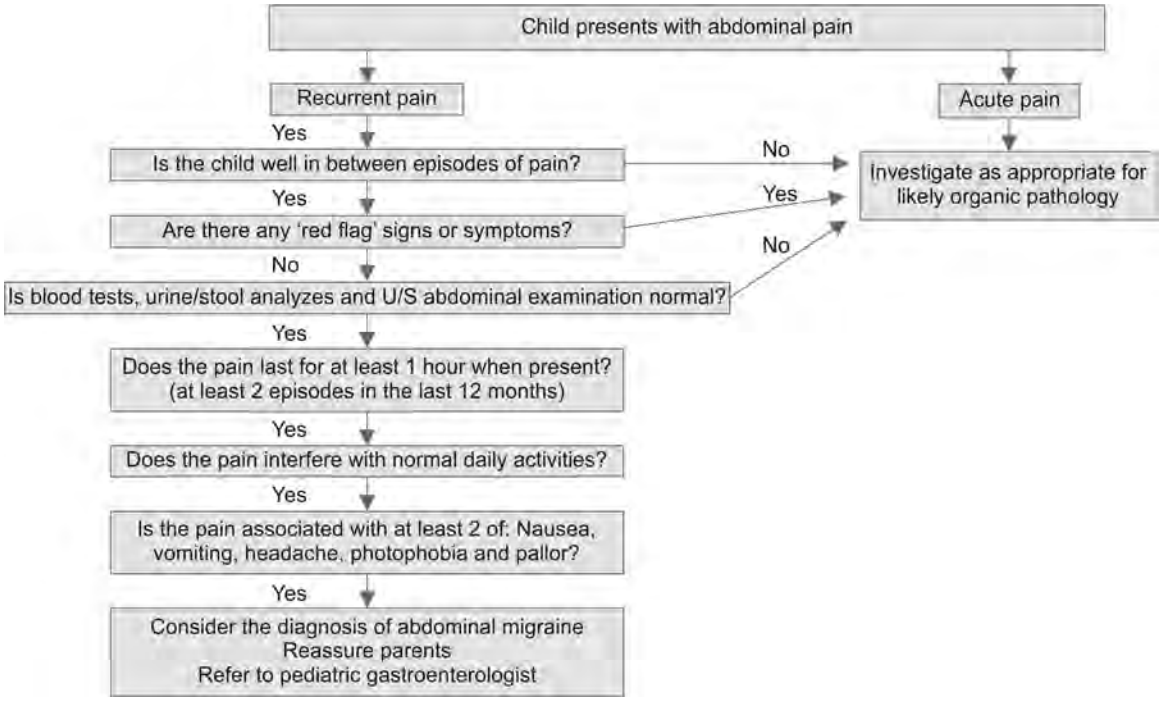
Careful and detailed history and physical examination in combination with judicious and selective use of diagnostic studies are required to delineate the underlying cause of chronic abdominal pain in children. Routine testing in patients with chronic abdominal pain without any "*red flag or alarm findings*" is not useful, though it may be reassuring for the parents. A 2005 systematic review found little or no evidence to suggest that laboratory, ultrasonography, endoscopy, or esophageal pH monitoring increases the yield of organic disease in the absence of "red flags"/"alarm findings". Laboratory tests to consider in patients with alarm findings are complete blood count with differential for anemia or infection, C-reactive protein or erythrocyte sedimentation rate for inflammation or infection, metabolic panel, liver function test, lipase, pregnancy test, tissue transglutaminase antibody for screening celiac disease, thyroid stimulating hormone and free thyroxine (T4) to evaluate for hypothyroidism as a cause of chronic constipation, urinalysis and culture for urinary tract infection, stool guaiac test for gastrointestinal bleeding, stool ova, and parasite. *Helicobacter pylori* stool antigen or urea breath test, the fecal calprotectin test had a pooled sensitivity of 92% and a pooled specificity of 76% for IBD. A child with weight loss, anemia, and blood in the stool should be evaluated for Crohn's disease because these conditions have a cumulative sensitivity of 94% for Crohn's disease in children. Abdominal radiography may be helpful in the diagnosis of obstruction,

foreign body, or constipation. Abdominal ultrasound abnormalities are found in about 10% of children who have jaundice, persistent fever, urinary symptoms, significant weight loss, back or flank pain, vomiting, abnormal abdominal examination findings, abdominal pain away from midline, and gastrointestinal bleeding, compared with <1% of those without these findings. Pelvic ultrasonography—is done to evaluate ovarian masses or pregnancy. Upper gastrointestinal series is done to assess bowel obstruction. Computed tomography of the abdomen with contrast is done to evaluate retroperitoneal or intraperitoneal abscess; usually reserved for urgent evaluation because of the risk of exposure to radiation in young children. Magnetic resonance enterography will be done, if IBD is suspected. Esophagogastroduodenoscopy and colonoscopy with ileoscopy can be done if Crohn's disease is suspected. Diagnosis of functional abdominal pain can be made without additional diagnostic testing in children with chronic abdominal pain who meet the following criteria: no alarm findings, normal physical examination, and stool sample negative for occult blood. A simplified diagnostic algorithm for the assessment of children presenting with recurrent abdominal pain is shown in **Flowchart 1**. Diagnostic imaging pathways for children presenting with chronic abdominal pain is depicted in **Flowchart 2**.

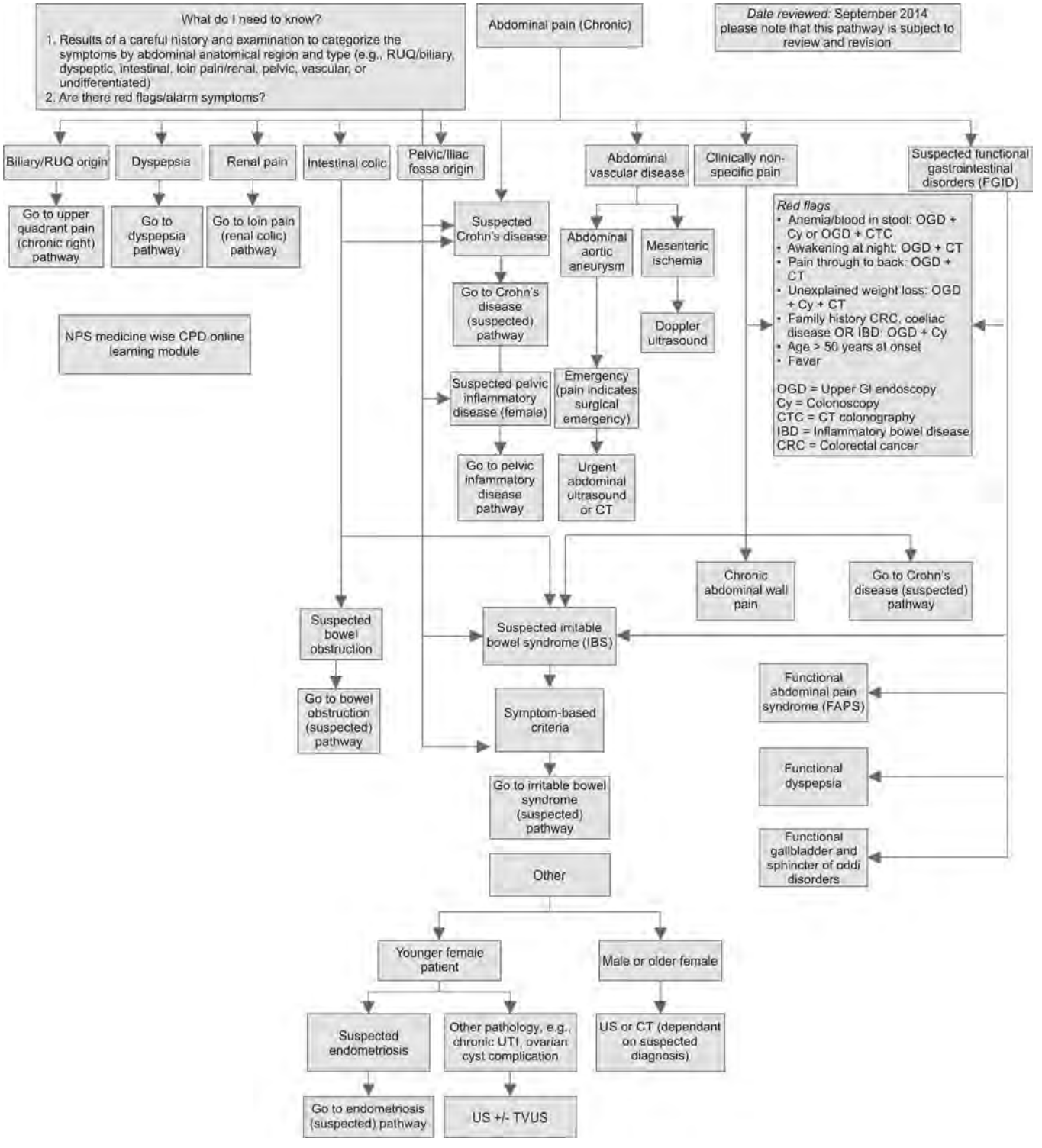
Treatment

Treatment depends on the cause of pain and whether the abdominal pain is organic or functional. The primary goal of therapy is improving quality-of-life, reducing parent and child concern about the seriousness of the condition, and reducing disability associated with pain rather than complete resolution of pain. In children with functional abdominal pain, use of probiotics, such as lactobacillus, reduces the intensity and frequency of abdominal pain and is safe for children. Cognitive behavior therapy is an evidence-based psychosocial method that focuses on changing the patterns of thinking that causes unwanted behaviors. Hypnotherapy is another promising psychological therapy in which a hypnotized child visualizes relaxing images to ease symptoms such as pain and anxiety. Gut-directed hypnotherapy demonstrates sustained long-term effects, with continued pain relief 5 years after treatment in 68% of the patients. Following interventions may be beneficial in conjunction with supportive management:

- *Acid reflux*: Antacid and H2 receptor antagonists.
- *Dyspepsia*: Proton-pump inhibitors, including lansoprazole and pantoprazole, are safe and effective for the treatment of dyspepsia in children, with the improvement of pain in more than 70% of patients.
- *Celiac disease*: A gluten-free diet should be initiated.
- *Inflammatory bowel disease*: Children should be referred to a pediatric gastroenterologist for anti-inflammatory medications and biologics.
- *Chronic constipation*: Treatment includes dietary interventions, such as increased fluids, fiber, and prune, pear, and apple juices; behavioral interventions, including regular toilet time for 5 or 10 minutes after meals and use of stool diaries; reward system; and parental education. Polyethylene glycol is the first-line therapy for children. Magnesium hydroxide is another option. Severe constipation may require manual disimpaction, enemas (e.g., saline, mineral oil, and polyethylene glycol), suppositories (e.g., bisacodyl and glycerine) or other laxatives (e.g., magnesium citrate, lactulose, sorbitol, docusate, and mineral oil).


Child presents with abdominal pain
Recurrent pain
Acute pain
Yes
Is the child well in between episodes of pain?
No
Investigate as appropriate for likely organic pathology
Yes
Are there any 'red flag' signs or symptoms?
Yes
No
No
Is blood tests, urine/stool analyzes and U/S abdominal examination normal?
Yes
Does the pain last for at least 1 hour when present? (at least 2 episodes in the last 12 months)
Yes
Does the pain interfere with normal daily activities?
Yes
Is the pain associated with at least 2 of: Nausea, vomiting, headache, photophobia and pallor?
Yes
Consider the diagnosis of abdominal migraine
Reassure parents
Refer to pediatric gastroenterologist

FLOWCHART 1: Simplified algorithm for the assessment of children presenting with recurrent abdominal pain.


What do I need to know?
1. Results of a careful history and examination to categorize the symptoms by abdominal anatomical region and type (e.g., RUQ/biliary, dyspeptic, intestinal, loin pain/renal, pelvic, vascular, or undifferentiated)
2. Are there red flags/alarm symptoms?
Abdominal pain (Chronic)
Date reviewed: September 2014 please note that this pathway is subject to review and revision
Biliary/RUQ origin
Dyspepsia
Renal pain
Intestinal colic
Pelvic/Iliac fossa origin
Abdominal vascular disease
Clinically non-specific pain
Suspected functional gastrointestinal disorders (FGID)
Go to upper quadrant pain (chronic right) pathway
Go to dyspepsia pathway
Go to loin pain (renal colic) pathway
Suspected Crohn's disease
Abdominal aortic aneurysm
Mesenteric ischemia
Red flags
• Anemia/blood in stool: OGD + Cy or OGD + CTC
• Awakening at night: OGD + CT
• Pain through to back: OGD + CT
• Unexplained weight loss: OGD + Cy + CT
• Family history CRC, coeliac disease OR IBD: OGD + Cy
• Age > 50 years at onset
• Fever
OGD = Upper GI endoscopy
Cy = Colonoscopy
CTC = CT colonography
IBD = Inflammatory bowel disease
CRC = Colorectal cancer
Go to Crohn's disease (suspected) pathway
Doppler ultrasound
NPS medicine wise CPD online learning module
Suspected pelvic inflammatory disease (female)
Emergency (pain indicates surgical emergency)
Go to pelvic inflammatory disease pathway
Urgent abdominal ultrasound or CT
Chronic abdominal wall pain
Go to Crohn's disease (suspected) pathway
Suspected bowel obstruction
Suspected irritable bowel syndrome (IBS)
Go to bowel obstruction (suspected) pathway
Symptom-based criteria
Functional abdominal pain syndrome (FAPS)
Functional dyspepsia
Go to irritable bowel syndrome (suspected) pathway
Functional gallbladder and sphincter of oddi disorders
Other
Younger female patient
Male or older female
Suspected endometriosis
Other pathology, e.g., chronic UTI, ovarian cyst complication
US or CT (dependant on suspected diagnosis)
Go to endometriosis (suspected) pathway
US +/- TVUS

FLOWCHART 2: Diagnostic imaging pathways in children presenting with chronic abdominal pain.

SUMMARY

Evaluation of pediatric abdominal pain is challenge, it is very important to differentiate the cause of the acute abdominal pain in children because this may be life-threatening. Chronic abdominal pain is defined, if present for at least 2 months. Two major causes of chronic abdominal pain are organic disorders and functional disorders. The initial evaluation of chronic abdominal pain includes history, physical examination, and stool guaiac test. If there are no "alarm findings", no further evaluation is necessary in most cases. Patients with alarm findings require additional laboratory and imaging studies to look for organic causes.

MULTIPLE CHOICE QUESTIONS

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167 CHAPTER

Vomiting, Diarrhea, Dehydration in Children

Deepak Goyal

INTRODUCTION

Diarrhea is defined as the passage of *three or more loose or liquid stools per day*. Acute diarrhea is defined as diarrhea, which lasts <14 days. Frequent passing of formed stools is not diarrhea, nor is the passing of loose and pasty stools by breastfed infants. *Childhood diarrhea* is one of the leading causes of morbidity and mortality throughout the world. Dysentery is diarrhea with presence of visible blood in stools with presence of cramps and or fever. Dysentery does not include blood streaks on surface of formed stool or blood detected by microscopy/biochemical examination. *Nausea* is the sensation of impending emesis and is frequently accompanied by autonomic changes, such as increased heart rate and salivation. *Vomiting* is forceful expulsion of gastric contents from the mouth. In 2015, diarrheal disease caused an estimated 688 million illnesses and 499,000 deaths worldwide among children <5 year. In India, approximately 140,000 deaths among children under-5 were attributable to diarrhea in 2013. Diarrhea is a leading cause of malnutrition in children under 5-year-old.

ETIOLOGY

Table 1 shows the common infectious agents of acute diarrhea. *Rotavirus* accounts for 40% of all hospital admission worldwide. Rotavirus was identified as an etiological agent in 5.2–80.5% cases of nosocomial diarrhea. Compared with other viral infections, rotavirus infection is associated with fever, more frequent diarrheal episodes (>7/day) and longer lasting diarrhea. Although it is difficult to differentiate clinically but presence of high fever, overt fecal blood, abdominal pain, or central nervous system (CNS) involvement favors bacterial origin. **Table 2** highlights etiology of acute vomiting in infants and children.

TABLE 1: Etiology of acute diarrhea.

Viruses	*Bacterial*	*Parasites*
• Rotavirus • Norwalk virus • Adenovirus • Astrovirus • Calicivirus	• *E. coli* • *Shigella* • *Salmonella* • *V. cholera* • *Campylobacter jejuni* • *Clostridium difficile*	• *Giardia* • *Entamoeba* • *Cryptosporidium* • *Isospora belli*

ASSESSMENT OF CHILD WITH VOMITING AND DIARRHEA

Child with diarrhea *should be assessed for* (1) dehydration, (2) blood in diarrhea, (3), coexisting malnutrition, and (4) serious nonintestinal infections.

History should focus on duration of diarrhea and number of watery stools per day; volume of water in stool; presence of blood in the stool; frequency of urination; presence of vomiting, fever, cough, or seizures; preillness feeding practices; and fluids, food and drugs taken during illness, and immunization history.

Examination should include general condition of child; signs of dehydration; nutritional status [weight/weight for height/mid-upper arm circumference (MAC)] and severity of malnutrition if any; and presence of blood in stool besides general physical and systemic examination. Classification of dehydration (**Table 3**) is of utmost importance in the management.

TABLE 2: Causes of acute vomiting in infants and children.

Infants	*Children*
Viral gastroenteritis	Viral gastroenteritis
Gastroesophageal reflux	Sepsis
Pyloric stenosis	Meningitis/encephalitis
Intussusception	Appendicitis/pyelonephritis
Sepsis	Hepatitis
Malrotation	Raised intracranial tension
Food intolerance	Toxic ingestion
Metabolic disorders	Adverse drug reactions
	Cyclic vomiting syndrome

TABLE 3: Classification of dehydration.		
Severe (two of the following are present)	***Some (two of the following are present)***	***No dehydration***
Lethargy/unconscious	Restless, irritable	Not enough signs to classify some or severe dehydration
Sunken eyes	Sunken eyes	
Not able to drink/ drinking poorly	Drinks eagerly, thirsty	
Skin pinch goes back very slowly	Skin pinch goes back slowly	

DEHYDRATION IN DIARRHEA

During diarrhea, there is an increased loss of water and electrolytes (sodium, chloride, potassium, and bicarbonate) in the liquid stool. Water and electrolytes are also lost through vomit, sweat, urine, and breathing. Dehydration occurs when these losses are not replaced adequately and a deficit of water and electrolytes develops.

How to assess skin pinch?

Locate the area on the child's abdomen halfway between the umbilicus and the side of the abdomen. Use your thumb and first finger to pinch. The fold of the skin should be in a line up and down the child's body. Firmly pick up all of the layers of skin and the tissue under them. Pinch the skin for one second and then release it. When you release the skin, look to see if the skin pinch goes back: Very slowly (>2 sec), slowly (skin stays up even for a brief instant), and immediately (normal).

For children with vomiting history should determine onset and frequency of vomiting; character of episodes (projectile, bilious, or small in amount and more consistent with spitting up); any precipitating factor to vomiting (only with specific foods, after feeding, primarily in the morning or in recurrent cyclic episodes). Any associated symptoms including diarrhea (with or without blood), fever, anorexia, and abdominal pain, distention should be looked for. Stool frequency and consistency and urinary output should also be noted.

General examination should include signs of distress (e.g., lethargy, irritability, and inconsolable crying) and signs of weight loss. Skin and extremities should be examined for purpura or petechiae (sepsis) or any other rash (possible viral infection or atopy), jaundice (hepatitis/metabolic disorder), and signs of dehydration (e.g., poor skin turgor and delayed capillary refill). The head and neck examination should focus on signs of infection (e.g., red, bulging tympanic membrane; bulging anterior fontanel; and erythematous tonsils). *Systemic examination* should seek symptoms suggestive of causative disorders, including weakness, poor suck, and failure to thrive (CNS infections/metabolic disorders); abdominal distention (intestinal obstruction); headache, nuchal rigidity, and vision changes (intracranial etiology); ear pain or sore throat (focal infection); and fever with headache, neck or back pain, or abdominal pain (meningitis, pyelonephritis, or appendicitis). Cardiac examination should note presence of tachycardia (dehydration, fever, and distress). Abdominal examination should note distension; presence and quality of bowel sounds (high-pitched, normal, and absent); tenderness and any associated guarding, rigidity, or rebound (peritoneal signs); and presence of organomegaly or mass.

Features of concern (red flags):

- Bilious emesis
- Peritoneal signs or abdominal distention (surgical abdomen)
- Persistent vomiting with poor growth or development
- Lethargy or listlessness
- Inconsolability and bulging fontanel in infant
- Nuchal rigidity, photophobia, and fever in older child

TREATMENT

Plan of treatment for acute diarrhea has been shown in **Table 4**. Management of acute vomiting consists of assessment and correction of dehydration and correction of specific etiology besides symptomatic management. Since acute vomiting is mostly seen as a part of acute gastroenteritis, our discussion here will be focused on that objectives—(1) prevent and treat dehydration, (2) drugs (antibiotics, zinc), (3) nutritional management, and (4) education. *Indications for hospital admission are* (1) shock, (2) severe dehydration, (3) neurological abnormalities (lethargy, seizures), (4) intractable or bilious vomiting, (5) failure of oral rehydration, (6) suspected surgical condition, and (7) conditions for a safe follow-up and home management are not met.

Plan A: No Dehydration—Home Care

No blood tests are required. Give the child more fluids than usual, to prevent dehydration. Low osmolarity oral rehydration solution (ORS) is the preferred solution for this. Currently in India, only low osmolarity ORS (**Table 5**) is available. If ORS is not available or child is not taking it, other fluid like salted drinks (e.g., salted rice water or a salted yoghurt drink), vegetable, or chicken soup with salt or yoghurt drinks without salt or coconut water can be used. Commercial carbonated beverages or fruit juices should not be used.

TABLE 4: Plan of treatment for dehydration.		
Severe dehydration	***Some dehydration***	***No dehydration***
Plan C	*Plan B*	*Plan A*
Urgent care in hospital	Treat dehydration with ORS/ IV fluid	Home care

TABLE 5: Composition of standard and low osmolarity ORS solutions.		
	Standard ORS solution (mEq)	***Low osmolarity ORS (mmol/L)***
Glucose	111	75
Sodium	90	75
Chloride	80	65
Potassium	20	20
Citrate	10	10
Osmolarity	311	245

Up to 5–10 mL/kg fluid should be given orally after each loose stool depending upon the volume of stool. Older children can have as much as they want. Continuation of normal (age appropriate) feeding is advised and it should not be stopped as it can aggravate existing malnutrition.

Red flag signs: Educate patient to return to hospital if any one of the flowing occurs, high purge rate; repeated vomiting; very thirsty; oral intake poor; develops fever or blood in stools; and failure to pass urine for >6 hours.

Plan B: Some Dehydration

Routine blood tests are again not indicated in some dehydration. ORS is the mainstay of management along with nutrition. Approximately 75 mL/kg of ORS should be given in around 4 hours to correct dehydration. Asses the child regularly during rehydration to know the purge rate; whether the child is able to accept the ORS and whether signs of dehydration are not worsening. In infants, continue breastfeed as often and as long as the infant wants. For older children, offer as much plain water to drink as they wish, in addition to ORS solution.

How to give ORS?

The solution should be given to infants and young children using a spoon or cup. For young infants, a dropper or syringe can also be used. Children under 2 years of age should be offered a teaspoonful every 1–2 minutes; older children may take frequent sips directly from the cup. If the child vomits, wait 10 minutes and then give ORS solution again, but slowly.

After 4 hours: Asses the Child Again

If the child still has signs indicating some dehydration, continue oral rehydration therapy by repeating treatment plan B. If signs of severe dehydration, give IV fluids as in plan C (discussed later). This can be there in children who drink ORS solution poorly and pass large watery stools frequently during the rehydration period. If there are no signs of dehydration, the child should be considered fully rehydrated and can be sent home.

Before Sending the Child Back

Teach the mother how to treat her child at home with ORS solution and food (treatment plan A). Ensure she has enough ORS packets. Also educate about red flag signs (as described in plan A).

Plan C: Severe Dehydration

Investigations

Complete blood count (CBC), electrolytes, venous blood gas (VBG), and renal function test (RFT) are preferred. Stool for hanging drop and culture should be sent when cholera is suspected *(If clinical suspicion)*. Stool routine and culture is normally not indicated in management of acute watery diarrhea as they do not change the management. Assess the child carefully for presence of shock as early recognition of shock is important. Though isonatremic dehydration is most common but hypo- or hypernatremic dehydration can be present and should be treated as per protocol. There is no role of intravenous (IV) bicarbonate in correction of acidosis and IV fluid alone is sufficient (**Table 6**).

TABLE 6: Treatment plan C (severe dehydration).

Age	*First give 30 mL/kg in:*	*Then give 70 mL/kg in:*
Infants (under 12 months)	1 hour	5 hours
Older	30 minutes	2.5 hours

Intravenous fluid with close monitoring is the mainstay of treatment. Establish IV or intraosseous access (if IV access not available). Ringer's lactate (RL) is preferred fluid. It can be used in all age groups for the initial treatment of severe dehydration caused by acute diarrhea of any etiology. Normal saline is a good alternative (dextrose normal saline is preferred for malnourished). Plain dextrose solution should not be used since it does not contain electrolytes and thus does not correct the electrolyte losses or the acidosis. It does not effectively correct hypovolemia.

Reassess the patient every 15 minutes till strong radial pulse is felt. Thereafter assess every 1–2 hours. If hydration is not improving, increase the IV drip infusion. If the patient is able to drink, give ORS by mouth. *Beware of fluid overload (congestive cardiac failure and hepatomegaly) in severely malnourished children.*

ORS in Severe Dehydration

Children who can drink, should be given ORS until the IV drip is running. In addition, all children should start to receive ORS solution (about 5 mL/kg/h) when they can drink without difficulty, which is usually within 3–4 hours for infants or 1–2 hours for older children. ORS provides additional base and potassium, which helps in recovery. Oral/IV ondansetron is the preferred and safe antiemetic in case of vomiting and it is preferred over oral domperidone.

Reassess after Resuscitation

After 6 hours in infants and 3 hours for older patients, evaluate hydration status again and choose the appropriate plan (A, B, or C) (*see* **Table 4**). Observe for at least 8–12 hours after the child has been fully rehydrated. Give extrafluids, zinc supplement, feeding advice, and counseling regarding when to return immediately as in plan A before discharge.

Role of Nutrition

Age appropriate feeding during diarrhea is encouraged to decrease stool output, shorten the duration of illness, and to improve nutritional status. *Early feeding* enhances enterocyte regeneration, promotes recovery of brush border disaccharidases, nutrient absorption, and weight gain. On demand, breastfeeding should be continued for infants who are already breastfed. Infants who are not breastfed should be given their usual milk or formula feed at least every 3 hours. Infants >6 months should be given mashed cereals, vegetables, and other complimentary foods in addition to milk. Recommended foods should be culturally acceptable, readily available, and should have a high energy content, and provide adequate micronutrients. Frequent, small feedings are tolerated better than large feedings. Same energy-rich foods should be continued even after the diarrhea stops.

If the child is malnourished, extrameals should be given until the child has regained normal weight-for-height.

Role of Antibiotics in Acute Diarrhea

Most cases of acute watery diarrhea are viral and are self-limiting. Blanket antibiotic cover is not justified. Unnecessary use of antibiotics leads to destruction of normal gut flora and can be a risk factor for persistent diarrhea. They may increase costs, prolong diarrheal episodes, and contribute to spreading antibiotic resistance. Indications for use of antibiotics in diarrhea:

- Dysentery
- Presence of systemic infection/sepsis
- Associated infection—urinary tract infection (UTI), acute suppurative otitis media (ASOM), and pneumonia
- Severe malnutrition
- Cholera
- Cryptosporidium
- Immune deficiency
- Proven giardiasis/amoebiasis

Zinc Supplementation in Diarrheal Diseases

20 mg per day of zinc for 14 days should start as early as possible after onset of diarrhea and 10 mg per day for infants 2–6 months should be given. Zinc sulfate, acetate, and gluconate are all acceptable zinc salt formulations. There is no need to repeat zinc in case of a second attack of diarrhea within next 3 months.

Mechanism of action—(1) improves absorption of water and electrolytes by the intestines by regeneration of gut epithelium, (2) enhances immunologic mechanisms for the clearance of infection including T cell-mediated immunity and induces higher levels of secretory antibodies, and (3) increases level of enterocyte brush-border enzymes.

SUMMARY

Diarrhea contributes significantly to under-5-year age mortality and morbidity (malnutrition) in our country. Assessment of dehydration is the most important step in the management of acute diarrhea. It is important to identify patients with severe malnutrition. Rehydration and zinc supplementation are the mainstay of management. Low osmolarity ORS should be used for prevention and correction of dehydration. Patient with some dehydration should be under observation for 4–6 hours to ensure dehydration is corrected and not progressive. Patients with severe dehydration are at a very high risk and should receive IV fluids and should be appropriately investigated and closely monitored. Antibiotics are indicated in dysentery, severely protein-energy malnutrition (PEM), immunocompromised, and in presence of systemic infection, cholera, or giardiasis. Oral ondansetron is the preferred antiemetic to control vomiting. Antimotility agents can be harmful in children and are to be avoided in acute diarrhea.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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168 CHAPTER

Pediatric Fluid and Electrolyte Therapy

Devendra Richhariya

INTRODUCTION

Fluid and electrolyte therapy are an important part of the care in hospitalized children in emergency department, and emergency physician should have a thorough knowledge of the changing requirements of growing children along with pharmacokinetic changes that occur from birth to adulthood. For practical purpose, fluid therapy can be divided into maintenance therapy, calculating fluid deficit, and fluid replacement as per deficit, patient response to fluid therapy and then monitoring makes fluid therapy manageable.

PHYSIOLOGIC DIFFERENCES

As the age, increases from birth until 1 year of age total body water content changes drastically. A baby's total body water content is close to 80% of total body weight at 24 weeks gestational age, slowly decreases (60% of total body water) around 1 year of age; in most adults, total body water is between 50% and 60% of total body weight. Infants loss about 5–15% of their body weight after birth, newborn babies have more extracellular water (45% of total body weight)—compared with intracellular water (35% of total body weight). Total body fluid has important role in drug therapy, especially for water soluble drugs.

FLUID THERAPY

Physiologic differences and changes that take place as a child grows have a great effect on fluid requirements. Special attention is required while deciding fluid therapy essential in pediatric age group. Fluid therapy can be divided into three part, (1) maintenance, (2) deficit estimation, and (3) replacement. Careful consideration should be paid to each component of fluid therapy while choosing the type of fluid and volume to be administered.

Maintenance Fluids

Ongoing fluid losses are compensated by maintenance fluids and are required for all patients. Maintenance fluids are frequently given through an intravenous access, but if the patient is able to tolerate oral therapy can also be given orally. Majority of ongoing losses are sensible losses (urine output and fecal water), adding with insensible losses such as respiration and perspiration. Fluid requirements are higher for children than adults for multiple reasons. First, greater caloric expenditure in children due to the higher metabolic rate, which needs higher fluid requirements. Secondly, children, especially infants, have higher body surface area to weight ratio so more water loss from skin compared with adults. In addition, higher respiratory rates in children and infants translate in more insensible losses from the respiratory tract.

Maintenance fluid requirements are determined by many mechanisms for children. When calculating maintenance fluids, emergency physician must aware about factors that may affect fluid balance. Maintenance fluid requirements are increased in hospitalized children due to their illness and associated problems such as fever, burn injuries, hypermetabolic states, pain, asthma, and increased intestinal losses. Holliday-Segar method is most commonly used technique to calculate maintenance fluids for children. The Holliday-Segar method is usually preferred due to its ease of calculation; however, the other methods are also exists employed in some instances but an expensive piece of equipment. The Holliday-Segar method may be simplified by estimating the fluid requirements in rate required per hour (**Table 1**).

Deficit Fluids

"Fluids deficit" means fluids lost prior to get medical care, e.g., clinical conditions in which patient present to emergency department with fluid deficit includes acute gastroenteritis with vomiting and diarrhea, significant blood loss in traumatic injuries, and inadequate fluids intake over a period of time. Most of the conditions associated with fluid deficit

TABLE 1: Holliday-Segar method for calculating maintenance fluid requirements in children.

	Holliday-Segar method	***Holliday-Segar estimate***
First 10 kg	100 mL/kg/day	4 mL/kg/h
Second 10 kg	50 mL/kg/day	2 mL/kg/h
Every kg thereafter	20 mL/kg/day	1 mL/kg/h

TABLE 2: Clinical signs of dehydration.

Clinical signs	*Mild dehydration*	*Moderate dehydration*	*Severe dehydration*
Weight loss in %	3–5	6–9	>10
Alertness	Normal	Listless	Normal lethargic coma
Thirst	Slight	Moderate	Intense
Mucus membrane	Normal	Dry	Dry
Anterior fontanel	Flat	Sunken	Sunken
Eyes	Normal	Sunken	Deeply sunken
Skin turgor	Normal	Decreased	Decreased
Blood pressure	Normal	Normal	Normal to decreased
Heart rate	Normal	Increased	Increased
Urine output	Decreased	Markedly decreased	Anuria
Degree of dehydration			
Older	3% (30 mL/kg)	6% (60 mL/kg)	9% (90 mL/kg)

can be approached by systematic manner. Clinical signs of dehydration provide useful insight into the fluid needs of the patient. Weight loss one of the important clinical sign of dehydration which can be used frequently by pediatrician, and compared with preillness weight. Other clinical signs include increased thirst, dry mucous membranes, and decreased urine output (**Table 2**). Clinical signs are important part of the physical examination for a dehydrated patient as they correlate fairly well with the degree of dehydration. After clinical signs have been observed, the degree (%) of dehydration should be determined. Degree of dehydration is calculated by dividing the difference between the preillness and illness weights by the preillness weight, then multiplying by 100. If a 10-kg patient, lost 1 kg is 10% dehydrated. Every 1 kg of weight lost is equivalent to 1 L of fluid loss. The degree of dehydration should be always be compared to the clinical signs, which may be better indicators of hydration status and useful when a preillness weight is unknown. Once the degree of dehydration is established, serum sodium concentrations, needs to be determined to ascertain the type of dehydration. Mostly patients have an isotonic dehydration, a serum sodium concentration of <135 mEq/L is considered hypotonic dehydration, while >145 mEq/L is considered hypertonic dehydration.

Oral rehydration therapy is required for patients with mild-to-moderate dehydration, even if diarrhea and vomiting continue. For mild dehydration volume of 50 mL/kg over 4 hours should be given in small quantity. Moderate dehydration patient should receive 100 mL/kg over 4 hours. The oral rehydration solutions (ORS) available commercially generally have appropriate amounts of carbohydrates and electrolytes, usually about 140 mmol/L of carbohydrate, 45 mmol/L (mEq/L) of sodium, and 20 mmol/L (mEq/L) of potassium. Liquids such as milk, juice, soda, tea, and sports beverages are not the substitute for ORS because they do not contain appropriate amounts of carbohydrates and electrolytes to fulfill the requirement of dehydrated patients. However, breastfeed may continue for infants if they have diarrhea.

Rehydration therapy is divided into three phases. *In phase I*, a bolus of fluid is recommended which restores blood volume and adequate perfusion of critical organs, such as the brain is maintained. Bolus fluids should be isotonic; either normal saline or ringers' lactated solution is recommended at a rate of 20 mL/kg, given over 60 minutes. If necessary, repeat boluses are given to maintain adequate perfusion. Isotonic fluids are preferred as they provide rapid volume expansion in the plasma and extracellular fluid. For estimation of amount of fluid required in phases II and III, the fluid volume given during phase I should be subtracted from the deficit fluid. *Phase II fluid therapy* should be given over 8 hours. Fluid requirement in phase II is equivalent to one-third of the daily maintenance plus one-half of the remaining deficit. During phase II, 5% dextrose with 0.45% sodium chloride should be used, with 20–30 mEq/L of potassium chloride added only if the patient has urine output. *Phase III fluid therapy* is given over 16 hours. The amount of fluid in phase III is equivalent to two-thirds of the daily maintenance plus the remaining deficit. During phase III, 5% dextrose with 0.2% sodium chloride should be used, again with 20–30 mEq/L of potassium chloride added only if the patient has urine output. So in short, in phases II and III of rehydration therapy maintenance fluid plus deficit fluid, given over 24 hours, with half of the deficit fluid given in the first 8 hours, and the second half of the deficit fluid given in the last 16 hours (**Table 3**).

Hypertonic dehydration (hyperosmolar state of their circulating blood) approach is quite different. The deficit fluid

TABLE 3: Method for calculating rehydration fluid in isotonic or hypotonic dehydration.

Rehydration phase	*Fluid volume*	*Example 10-kg child with 1-kg weight loss (deficit = 1,000 mL)*
Phase I (Emergency)	20 mL/kg may repeat if necessary	200 mL (remaining deficit = 800 mL)
Phase II (First 8 hours)	1/2 remaining deficit + 1/3 daily maintenance	400 mL + 333 mL = 733 mL = 92 mL/h
Phase III (Next 16 hours)	1/2 remaining deficit + 2/3 daily maintenance	400 mL + 666 mL = 1,066 mL = 67 mL/h
Monitoring parameters for parenteral fluid therapy: Oral intake, weight changes, urine volume and specific gravity physical signs and symptoms of dehydration, and serum electrolytes		

volume should be added to the maintenance fluid volume needed for 48 hours, and the total should be administered over 48 hours. Administering the deficit fluid faster causes osmotic fluid shifts, which can result in cerebral edema and convulsions. To avoid too quick rehydration, serum sodium should be checked frequently (every 2–4 hours) and serum sodium should not be corrected >10 mEq/L in 24 hours. The hypotonic fluid should be used, such as 5% dextrose with 0.2% sodium chloride.

Replacement Fluids

Replacement fluids are defined as fluids which are given to correct the ongoing losses during the medical treatment. Replacement fluids are required in various medical and surgical problems such as uncontrolled vomiting, continuing diarrhea, or cerebrospinal fluid shunts and in patients with chest tubes in place. In each of these situations, only maintenance fluids are not enough to recover the ongoing fluid loss. Replacement fluids differ from deficit fluids in that they are ongoing, as opposed to a loss of fluid that occurred prior to receiving medical treatment.

MAINTENANCE ELECTROLYTES

Renal functions represent the concentrations of electrolytes, vitally important for patient's clinical status. Frequent electrolyte monitoring is required in renal dysfunction. Components of intravenous fluids include electrolytes, sodium, potassium, and chloride. Requirements of chloride 5 mEq/kg/day, sodium 3 mEq/kg/day, and potassium 2 mEq/kg/day are usually fulfilled by administering the sodium and potassium as sodium chloride and potassium chloride salts. When choosing a maintenance fluid for a child, it is important to consider maintenance electrolyte requirements also. Commercially available fluids are adequately fulfilling requirements of electrolyte in children. For most children, a 5% dextrose solution with 0.2% sodium chloride provides the estimated needs of sodium when used as a maintenance fluid.

ELECTROLYTE ABNORMALITIES

Severe Hyponatremia

Serious central nervous system symptoms; lethargy followed by seizures is common in patients with serum sodium of <125 mEq/L. Hypertonic saline, usually 3% sodium chloride, is recommended due to emergent situation. The total volume of 3% sodium chloride required can be estimated by equation: (desired serum sodium concentration – current serum sodium concentration) × 0.6 × (weight in kg) Multiplying the sodium deficit by 2 gives the volume of 3% sodium chloride needed. Serum sodium should be checked periodically throughout the infusion order to avoid hypernatremia. Serum sodium should not be corrected faster than 12 mEq/L within 24 hours.

Hyperkalemia

Serum potassium of >6 mEq/L is considered as hyperkalemia this is where the electrocardiogram changes are usually seen. Before treating the hyperkalemia, check this is not a falsely elevated serum potassium. In infants, blood is acquired frequently from heel stick, which causes cell lysis due to the trauma of the needle and can cause rise in intracellular potassium. Hyperkalemia can be treated with a variety of medications which work through multiple mechanisms. In emergencies, those agents are helpful which cause a rapid influx of potassium intracellularly and provide an acute decrease in serum levels. These medications that can cause rapid decrease in serum potassium are insulin and beta adrenergic (albuterol). Sodium bicarbonate response is generally not immediate and mechanism in lowering the potassium is also not known. Sodium polystyrene sulfonate is an exchange resin, generally used for less emergent situations which exchanges sodium for potassium in the gut; diuretics such as furosemide is also used to increase potassium excretion into the urine, diuretics should be used cautiously in volume depleted situation. Calcium antagonizes the membrane effects of potassium so used in symptomatic patients for cardioprotective effects. Once emergent situation is managed, evaluation and long-term treatments are needed to control the cause of the hyperkalemia.

MONITORING FLUID AND ELECTROLYTE THERAPY

As per need of the children, initial fluid rate is determined. In hospitalized patient, need of fluid therapy frequently changes, so appropriate monitoring is necessary. The first parameter for monitoring is oral intake is preferred as soon as it is clinically indicated, as any intravenous administration brings with it the risk of infection. Patients with uncomplicated surgery who are not allowed anything by mouth for a short period of time, maintenance fluids are required, later fluids can be decreased and eventually stopped once they tolerate oral hydration. Patients who are on maintenance and deficit fluids therapy for dehydration, the most important monitoring parameters are clinical features of dehydration, such as skin turgor, urine output, and thirst. It is important to monitor patients' weights particularly in infants, as younger patients present with significant weight loss when dehydrated. Urine specific gravity can also be important for assessment of hydration status. Also, important to monitor, fluid which is given with parenteral antibiotics infusion, help in ensuring that the patient is not getting an excessive amount of fluids in medications can help prevent overhydration. The type of fluid used for medication should also be monitored using large volume of 5% dextrose for medication infusion could put the patient at risk for hyponatremia. If the patient has electrolyte abnormalities, monitoring serum electrolytes is necessary, but for hydration monitoring, the most important indices to watch are the clinical parameters mentioned earlier.

SUMMARY

Adopting a systematic, understandable approach for fluid therapy management and dividing fluid needs into maintenance, deficit, and replacement therapy can provide better monitoring in dehydrated child. By paying close attention to the fluid needs of pediatric patients and monitoring response to fluid therapy, the physician can have a positive influence on the health of the child. Stepwise approach should be adopted for determine the fluid requirement in child (**Table 4**). Particular attention should be given to the hydration status of patients, as the volume of drug is drastically affected by a change in volume status. Knowledge of fluid and electrolytes in children can help emergency physician to individualize medication therapy to the specific needs of the patient.

TABLE 4: Step-by-step determining maintenance fluids.

	Example determine the appropriate fluid and delivery rate for maintenance fluids and electrolytes for a 28-kg child	
Steps	***Calculation***	***Solution***
Step 1: Determine daily maintenance fluid requirement, using the Holliday-Segar method, determine the patient's fluid requirements (volume in liters) for 24 hours	• 100 mL/kg × 1st 10 kg = 1,000 mL • 50 mL/kg × 2nd 10 kg = 500 mL • 20 mL/kg × each additional kg (8) = 160 mL	1660 mL = 1.66 L
Step 2: • Deliver appropriate dose of electrolytes • Choose a commercially available fluid and determine how much sodium and potassium will be delivered considering the volume that will be administered	*Sodium requirements*: 3 mEq/kg × 28 kg = 84 mEq sodium: • D5 ¼NS × 1.66 L = 38.5 mEq sodium/L × 1.66 L = 63.9 mEq sodium • D5 ½NS × 1.66 L = 77 mEq sodium/L × 1.66 L = 128 mEq sodium • D5 NS × 1.66 L = 154 mEq sodium/L × 1.66 L = 255.6 mEq sodium *Potassium requirements*: 2 mEq/kg × 28 kg = 56 mEq potassium: • 10 mEq/L × 1.66 L = 16.6 mEq potassium • 20 mEq/L × 1.66 L = 33.2 mEq potassium • 30 mEq/L × 1.66 L = 49.8 mEq potassium • 40 mEq/L × 1.66 L = 66.4 mEq potassium	D5 ¼NS provides the most appropriate amount of sodium for this patient Generally, when beginning fluid therapy, more conservative potassium amounts, in this case 20 mEq/L, are used due to the risk of accumulation, particularly in hospitalized children
Step 3: Choose a fluid: Pick a commercially available fluid that delivers the desired amount of electrolytes		Answer D5 ¼NS with 20 mEq KCl per L at 69 mL/h
Step 4: Monitoring monitor patient fluid status and electrolytes and adjust the rate and fluid type accordingly		

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CHAPTER

Respiratory Problems in Infants and Children

Sandip Kumar

INTRODUCTION

In infants and children, respiratory problems are the most common illness requiring emergency room visit. Also, it remains one of the significant causes of mortality in children under 5 years of age (normal respiratory rate **Table 1**) although the mortality rates have fallen in past few decades due to increased vaccination. The principal cause of "pediatric medical" attendances at emergency departments is associated with "breathing difficulties", respiratory problems leading requiring emergency treatment and admission in hospital for management, presents to emergency department with respiratory failure which due to any airway, pulmonary parenchyma, or due to neuromuscular disorders which can lead to impairment in oxygenation and removal of carbon dioxide.

Largely the diagnosis of respiratory diseases is made clinically along with the history and physical examination, and chest radiography aids to the diagnosis when necessary. Although many of respiratory illnesses are milder and usually self-limiting, but others being life threatening require prompt diagnosis and management. Prompt recognition, assessment, and expert management of respiratory emergencies are critical to obtaining the best possible outcome. Therefore, it is very important that the emergency clinicians be able to promptly recognize and manage these illnesses. Signs, which demonstrate significant work of breathing and respiratory failure, are given in **Table 2**.

Emergency physician must be able to recognize the feature of severe respiratory distress like on examination severe chest wall retraction, paradoxical breathing pattern, head bobbing, cyanosis and pallor while on auscultation snoring, grunting stridor and wheezing. Altered sensorium, decreased or absence of breath sound on either side, evidence of shock (bradycardia, tachycardia, extended capillary filling time) are the features of worsening of the condition.

Among the multiple potential causes of respiratory emergencies in children, including infections/inflammatory causes and noninfectious causes (allergic processes, foreign body aspirations, trauma, chemical injuries, neoplasms, and neurological syndromes), we will focus on some of the most common encountered problems and their management in this chapter.

TABLE 1: Normal respiratory range in children.

<2 months	>60/min
2 months–1 year	>50/min
1–5 year	>40/min
5 years	>30/min

ETIOLOGY

Infants and young children presenting with common emergencies are as follows:

- *Infections-related problems involving upper airway*:
  - *Croup (laryngotracheobronchitis)* is seen in children of age from 3 months–3 years and common cause is viral infections like parainfluenza, influenza, respiratory syncytial virus (RSV), and adenovirus.
  - *Epiglottitis* is seen in children above 3 years of age up to 7 years during winter months and caused mainly by *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Group A streptococcus*, and *Staphylococcus aureus*.
  - *Bacterial tracheitis* is an invasive exudative bacterial infection of trachea affecting children of age group as early as 1 month till 15 years of age. It is caused by *S. aureus*, *Streptococcus pyogenes*, *S. Pneumoniae,* and *H. Influenza B* (Hib).
  - *Stridor* is a high-pitched, sound caused by disrupted airflow due to multiple reasons such as spasmodic

TABLE 2: Features of respiratory distress.

Respiratory distress (early signs)	*Respiratory failure (late signs)*
Tachypnea	Bradypnea
Increased respiratory efforts, chest wall retraction	Head bobbing, see-saw breathing
Tachycardia	Bradycardia
Irritability	Decreased level of consciousness
O_2 sat > 94%	<94% with high flow O_2

cough, retropharyngeal abscess, foreign body, tracheomalacia, vascular rings, pulmonary artery sling, inhalation injuries, and few other infective causes such as tracheitis, croup, and diphtheria.

- Infections-related problems involving lower airways:
  - *Bronchiolitis*: It is primarily seen in infants from 2 months up to 2 years of age and has viral etiology, such as RSV, influenza, parainfluenza, adenovirus, and others.
  - *Pneumonia* involves lower airway in almost all age groups, though younger patients and chronically ill and immunocompromised patients may be at higher risk. It can be caused by both bacteria and viruses.
- *Noninfectious causes of respiratory emergencies*: Retropharyngeal abscess, foreign body aspiration, tracheomalacia, vascular rings, and inhalation injury.

PATHOPHYSIOLOGY

In children, the subglottis is the narrowest part of the airway, and the cartilage rings are completely encircling which does not allow any further expansion. The loose connective tissue of the airway obstructs the lumen whenever gets inflamed of edema develops. And this reduction in lumen caliber leads to higher resistance to air flow which is apparent by Poiseuille's law.

Infants and younger children are more susceptible for airway compromise as compared to adults and adolescent, mainly due to anatomical differences. Younger children have much prominent occiput and relatively larger head size and lesser cervical support, which results in higher chances of acute airway compromise in supine position. Also, a relatively smaller oropharynx and larger tongue also contributes to more airway issues with this background of information, now we will discuss the disease-specific pathophysiology:

- *Croup* manifests as inflammation of the larynx, trachea, and large bronchi due to infiltration of white blood cells leading to the partial airway obstruction. As the inflammation progresses, it leads to increased work of breathing due to narrow lumen. When it causes significant obstruction, during respiration due to the negative-pressure inspiration pulls airway walls closer together, causing turbulence and noisy breathing called stridor (**Table 3**).
- *Epiglottitis* is the soft tissue swelling of epiglottis and its surrounding. Causative bacteria such as Hib or *S. pneumoniae* once penetrates, the mucosal barrier enters into the blood stream and subsequently seeds into epiglottis causing acute inflammatory edema. The inflammation usually begins from the lingual surface as the mucosa is loosely attached, and later progresses to aryepiglottic folds, arytenoids, and entire supraglottic larynx. The swelling is further halted at the vocal cords as the epithelium is tightly bound. The swelling significantly reduces the airway aperture and can lead to frank airway obstruction, aspiration of secretions, or mucus plugging leading to respiratory distress. Also, the noninfectious inflammation of any of the structures around the epiglottis may also result from thermal or chemical injury or from local trauma, including blunt trauma to the neck. Rarely, the inflammation may lead to necrotizing epiglottitis in case of infections such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV) in immunocompromised population.
- *Bacterial tracheitis* is caused by opportunistic bacteria, which invades and damages the mucosa and stimulates local and systemic inflammatory response. Tracheitis is most commonly seen in healthy children presiding a viral infection or in a patient with tracheostomy, due to seeding from colonized tracheostomy tube. The response to the infection-caused edema, thick mucopurulent secretion, ulceration, and mucosal sloughing which results in subglottic narrowing. On the other hand, the systemic inflammation may sometimes lead to sepsis in immunocompromised children. Pathophysiology of stridor depends on the anatomical location involved and the disease process. The supraglottic area does not contain any cartilage, hence it can collapse rapidly. In infants even a minimal narrowing of the airway results in dramatic increase in airway resistance, hence the subglottic area is of most concern. Any obstruction in the extrathoracic region causes inspiratory stridor, and the obstruction in intrathoracic region leads to expiratory stridor.
- *Bronchiolitis* occurs due to the bronchiolar injury and its interplay with the inflammatory and mesenchymal cells. The effect of these damages is caused due to inflammation usually seen in between 18 and 24 hours postinfection. Injury to the bronchioles leads to increased mucus secretions, obstruction of bronchus, air trapping, and atelectasis ventilation perfusion mismatch. Immunologic mechanisms also play a role in the pathogenesis of bronchiolitis. Cytokines released by infected respiratory epithelial cells, aggravates the immune response by increasing cellular recruitment into infected airways. Interferon and interleukin (IL)–4, IL-8, and IL-9 are found in high concentrations in respiratory secretions of infected patients. Allergic reactions mediated by IgE may account for clinically significant bronchiolitis. Infants who are breastfed with colostrum rich in immunoglobulin A (IgA) appear to be relatively protected from bronchiolitis.

TABLE 3: Westley croup score.

	0	*1*	*2*	*3*	*4*	*5*
Stridor	Nil	When agitated	At rest			
Intercostal recession	Nil	Mild	Moderate	Severe		
Decreased air entry	Normal	Mild	Severe		When agitated	At rest
Cyanosis	None					Altered
Consciousness level	Normal					
Possible score 0–17: 0–3 = mild croup, 4–6 = moderate croup, >6 = severe croup						

- *Pneumonia*: The organism which causes pneumonia and enters alveoli are likely to be highly virulent as they have already evaded host's physical defenses. Due to the infection, the macrophages activity is overwhelmed which in-turn results in production of high fibrin rich exudates which fills the infected and neighboring alveolar spaces. As a result of the ongoing inflammatory process, the alveolis becomes nonaerated and neutrophil proliferation is triggered. Once the inflammatory process is un-checked, it leads to the damage of lung tissue, fibrosis, and pulmonary edema which impairs total lung expansion.

CLINICAL PRESENTATION

The clinical sign and symptoms largely vary in pediatric patients due to the peculiarities discussed above. The presentation depends upon the age of the child, the specific pathogen and also the severity, and the duration of disease onset. Usual presentation of a young infant (3–5 months) of age is predominantly respiratory symptoms such as tachypnea, cough, chest wall retractions, noisy breathing, and grunting. Often pediatric patients may present without any localizing symptoms as well, and may show features as isolated fever, irritability, lethargy, and refusal of feeds also. Clinical features of concern *(red flag sign)* to be considered in case of any respiratory emergencies—respiratory distress, decreased level of consciousness, stridor or grunting, sudden onset dyspnea, cyanosis, sweating, seizures/abnormal tone, or posturing. Disease-specific clinical presentation is summarized in **Table 4**.

TABLE 4: Disease-specific clinical presentation.

Disease	*Clinical presentation*
Croup	Acute stridor, barking cough after mild URI, and low grade fever
Retropharyngeal abscess	Fever, toxicity, distress after URI or pharyngitis, drooling, and neck pain/swelling
Bacterial tracheitis	Acute onset high grade fever, toxic appearance, harsh cough, no drooling, chest pain, and distress+
Foreign body aspiration	Choking episode resulting in immediate or delayed respiratory distress, unilateral wheeze
Peritonsillar abscess	Acute onset high grade fever, toxicity, distress with unilateral throat pain, "hot potato speech"
Epiglottitis	Drooling, high grade fever, toxic, muffled voice, cough minimal, and sitting forward, open mouth
Anaphylaxis/angioneurotic edema	Swelling of lips, erythematous rash with itching
Bronchiolitis/pneumonia	Fever, cough, coryza, post-tussive vomiting, irritability, and refusal of feeds

EVALUATION

All children arriving to emergency room should be presumed to be sick and requires immediate help or rescue from the problem. To ensure the safety of the child and initiation of the management pertinent to the condition, it is very important to collect relevant history quickly from the caregiver and examine the child to pick up danger signs.

History

Collecting a quick and relevant history is the most important step in understanding the general wellbeing and the probable cause which had led to this emergency situation. The main points which should always be included in history taking are as follows:

- General growth and development of the child and vaccination history
- Duration of illness
- Sudden or gradual onset
- Any other associated complaints (fever, loose stools, and vomiting)
- History suggestive of aspiration, nasal regurgitation
- Noisy breathing
- Birth history, neonatal intensive care unit (NICU) stay with ventilator/oxygen requirement
- Increased sweating, suck-rest-suck cycle
- Accidental ingestion of any foreign body or drugs
- Any bad child rearing practices (oil, camphor nasal instillation).

Physical Examination

In pediatric, the evaluation starts with primary assessment, with "pediatric assessment triangle-pentagon" which consists of:

- Appearance; interaction, muscle tone, consolability, cry, and speech
- Airway/Breathing; work of breathing, use of assessor muscles
- Circulation; abnormal skin color, pallor, or cyanosis.

Assessment pentagon:

- *Airway*—assessment of the airway should be aimed to decide whether the airway is clear, i.e., whether it is open and unobstructed.
  - Maintainable airway: Example, is the airway is maintained by simple measures like position, suction, etc.
  - Nonmaintainable airway: Example, any need of advance airway measures like intubation. Any audible sounds, such as stridor, grunting, and wheezing usually point toward airway narrowing or laryngomalacia/tracheomalacia, pooling of secretions, or a foreign body in the airway.
- *Breathing*—infants and young children most commonly present with fast breathing which is usually noted by mother or caregiver. Child may present with bradypnea, chest wall indrawing, or abnormal chest wall movement during quiet respiration, these are the signs which are noted by physician on careful examination. Paradoxical breathing (sea saw respiration) pattern usually indicates that the child is in respiratory failure and requires

immediate intervention. Pulse oximetry can help in picking up hypoxemia early.
- *Circulation*—checking both peripheral and central pulses, capillary refill time and blood pressure helps to identify shock, or compromised perfusion.
- *Disability*—as a result of reduced oxygen supply to brain, the level of consciousness, pupillary reaction, and muscle tone may be affected. Child may be irritable, agitated, or through seizures due to prolonged hypoxia.
- *Exposure*—if indicated, it is done to look for evidence of trauma, petechiae and purpura, etc. After completing, the physical examination findings are interpreted (**Table 5**).

INVESTIGATIONS

For all children presenting to emergency, once the clinical assessment is done and the management is initiated, it is very important to plan investigations to narrow down the diagnosis and to provide specific treatment:
- Basic blood investigations—complete blood count, serum electrolytes, blood gas analysis, urea, creatinine, and liver function test
- Sepsis workup—C-reactive protein (CRP), procalcitonin, and blood culture
- Radiological—chest X-ray PA view/lateral view, lung ultrasonography
- Direct laryngoscopy and flexible fiberoptic bronchoscopy in suspected upper airway obstruction or foreign body aspiration.

TREATMENT

General Considerations

- First step in the management of a sick child is to stabilize *A*irway, *B*reathing, and *C*irculation; once *A-B-C* have been taken care of, proceed toward the disease-specific treatment.
- Leave the child with parent in a comfortable position (even sitting is fine if unable to lie down).
- Do not insert tongue depressor or attempt IV access or blood tests.
- Give oxygen in non/least threatening way. Do not force an oxygen mask over face.
- Supplement oxygen even if the oxygen saturation is normal to decrease work of breathing.
- Do not sedate the child until airway is secured.
- Pulse oximetry is a poor indicator of severity of obstruction especially when supplementary oxygen is being given.
- Always anticipate difficult airway while intubation and so high level of anticipation with multidisciplinary team including anesthetists, ENT, and pulmonologists may be required for good outcomes.
- Disease-specific treatment is summarized in **Table 6**.

TABLE 5: Interpretation of common findings.

Sign	*Extrathoracic airway obstruction*	*Intrathoracic airway obstruction*	*Intrapulmonary airway obstruction*	*Parenchymal pathology*
Tachypnea	+	+	++	++++
Retractions	++++	++	++	+++
Stridor	++++	++	–	–
Wheezing	+/–	+++	++++	+/–
Grunting	+/–	+/–	++	++++

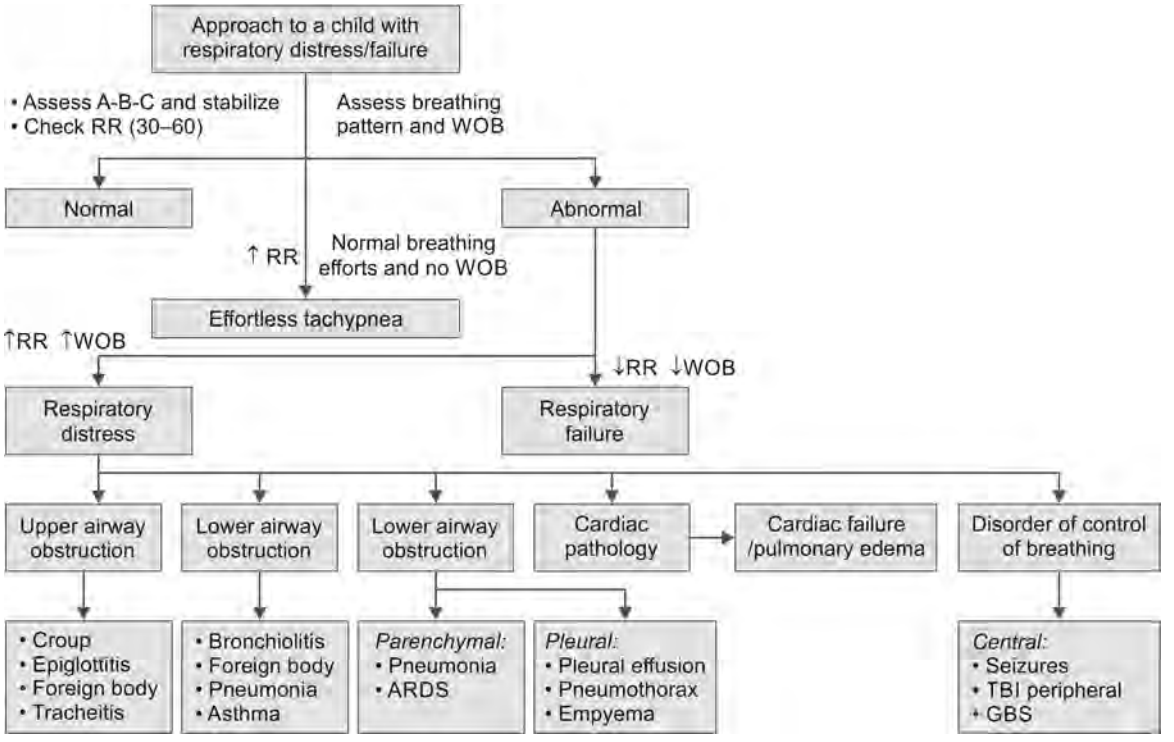
TABLE 6: Disease-specific treatment.

Disease	*Management*
Croup	Managed as per severity. IV dexamethasone, nebulized adrenaline
Acute epiglottitis	• Give oxygen at any comfortable position in nonthreatening manner, do not upset child, nebulized adrenaline (1:1,000) 5 mL till help arrives • If epiglottis visualized by direct laryngoscopy and if obstruction severe and airway not secure call for help (ENT/anesthesia) immediately and intubate in OT with inhalational anesthesia. Start antibiotics (ceftriaxone). Rifampicin for contacts
Foreign body aspiration	High degree of suspicion as clinical findings varies widely. Heimlich maneuver or back slap and chest thrust in infants if complete obstruction. Rigid bronchoscopy is procedure of choice
Anaphylaxis/ angioneurotic edema	May need fluid bolus, intubation if stridor present, immediate I/M injection adrenaline (1:1,000) 0.01 mL/kg (max 0.3 mL), hydrocortisone 10 mg/kg, antihistamines
Bacterial tracheitis	Endotracheal intubation if audible stridor (low threshold), IV antibiotics—cloxacillin, clindamycin, and amikacin*
Retropharyngeal abscess	Lateral neck and chest X-ray, CT neck, orotracheal intubation is preferred if needed because chance of abscess rupture. IV antibiotics (cloxacillin, clindamycin, and amikacin)*, surgical drainage by ENT surgeon
Subglottic stenosis	Early tracheostomy and subglottic dilatation
Airway burns	Intubate early if facial burns with smoke inhalation present before complete obstruction by soot, plan tracheostomy if stridor, simultaneously manage surface burns with other supportive measures

* Cloxacillin (50 mg/kg/dose q 6 hourly), amikacin (15 mg/kg/day in once a day dose), and clindamycin (10 mg/kg/dose TID).

SUMMARY

In pediatric population, most common presentation is seen as obstructive respiratory emergencies. Many of these entities can progress rapidly, leading to a life-threatening situation. Thus systematic approach is adopted (**Flowchart 1**). The clinician must have a high index of suspicion and makes a rapid and precise diagnosis, oftentimes based solely on the patient's brief history and a limited examination. In the setting of obstructive airway or respiratory failure emergencies, appropriate treatment needs to be implemented without delay. This generally involves assuring the presence of a patent airway while time, supportive therapies, and appropriate antibiotics contribute to the resolution of the baseline process.



(ARDS: acute respiratory distress syndrome; GBS: Guillain–Barré syndrome; RR: respiratory rate; TBI: traumatic brain injury; WOB: work of breathing)

FLOWCHART 1: Approach to a child with respiratory distress or respiratory failure.

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CHAPTER

Pediatric Cardiac Emergencies

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INTRODUCTION

Cardiac emergencies in children can be either due to congenital or acquired causes. The prevalence of congenital cardiac diseases has been reported to be 8–10/1,000 and is responsible for most of the morbidity and mortality in pediatrics. It has the highest risk of presenting with life-threatening emergencies. While most of pediatric cardiac emergencies eventually require treatment at multidisciplinary centers with pediatric cardiologist, pediatric cardiovascular surgeon, and pediatric cardiac anesthetist, the suspicion of the cardiac disease and its initial stabilization and management lies on the neonatologist, primary pediatrician, and the emergency physician. Pediatric cardiac emergencies can be broadly classified into two groups depending on the age of presentation—(1) neonatal cardiac emergencies and (2) presentation in postneonatal period. Both can be further subclassified into congenital and acquired causes. Common causes are given in **Table 1**.

Most neonates with heart disease presenting in emergency have duct-dependent circulation either:

- To ensure adequate mixing as in conditions with parallel nonmixing circulations such as complete transposition [dextro-transposition of the great arteries (d-TGA)]
- To maintain adequate pulmonary blood flow in lesions causing right ventricular outflow tract obstruction (RVOTO) or
- To maintain adequate systemic perfusion as in left-sided obstructive [left ventricular outflow tract obstruction (LVOTO)] or hypoplastic lesions
- *These neonates require intervention (surgical or catheter) within the first weeks of life in order to sustain life or prevent major morbidity.*

NEONATAL CARDIAC EMERGENCIES: AN OVERVIEW

Heart disease in newborn can have varied presentations. The diagnosis is usually not straightforward because of the nonspecific clinical picture of various congenital heart defects and difficult interpretation of electrocardiogram (ECG) and chest X-ray (CXR). Neonates with pulmonary symptoms unresponsive to standard therapies indicate strong suspicion for congenital heart disease.

They are mainly classified into those who need an immediate intervention (catheter/surgical) and those who have a nonurgent disease and require medical management or close follow-up. In neonates, many patients show acute worsening on day 3–4 of life after discharge due to restriction or closure of ductus arteriosus which compromises the cardiac defects with duct-dependent circulation. Prostaglandin E1 (PGE1) infusions or emergency interventional cardiac catheterization is used as life-saving initial measures.

PRESENTATION

Almost half of congenital heart diseases present in the neonatal period with an incidence reported to be around 3–3.5/1,000 live births. The various presentations in the neonatal period include cyanosis, shock, congestive cardiac failure, and rarely with arrhythmias. As the diagnosis and pick up rate of congenital heart disease in antenatal period by level II antenatal fetal scan followed by detailed fetal echocardiography continues to be low because of lack of expertise and resources, majority of the neonates with critical congenital heart defect (CHD) are detected for the first time after birth. Neonates with CHDs usually present to the emergency with: cyanosis shock acute congestive heart failure (CHF) tachyarrhythmias/bradyarrhythmia.

CASE SCENARIOS—CYANOSIS

Case Scenario

A 15-day-old neonate, born at full-term gestation via normal vaginal delivery was noted to have respiratory distress and bluishness by parents. The baby was referred to tertiary center for further management where at presentation, the baby was found to be lethargic, in distress and had central cyanosis. On auscultation, no significant murmur could be appreciated. His arterial blood gas showed severe hypoxemia with metabolic acidosis. CXR had mild cardiomegaly with increased pulmonary vascular markings (**Fig. 1**). Respiratory and cardiac pathologies are the main differential diagnoses with such presentations, and it is very important to distinguish between respiratory and cardiac causes of cyanosis so that the management can be done accordingly (**Table 2**).

TABLE 1: Causes of pediatric cardiac emergency.

	Congenital	*Acquired*
Neonatal	• Duct dependent pulmonary blood flow • Critical pulmonary stenosis/pulmonary atresia with ventricular septal defect (VSD) or with intact ventricular septum • Duct dependent systemic blood flow • Critical aortic stenosis • Critical coarctation of aorta • Hypoplastic left heart syndrome • Admixture lesion with restrictive interatrial communication • Transposition of great vessels • Total anomalous pulmonary venous connection (TAPVC) • Obstructed TAPVC • Anomalous origin of left coronary artery from pulmonary artery (ALCAPA) • Ventricular dysfunction due to inborn error of metabolism E.g., glycogen storage defects, fatty acid oxidation defects, and mitochondriopathies	Ventricular dysfunction due to: • Sepsis • Metabolic and electrolyte imbalance (metabolic acidosis and hypocalcemia) • Hypothermia
Older children	• Severe obstructive lesions (left side/right side) with ventricular dysfunction, e.g., severe aortic stenosis, severe pulmonary stenosis, and severe coarctation • Shunt lesions decompensated by infection or arrhythmia • Anomalous origin of left coronary artery from pulmonary artery	• Rheumatic heart disease with severe valvular stenosis/regurgitant lesions (mitral, aortic, and/or tricuspid) • Bacterial endocarditis • Kawasaki disease
All age groups	• Arrhythmias	• Arrhythmias • Dilated cardiomyopathy • Pericardial tamponade

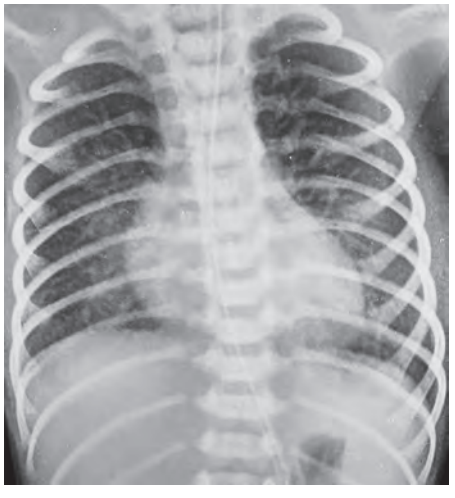


FIG. 1: Chest X-ray (frontal view) of 15 days old neonate with cyanosis showing cardiomegaly, increased pulmonary blood flow with narrow mediastinum (Egg-on-side appearance).

TABLE 2: Differentiation between cardiac and respiratory causes of cyanosis.

	Respiratory	*Cardiac*
History	H/o meconium aspiration, prematurity, risk factors for sepsis	Diabetic mother, H/o previous child affected with CHD
Examination	Respiratory distress—grunting cyanosis and tachypnea	Cyanosis disproportionate to respiratory distress
Onset	Usually at birth or within hours of birth	Hours/days after birth
Auscultation	Altered air entry, lung crepts/wheeze	Clear lungs, normal air entry, murmur may or may not be present
Blood gas	High pCO_2, Low pO_2	Normal/low PCO_2, Low PO_2
Hyperoxia test	Passed	Failed
Chest X-ray	Lung infiltrates, normal heart size	Clear lung fields, heart ± enlarged, oligemic/plethoric lung fields
ECG	Normal	May be abnormal

Hyperoxia test differentiates cardiac from pulmonary causes of cyanosis. Arterial oxygen tension is measured in the right radial artery (preductal) while the patient on 100% oxygen for 10 minutes. Oxygen is administered via hood or endotracheal tube if the patient is already intubated. The preductal oxygen tension while breathing 100% oxygen concentration rarely exceeds 150 mm Hg in cyanotic heart disease and usually exceeds this value in pulmonary disease. In case of failed hyperoxia test, an echocardiogram is needed to establish the underlying diagnosis.

A pulse oximeter should not be used for the hyperoxia test because it may not detect an inadequate increase in oxygen tension. Because of the characteristics of the oxygen dissociation curve, normal hemoglobin is fully saturated with

oxygen when the arterial PO_2 exceeds 70 mm Hg. Therefore, a patient receiving 100% inspired oxygen concentration may have an oxygen saturation of nearly 100% associated with an arterial PO_2 of 75 mm Hg, a value that is abnormal. Thus, discrimination between cardiac lesion and pulmonary disease may be limited. *It is useful to remember the most common CHDs that present with neonatal cyanosis include*—Complete TGA, tetralogy of Fallot (TOF) (with critical pulmonary stenosis or pulmonary atresia), obstructive total anomalous pulmonary venous connection, single ventricle with critical pulmonary stenosis/pulmonary atresia, tricuspid atresia with critical pulmonary stenosis/pulmonary atresia, and critical pulmonary stenosis/pulmonary atresia with intact interventricular septum (**Flowchart 1**).

Management

The definitive diagnosis is readily established by detailed echocardiography. PGE1 (alprostadil) intravenous (IV) infusion is done to keep the patent ductus arteriosus (PDA) open (dose 10–60 ng/kg/min, if poor response saturations and acidosis are not improving), the dose can be increased to max 300–400 ng/kg/min. Apnea is a common side effect of PGE1 so infusion should be started in ICU settings with ventilator support available. Flushing, diarrhea, and hypotension are other common side effects. IV fluid for blood volume expansion 10 mL/kg 0.9% saline bolus improves preload repeat until liver edge is palpable, and enhances further opening of the PDA and pulmonary blood flow through the duct. Correction of metabolic abnormalities, e.g., hypoglycemia, hypocalcemia, acidosis, and sepsis. Oxygen to maintain the saturations 75–85% (do not give 100% oxygen by mask in patients with duct-dependent lesions as high level of oxygen triggers closure of ductus arteriosus). Inotropes/vasopressors are required to maintain adequate systemic perfusion. If above measures are not helpful, intubation and ventilation with adequate sedation are required to improve oxygenation and minimize the metabolic demands.

Definitive management includes—for transposition of great vessels—arterial switch operation, total anomalous pulmonary venous connection—surgical rerouting of pulmonary veins, severe valvular pulmonary stenosis—balloon valvotomy, and ductal stenting/Blalock—Taussig (BT) shunt for duct-dependent pulmonary circulation.

CASE SCENARIO—CARDIOVASCULAR COLLAPSE

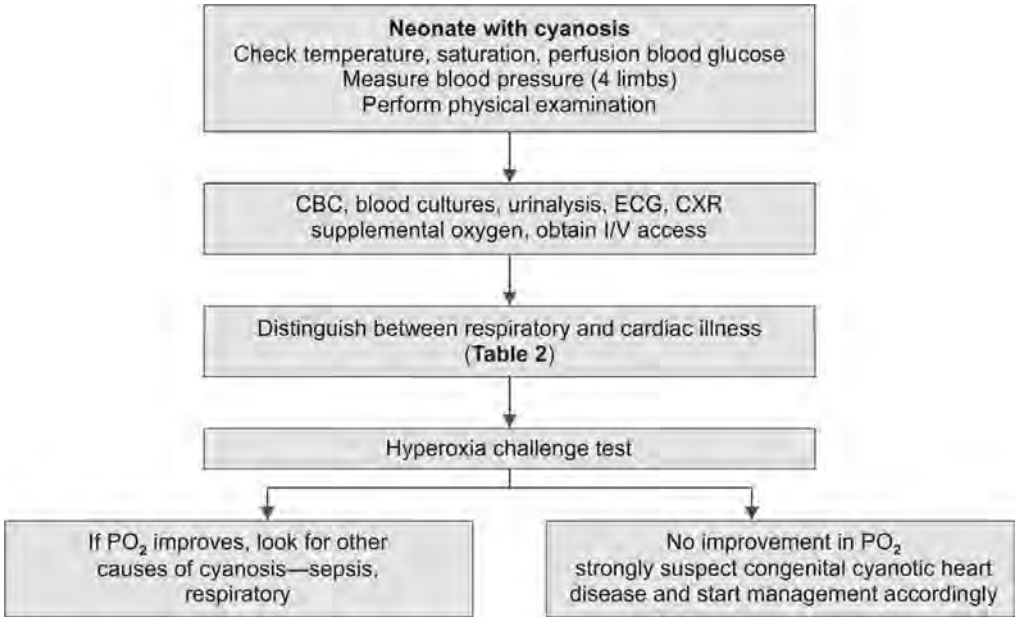
Case Scenario

A 6-day-old term neonate presented in medical emergency with complaints of lethargy, increased respiratory rates and refusal to feed. The baby was mottled in color with poor peripheral perfusion. While the central pulses were palpable, the lower limb pulses were feeble.

Chest X-ray revealed cardiomegaly with prominent pulmonary vascular markings (**Fig. 2**). On echocardiography, the baby was diagnosed to have interrupted aortic arch and restrictive PDA which was supplying descending aorta. Baby also had severe LV dysfunction with ejection fraction (EF) 15–20% (**Fig. 3**). Further restriction and impending closure of the ductus on day 5–6 of life had led to acute loss of lower body perfusion causing shock and severe metabolic acidosis. Patients with this presentation are grouped under lesions with duct-dependent systemic circulation. These babies can present directly with cardiovascular collapse after ductal closure and are therefore often critically ill at presentation.

It is very important to have a high index of suspicion for congenital heart disease in neonates presenting with shock as most commonly it is mistakenly diagnosed and managed as neonatal sepsis. While babies with sepsis are medically managed those with duct-dependent systemic circulation need aggressive resuscitation and prompt intervention usually.

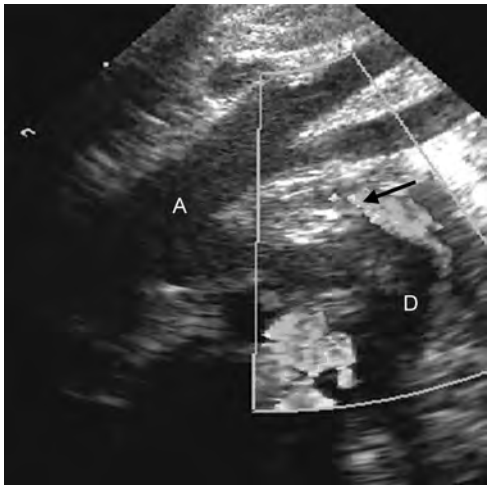
Lesions presenting with duct-dependent systemic circulation include the critical left-sided outflow tract


Neonate with cyanosis
Check temperature, saturation, perfusion blood glucose
Measure blood pressure (4 limbs)
Perform physical examination
CBC, blood cultures, urinalysis, ECG, CXR
supplemental oxygen, obtain I/V access
Distinguish between respiratory and cardiac illness
(Table 2)
Hyperoxia challenge test
If PO2 improves, look for other causes of cyanosis—sepsis, respiratory
No improvement in PO2
strongly suspect congenital cyanotic heart disease and start management accordingly

(CBC: complete blood count; CXR: chest X-ray; ECG: electrocardiogram)

FLOWCHART 1: Approach to cyanosis.

FIG. 2: Chest X-ray (frontal view) of a neonate presenting in emergency with shock. X-ray reveals cardiomegaly, prominent vascular markings with retrocardiac lung collapse.



(AAO: ascending aorta, DAO: descending aorta)

FIG. 3: Echocardiography with color flow mapping of a neonate with aortic arch interruption, restrictive PDA and LV dysfunction. Suprasternal long axis view showing arch interruption, small PDA (black arrow) filling descending aorta. ***(For color version, see plate 28)***

obstructions—critical aortic stenosis (AS), hypoplastic left heart syndrome (HLHS), severe coarctation of aorta, and interrupted aortic arch.

Management includes prostaglandin therapy, blood volume expansion, stabilization with inotropes and oxygen, and mechanical ventilation in unresponsive cases. Confirmation of diagnosis by echocardiography is followed by relief of obstruction by surgical correction.

CASE SCENARIO—ACUTE CONGESTIVE HEART FAILURE

Case scenario

A 3-week-old neonate presented with tachypnea, tachycardia, and refusal to feed for 3 days. There was hepatomegaly and cardiomegaly on examination. Auscultation revealed gallop rhythm, no significant murmur. CXR *frontal view showed cardiomegaly, no parenchymal lesion. 12-lead ECG showed sinus tachycardia, deep "q" wave in I, aVL, V_5, and V_6 with ST-T wave changes* (**Fig. 4**). *Echocardiography revealed severe LV dysfunction with EF—15–20%. On echocardiography, left coronary was seen arising anomalously from pulmonary artery and baby was diagnosed to have anomalous origin of left coronary artery from pulmonary artery (ALCAPA).* The baby underwent successful surgical correction of ALCAPA with slow but complete recovery of ventricular function in postoperative period.

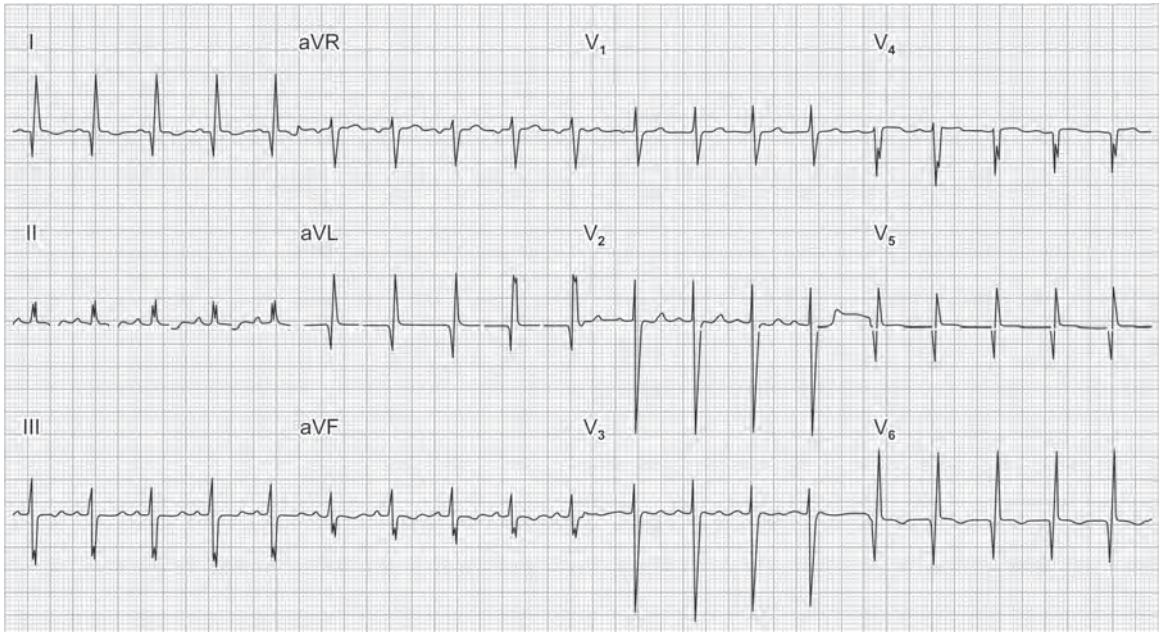
In ALCAPA, the babies usually present with features of CHF due to myocardial ischemia leading to LV dilatation and dysfunction. The presentation can be delayed up to 3–4 weeks of age till the pulmonary vascular pressures fall substantially. Babies with CHF (**Table 3**) usually present with feeding difficulties and excessive sweating. They are tachypneic and tachycardiac at rest and can have wheeze due to LV failure. Gallop rhythm, hepatomegaly, and cardiomegaly are other important signs. Cold extremity and low blood pressure are signs of low pulse volume and indicate CHF. However, bounding pulses may be present in CHF due to lesions causing aortic runoff like PDA and arteriovenous malformations. CXR is especially useful in evaluation of neonates. Cardiac enlargement is always present if CHF exists, in addition, pulmonary pathologies can also be detected. It is important to differentiate neonatal CHF from respiratory distress due to lung disease and neonatal sepsis clinically. This differentiation is difficult due to overlapping signs such as Rales and Rhonchi. The most important signs for diagnosing heart failure are cardiomegaly and hepatomegaly.

Management

- Oxygen therapy is very useful in babies with CHF with pulmonary edema as the cause of hypoxia. Oxygen raises the alveolar PO_2 and helps alleviate hypoxia.
- General neonatal care which includes maintenance of temperature and glucose levels.
- Nasogastric feeding is preferred over oral feed to avoid aspiration in the distressed infant and also to increase the amount of caloric intake.
- Diuretics, usually furosemide 1–4 mg/kg 8–12-hourly IV (bolus or continuous infusion) or orally with spironolactone 1 mg/kg 12-hourly to decrease pulmonary congestion.
- Correction of coexistent metabolic derangements such as anemia, hypoglycemia, electrolyte imbalance, and acidosis.
- Inotropes/vasodilators such as low-dose dobutamine, dopamine, and milrinone to decrease systemic vascular resistance and improve cardiac contractility.
- Mechanical ventilation is usually required in heart failure with impending cardiogenic shock.

PEDIATRIC CARDIAC EMERGENCIES

The various presentations of pediatric cardiac emergencies include CHF cyanotic spell, pericardial tamponade, arrhythmia/palpitations, and sudden death. Among the various presentations, CHF and spell attribute to 70–80% of pediatric cardiac emergencies. In neonates while structural diseases of the heart are the most common causes of CHF, in older children acquired causes are also attributed. Fluid restriction and inotropic support followed by definitive correction of the



(ALCAPA: anomalous origin of left coronary artery from pulmonary artery; ECG: electrocardiogram)

FIG. 4: 12-lead ECG of an infant with ALCAPA. Deep Q waves in leads I, aVL, V_5, and V_6 and T-wave inversion seen in lead I.

TABLE 3: Structural causes of CHF in neonatal period.

Large left to right shunt	• Large/multiple VSD • Complete AV canal defect with AV regurgitation • Large PDA • AV malformation
Heart failure with mild cyanosis	• Total anomalous pulmonary venous connection • Truncus arteriosus • Single ventricle physiology without pulmonary stenosis
Ventricular dysfunction: Coronary anomaly	ALCAPA

(ALCAPA: anomalous origin of left coronary artery from pulmonary artery; AV: arteriovenous; PDA: patent ductus arteriosus; VSD: ventricular septal defect)

established cause mainstay of treatment. Cyanotic congenital heart disease such as TOF and pulmonary atresia presents with cyanotic spells. They usually occur in the morning and can be provoked by stress crying, or periods of dehydration. Their presentation can vary from minor spells to seizure to severe life-threatening episodes. Isolated arrhythmias though relatively less common can present with palpitations or hemodynamic instability in infants and children. Supraventricular tachycardia (SVT) is the most common presentation in the pediatric population. Early recognition and appropriate therapy in pediatric cardiac emergencies are essential for better outcomes.

Congestive Heart Failure

Case Scenario

An 8-year-old boy presented to the medical emergency department with complaints of respiratory distress. Patient had history of breathlessness on exertion and orthopnea since months. Patient had past history of swelling in left knee followed by swelling of left ankle 2 months ago. He had tachycardia, cardiomegaly, and a loud apical pansystolic murmur with radiation to axilla. He also had hepatomegaly with liver 5 cm below costal margin. CXR showed cardiomegaly with straightening of left heart border (left atrial enlargement), LV type of apex and signs of pulmonary venous hypertension (**Fig. 5**). *Echocardiography revealed rheumatic involvement of mitral valve with thickened leaflets and ruptured chordae leading to severe mitral regurgitation (MR).* Congenital cardiac defect associated with CHF in pediatric age-group is large/multiple VSD, complete AV canal defect with AV regurgitation, large PDA, and AV malformation. Acquired causes of pediatric CHF are rheumatic heart disease, cardiomyopathy arrhythmia,

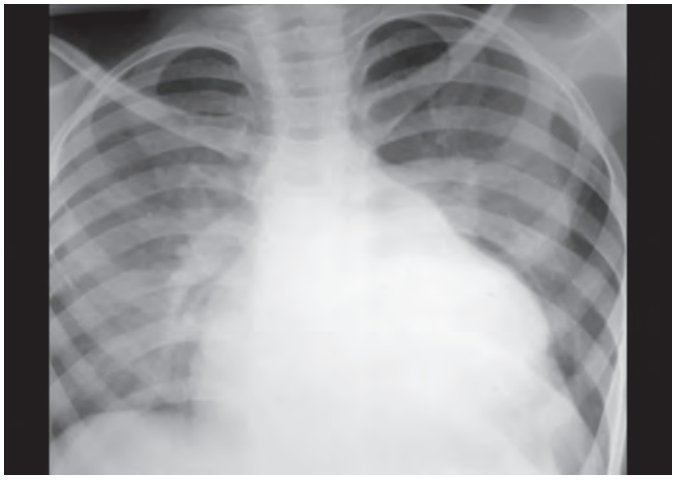


FIG. 5: Chest X-ray frontal view of an 8 years old child with rheumatic heart disease, severe mitral regurgitation. There is cardiomegaly with pulmonary venous hypertension. Features of LA dilatation, i.e., straightening of left heart border and widening of carinal angle are seen.

and pericardial tamponade. Heart failure secondary to congenital heart disease is a gradual process while heart failure due to acquired causes is more commonly an acute process.

Clinical Features

Common manifestations of CHF in the infant in the approximate order of frequency include tachypnea, tachycardia, liver enlargement, cardiomegaly, pulmonary Rales and Rhonchi, and feeding difficulties. Less common signs and symptoms include peripheral edema, measurable elevated systemic venous pressure, inappropriate diaphoresis at normal room temperature, gallop rhythm, pulsus alternans, and ascites. A child with large left to right shunt usually presents with CHF at 6–8 weeks of age when the pulmonary vascular resistance naturally drops, while a child with myocarditis may present at any age.

Management

Treatment of the precipitating factors such as infective endocarditis, intercurrent infections, anemia, electrolyte imbalances, arrhythmia, pulmonary embolism, and drug toxicity should be done. Treatment of the congested state includes:

- Nonpharmacological measures, e.g., modest fluid restriction, propped up posture, supplemental humidified oxygen if desaturated, and optimization of nutrition.
- Diuretics, usually furosemide 1–4 mg/kg 6–12-hourly IV or orally provide quick relief in systemic and pulmonary venous congestion. If child is having grossly edematous or in pulmonary edema, IV infusion of furosemide (0.1–0.4 mg/kg/h) should be given. After stabilization, patient can be shifted to bolus doses of furosemide.
- Secondary hyperaldosteronism occurs in infants with CHF and addition of spironolactone 1 mg/kg single dose to other diuretics helps with diuresis as well as conserves potassium.
- Vasodilators, e.g., angiotensin-converting enzyme (ACE) inhibitors, are useful in the presence of large shunts, or in those with an elevated systemic vascular resistance. These drugs are contraindicated in patients with obstructive lesions such as aortic or mitral stenosis. Enalapril is most commonly used ACE inhibitor in pediatric age-group. It is important to ensure normal renal function and K^+ during therapy.
- Augmenting myocardial contractility by inotropic drugs such as dopamine, dobutamine, milrinone, levosimendan and digitalis improves cardiac output and is useful in low cardiac output states. Digitalis is especially useful as it decreases heart rate and increases myocardial contractility, however, its use has to be closely monitored in view of its narrow therapeutic index (**Fig. 6**).
- Coexistent metabolic derangements such as anemia, hypoglycemia, electrolyte imbalance, and acidosis should be evaluated and corrected. Hypocalcemia and vitamin D deficiency must always be ruled out as a cause in cases of dilated cardiomyopathy.
- *Treat underlying pathology*: Corrective surgery for structural defect—the curative therapy is directed toward the cause of CHF, wherever possible, e.g., surgical correction of congenital or acquired heart defects. Precipitating factors—Hypocalcemia secondary to vitamin D deficiency, hypoparathyroidism, anemia, hyper-/hypothyroidism, and Beriberi

Cyanotic Spell

It usually occurs in children with unrepaired TOF or other cardiac defects with large interventricular communication and pulmonary outflow tract obstruction. Cyanotic spell is a clinical

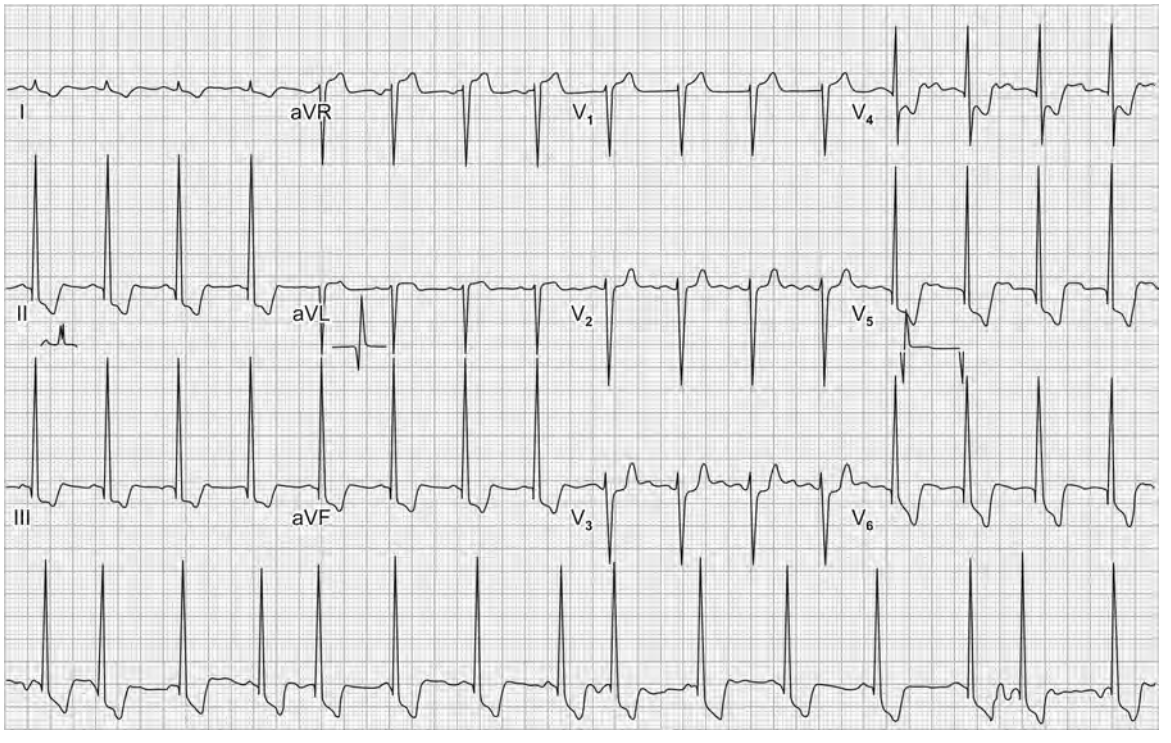


FIG. 6: 12-lead ECG of an infant taking high dose of digoxin by mistake. ECG shows digitalis effect, i.e., prolongation of PR interval with sagging of ST segment.

state of acutely reduced pulmonary blood flow which leads to severe hypoxemia and metabolic acidosis. They are usually self-limited and may last from few minutes to few hours. They may occur at any time of day, but are most common in the morning with defecation, crying, and feeding as usual triggers. The spells may also occur after episodes of stress such as excess activity and dehydration. They can even occur without a precipitating cause. During the spell, the infant becomes hyperpneic and restless, and as cyanosis increases, syncope, convulsions, or cerebrovascular accidents can develop rarely. Hypoxic spells are most common between 1 and 12 months of life and are a particular problem during the 2nd–6th month of life. Structural anomalies presenting with cyanotic spells are the most common are TOF, double outlet right ventricle with pulmonary stenosis, tricuspid atresia with pulmonary stenosis, transposition of great vessels, and single vessel physiology.

One of the mechanisms of cyanotic spell is believed to be acute infundibular spasm of right ventricular outflow tract precipitated by endogenous catecholamines which results in markedly decreased pulmonary blood flow along with right to left shunting across the ventricular septal defect. An alternative explanation is sudden increase in activity causes increased oxygen demand which stimulates respiratory center and leads to hyperpnea. Hyperpnea reduces intrathoracic pressure which decreases systemic and pulmonary resistance and leads to greater right to left shunt in view of increased systemic flow which is not matched by pulmonary flow.

Management

- The first step is to attempt and place the infant in knee-chest position which increases systemic vascular resistance and decreases right to left shunting at VSD level.
- Keep the child calm and quiet and to avoid any painful procedures.
- It is reasonable to administer oxygen, however, if it causes agitation, then oxygen should be removed.
- Sedation in the form of morphine (0.1–0.2 mg/kg IM/IV/SC) or ketamine (1–2 mg/kg IV) can be given and repeated as necessary. Morphine not only helps to keep child calm but also decreases patient's respiratory drive and hyperpnea which may help abort the spell.
- Blood volume expansion with crystalloids like initial IV saline bolus @10 mL/kg which can be repeated as per the hydration status until the liver is palpable. They increase the RV preload and therefore may increase the RV output.
- Metabolic acidosis usually develops when arterial PO_2 falls below 40 mm Hg, rapid correction with IV sodium bicarbonate (1–2 mEq /kg IV) is especially necessary if the spell is unusually severe and the child shows a lack of response to the ongoing therapy. Once the pH has returned to normal recovery from the spell is usually rapid.
- If spell continues, phenylephrine 0.01 mg/kg IV slowly or 0.1 mg/kg SC, or norepinephrine (0.05–0.5 μg/kg/min infusion) may be attempted which may help by increasing the systemic vascular resistance (the dose has to be titrated according to the BP response).
- Beta-blocker—injection metoprolol 0.1 mg/kg over 5 minute can be repeated every 5 minutes to max of three doses, or infusion can be given at dose of 1–5 μg/kg/min. Alternatively, esmolol can be given with loading dose of 500 mg/kg/dose followed by maintenance infusion of 50–100 μg/kg/min. IV beta-blockade helps by combination of relief of infundibular spasm and prevention of ventilatory response.
- In refractory cases, when there is no response to any of these measures intubation with ventilation and urgent transfer to a tertiary facility, where facilities of emergent surgical systemic-to-pulmonary shunt (BT Shunt) or definitive corrective procedure are available, should be done.
- *Response of treatment can be assessed in the form of increasing intensity of the ejection systolic murmur and rising oxygen saturations both the signs being reassuring.*

Pericardial Tamponade

Cardiac tamponade is one of the life-threatening emergencies which is caused due to slow or rapid accumulation of pericardial fluid, pus, blood which increases the intrapericardial pressure and causes compression of the heart. The clinical features depend not only on amount of fluid, but also on the speed of fluid accumulation. Patients can present with chest pain, impalpable apex beat, muffled heart sounds on auscultation, and pericardial friction rub. Rapid fluid accumulation can lead to cardiac tamponade which may present as cardiogenic shock. Beck's triad comprising hypotension, diminished heart sounds, and venous hypertension may not be evident until late in course in cardiac tamponade and therefore is not a sensitive indicator of tamponade. Straightening of the left heart border on chest radiograph is a useful finding. A progressively enlarging globular heart also is a reliable indicator of pericardial effusion, but this is characteristically a late finding (**Fig. 7**). Echocardiography is diagnostic modality of choice for diagnosing and evaluating a pericardial effusion (**Figs. 8** and **9**). Diastolic collapse of atria and ventricles is considered pathognomonic for cardiac tamponade on echocardiography.

Management

In hemodynamically stable patient with no features of cardiac tamponade, a definitive diagnosis by echocardiography and drainage via pericardiocentesis or surgical drainage is required. Urgent decompression of the pericardial space is mandatory and lifesaving if signs of cardiac tamponade are present. This is achieved by aspirating from a subxiphoid

FIG. 7: Chest X-ray (frontal view) showing cardiomegaly with globular heart shadow in a child with large pericardial effusion.

FIG. 8: Echocardiography of a child presenting with features of cardiac failure in emergency. Subcostal coronal view showing large pericardial effusion. On pericardial tap, serous fluid was drained and was of tubercular etiology.

FIG. 9: Echocardiography of a 1-year-old child presenting with fever for 1 month and respiratory distress. Apical four-chamber view showing large pericardial effusion all around with multiple strands on pericardial tap, purulent fluid was drained.

approach with a cannula aiming at left shoulder and at angle of 30–45 from skin and obtaining as much fluid as possible before removing cannula. Blood volume expansion with 20 mL/kg crystalloid IV bolus, repeated as necessary.

Arrhythmias

Several types of arrhythmias are seen in neonatal and pediatric age-group. They are broadly classified as tachyarrhythmias and bradyarrhythmias. The most common conditions predisposing to arrhythmias in children include congenital heart disease and postoperative cardiac surgery. Rhythm disturbances can cause hemodynamic compromise in children due to rate abnormalities or loss of synchrony. An appreciation of normal variation and disturbances in pediatric ECG with age and maturation is essential for interpretation of pediatric rhythm disturbances (**Table 4**).

TABLE 4: Heart rates and PR and QRS intervals according to age.

Age	*Heart rate/min*	*PR interval*	*QRS interval*
0–1 day	94–155 (122)	0.08–0.16 (0.107)	0.02–0.07 (0.05)
1–3 days	91–158 (122)	0.08–0.14 (0.108)	0.02–0.07 (0.05)
3–7 days	90–166 (128)	0.07–0.15 (0.102)	0.02–0.07 (0.05)
7–30 days	96–182 (149)	0.07–0.14 (0.100)	0.02–0.08 (0.05)
1–3 months	120–179 (149)	0.07–0.13 (0.098)	0.02–0.08 (0.05)
3–6 months	105–185 (141)	0.07–0.15 (0.105)	0.02–0.08 (0.05)
6–12 months	108–169 (131)	0.07–0.16 (0.106)	0.03–0.08 (0.05)
1–3 years	89–152 (119)	0.08–0.15 (0.113)	0.03–0.08 (0.06)
3–5 years	73–137 (109)	0.08–0.16 (0.119)	0.03–0.07 (0.06)
5–8 years	65–133 (100)	0.09–0.17 (0.128)	0.04–0.09 (0.06)
8–12 years	62–130 (91)	0.09–0.17 (0.128)	0.04–0.09 (0.06)
12–16 years	60–120 (80)	0.09–0.18 (0.135)	0.04–0.09 (0.07)

Tachyarrhythmias

An electrocardiography is essential for critical evaluation of tachycardia. They are suspected when the heart rate >180 beats/min in children and >220 beats/min in infants and is usually fixed between 250 and 280 beats/min with no variability, atrioventricular dissociation, abnormal P wave axis, narrow complex tachycardias (<90 ms) are due to AV re-entrant tachycardia via an accessory pathway (SVT) (**Fig. 10**). Nodal/junctional ectopic tachycardia, ectopic and multifocal atrial tachycardias, and atrial flutter (**Fig. 11**), wide complex tachycardia (>90 ms)—wide complex tachycardia in children is ventricular tachycardia until proven otherwise. So, all monomorphic wide complex tachycardias should be treated as VT without delay, especially if hemodynamically unstable (**Fig. 12**).

- *Clinical presentation*: Wide range of clinical presentation, asymptomatic to cardiogenic shock and even sudden cardiac death. Palpitations are the usual presenting symptom in older children with paroxysmal tachycardia, but other nonspecific symptoms such as light-headedness, syncope, chest pain, pallor, or nausea may occur. Tachycardia may go unrecognized for many hours and significant hemodynamic compromise may result. If the duration of the tachycardia exceeds 6–12 hours, symptoms and signs of HF may become apparent.
- *Management*: 12-lead ECG recording with a rhythm strip. Reversible causes of arrhythmias should be identified and treated, e.g., 5 Hs and 5 Ts that includes hypoxemia, hypovolemia, hypo- or hyperthermia, hyper- or hypokalemia, acidosis, and tamponade (cardiac), tension pneumothorax, and toxins, e.g., digoxin, beta-blockers, calcium channel blockers, and thrombosis (coronary and pulmonary).

Narrow Complex Tachycardia

- *Atrial flutter*: The treatment of choice is synchronized DC cardioversion, as little as 0.5 J/kg is often enough to

FIG. 10: Supraventricular tachycardia. HR—270 beats/min with narrow QRS complexes and P waves not seen.

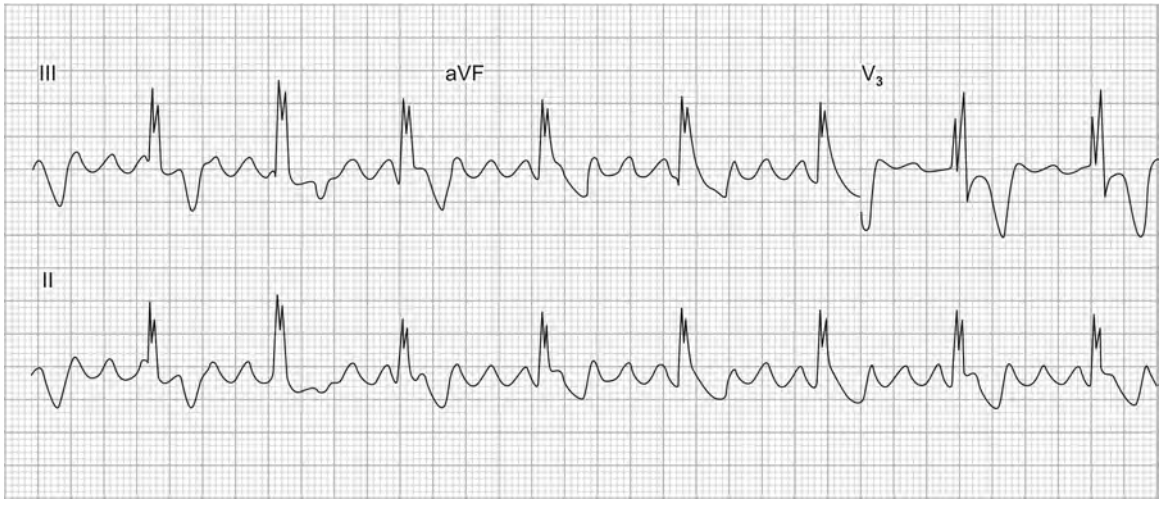


FIG. 11: A trial flutter: Ventricular rate—75 beats/min with 3:1 AV conduction. Sawtooth pattern P waves seen.

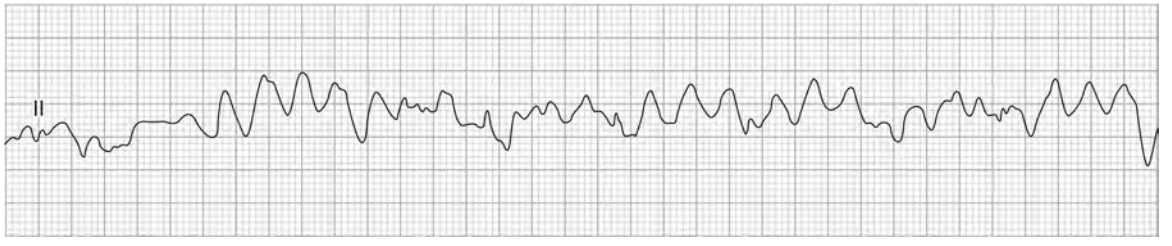


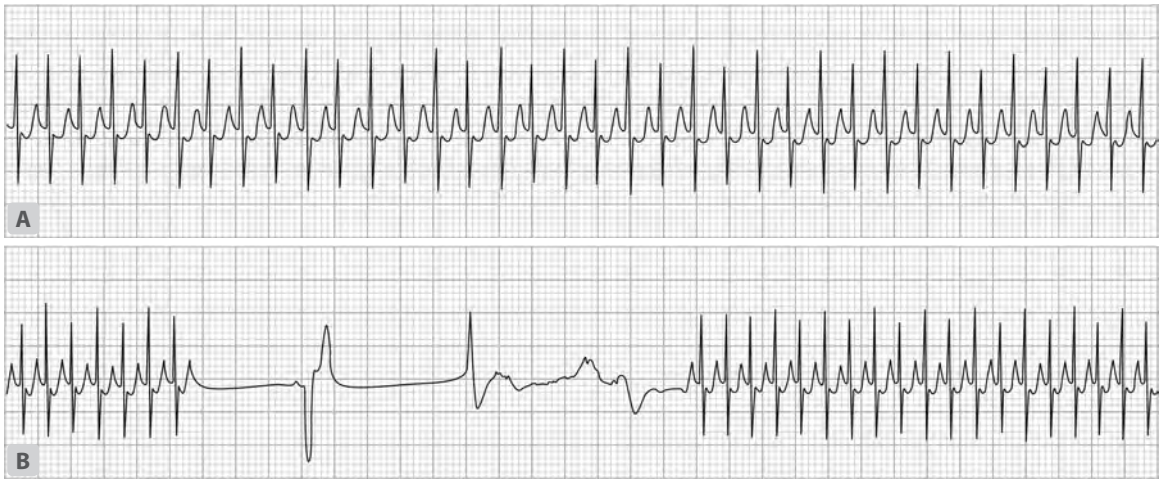
FIG. 12: Torsades de pointes with prolonged QT interval and changing ventricular rate in a child with long QTc syndrome (Jervell Lange-Nielsen syndrome).

cardiovert to sinus rhythm. Pediatric paddles should be used with electrode jelly and should be correctly applied. Children should be sedated for comfort. Adenosine is usually not effective.

- *Supraventricular tachycardia (SVT)*: In hemodynamically stable children, vagal maneuvers should be attempted and if arrhythmia does not resolve within 10–15 seconds, Adenosine should be administered. The IV line should be located as centrally as possible. In adults and children weighing 50 kg or more, the recommended initial adenosine dose is 6 mg. If the patient does not convert to normal sinus rhythm, a 12 mg dose may be given within 1–2 minutes. In children weighing <50 kg, IV adenosine dose is 0.05–0.1 mg/kg. If there is no response, subsequent doses may be increased by 0.5–0.1 mg/kg increments up to a maximum single dose of 0.3 mg/kg. In hemodynamically unstable children (**Figs. 13A** and **B**), synchronized DC cardioversion is the first-line therapy.
- *Wide complex tachycardia* (probable VT): In stable patients, consider amiodarone 5 mg/kg IV over 20–30 minutes or procainamide, If medical therapy is unsuccessful or in hemodynamically unstable patients synchronized cardioversion 0.5–2 J/kg should be attempted.

Bradyarrhythmia

- *Sinus bradycardia*: The most common cause of bradycardia is hypoxemia, which is an ominous sign and should be managed aggressively. Other causes include hypothermia, hypothyroidism, raised intracranial pressure, and drug intoxication. The diagnosis of sinus bradycardia is easily made by establishing the 1:1 relationship between P waves and QRS complexes on the surface ECG. An upright P wave in leads I, II, and aVL, and a negative P wave in lead aVR, indicates a sinus origin of the bradycardia. The three main causes of bradyarrhythmia include (1) sinoatrial (SA) node dysfunction, (2) second-degree AV block, and (3) complete AV block. The main cause of bradycardia in children presenting as cardiac emergency is complete heart block (CHB) (**Fig. 14**).
  - *Clinical presentation*: Dizziness or syncope is distressing symptom, which occurs at a heart rate below 40–45/min may present as cardiogenic shock or sudden cardiac death. May present as heart failure in congenital heart block.
- *Management*: In symptomatic bradycardias drugs used include atropine given at a dose of 20 μg/kg as bolus (minimum dose 100 μg, maximum 600 μg), adrenaline



FIGS. 13A AND B: (A) Supraventricular tachycardia; (B) supraventricular tachycardia treated with IV adenosine with only transient response.

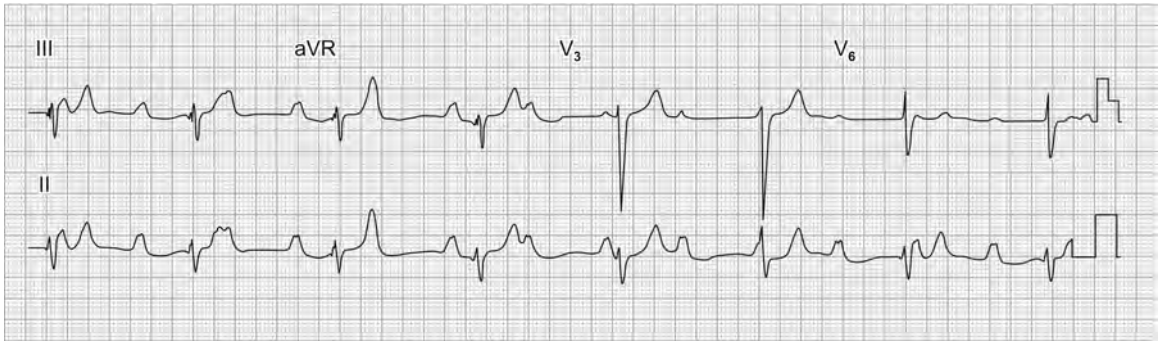


FIG. 14: Complete heart block with no relation between P waves and QRS waves with slow ventricular rate of 50 beats/min.

(10 μg/kg bolus) followed by infusions or isoprenaline infusion. Crystalloid bolus of 10–20 mL/kg IV is given if the patient is hypotensive or in shock. Patient should be referred to a tertiary care center where expertise for pacing is available and temporary pacing should be promptly instituted. In refractory cases, the definitive treatment is insertion of permanent pacemaker which can be endocardial or epicardial in position.

DRUGS COMMONLY USED IN CARDIAC EMERGENCIES

Prostaglandin E1 (alprostadil): 60 μg/kg in 50 mL 0.9% saline 0.5–3 mL/h (starting dose 10–60 ng/kg/min), if poor response (saturations and acidosis not improving), the dose can be increased to max 100–200 ng/kg/min.

Diuretics

- *Furosemide*: 0.5–1 mg/kg (adult 20–40 mg) 6–24 hours oral, IM or IV over 20 minutes. IV Infusion 0.1–0.4 mg/kg/h.
- *Spironolactone*: 1–3 mg/kg 6–12 hourly orally.

ACE Inhibitor

Enalapril: Test dose 0.05 mg/kg (adult 2.5 mg) oral with BP monitoring, increase over 2 weeks if required to max 0.5 mg/kg (adult 5–20 mg) twice daily orally.

Beta-blockers

- *Propranolol*: 0.2–0.5 mg/kg (Adult 10–25 mg) 6–12 hours oral, increase to max 1.5 mg/kg (max 80 mg) 6–12 hours, if required. IV 0.02 mg/kg (adult 1 mg) test dose then 0.1 mg/kg (adult 5 mg) over 10 minutes
- *Metoprolol*: IV 0.1 mg/kg (adult 5 mg) over 5 minutes, repeat every 5 minutes to max three doses, then 1–5 μg/kg/min. Oral 1–2 mg/kg (adult 50–100 mg) 6–12 hours.
- *Esmolol*: 0.5 mg/kg (500 μg/kg) IV over 1 minute, repeated if required. Infusion 25–300 μg/kg/min (undiluted 10 mg/mL solution) rarely given for >48 hours.
- *Carvedilol:* 0.1 mg/kg (adult 3.125 mg) 12 hours oral, if tolerated, increase by 0.1 mg/kg (adult 3.125 mg) every 1–2 weeks to max 0.5–0.8 mg/kg (adult 25 mg)12 hours.

TABLE 5: Digoxin doses in different pediatric ages.

Digoxin	*Digitalizing dose (mg/kg)*	*Maintenance dose (fraction digitalizing dose)*
Premature, neonates	0.04	1/4th
1 month–1 year	0.08	1/3rd to 1/4th
1–3 years	0.06	1/3rd to 1/4th
Above 3 years	0.04	1/3rd

Inotropes

- *Dopamine*: 5–20 μg/kg/min IV infusion. Central line preferred
- *Dobutamine:* 5–20 μg/kg/min IV infusion. Central line preferred
- *Milrinone* :50 μg/kg IV bolus over 10 minutes, 0.3–0.8 μg/kg/min IV infusion
- *Levosimendan:* Start with a bolus dose of 12–24 μg/kg IV over 10 minutes followed by 0.1 μg/kg/min IV infusion. Increase the dose slowly to 0.2 μg/kg/min and usually the total duration of the infusion was 24–48 hours. The bolus dose may be omitted in unstable hypotensive patients.

Digoxin

Digoxin doses in different pediatric age are summarized in **Table 5**.

SUMMARY

There are a number of congenital and acquired heart diseases in neonates, infants, and children that may present as life-threatening emergencies. These may be undiagnosed and present for the first time as emergencies, or they may present with complications in a child with a known diagnosis. Entertaining the possibility of a cardiac problem in neonates with pulmonary symptoms unresponsive to standard therapies is crucial for successful management of patients with CHD. In addition to ventilatory support, PGE1 infusions or emergency interventional cardiac catheterization is often a lifesaving initial measure in patients with acutely decompensated congenital cardiac lesions that require a PDA for survival. Every health practitioner caring for children should be aware of the common diagnoses, expected complications and their immediate management. The most commonly encountered emergencies are cyanosis or hypercyanotic spells, acute CHF, cardiogenic shock, tachyarrhythmias or bradyarrhythmia, and pericardial effusion or cardiac tamponade. The emphasis should be on early recognition of hemodynamic derangements and immediate appropriate intervention in order to prevent death and significant morbidity. Early consultation with a pediatric cardiologist is desirable especially if there is doubt as to the diagnosis or poor response to initial treatment. Once a child is stabilized, prompt referral to a tertiary pediatric cardiac center is usually required for definitive diagnosis and management.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Pediatric Diabetic Ketoacidosis

Devendra Richhariya

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases among children and adolescents worldwide. Over the past 20 years, the incidence of type 2 diabetes mellitus (T2DM) (formerly known as adult-onset diabetes) has increased among children. A major complication of diabetes, diabetic ketoacidosis (DKA), is characterized by the metabolic triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia that develops from an absolute or relative insulin deficiency and excess of counterregulatory hormone. DKA results in dehydration and electrolyte derangements. This combination, along with the major complication of cerebral edema, is the most important cause of morbidity and mortality among children with DKA. The mainstay of therapy is rehydration with intravenous (IV) fluids, insulin, and potassium repletion, as needed. Bicarbonate therapy is rarely, if ever, indicated and can lead to complications.

EPIDEMIOLOGY

Despite significant advances in diabetes management, the incidence of DKA and diabetes complications remains high, probably as a result of the alarming increase in childhood obesity and its direct link to diabetes. The incidence of DKA at the time diabetes is diagnosed varies by geographic location, ranging from 12 to 80%; approximately one-third of type 1 diabetes mellitus (T1DM) patients have DKA at the time of diagnosis. Young children, especially those younger than 5 years of age, are at high risk for DKA. The severity of DKA is also inversely related to age, placing the youngest children at the greatest risk. Other factors that increase the likelihood of DKA at the time of diagnosis of diabetes include lower body mass index, missed diagnosis at previous healthcare visits, delayed treatment, and preceding infection. The incidence of DKA among established diabetics is 25%. T2DM is becoming increasingly common among children as a result of obesity. DKA also occurs in T2DM patients; 5–25% of T2DM patients present with DKA at the time of diagnosis. In a study of T1DM and T2DM patients, the most common cause of DKA was insulin omission, especially in T1DM patients. Although less common overall, infection is more often associated with DKA in T2DM patients. Although acidosis tends to be more severe in T1DM patients, T2DM patients require a longer duration of insulin infusion to achieve ketone-free urine, possibly because of underlying insulin resistance. DKA is associated with significant cost and morbidity.

Although the mortality rate associated with DKA is <1%, this imbalance accounts for most diabetes-related deaths in children, most of which result from cerebral edema that progresses to brain herniation. Cerebral edema, a rare and devastating complication of DKA, is clinically apparent in 1–5% of patients with DKA. Mortality rates ranging from 20 to 90% have been reported. A large proportion of survivors, up to 26%, experiences permanent neurologic deficits. Studies have also demonstrated risks of long-term memory dysfunction in children who experienced DKA without cerebral edema.

PATHOPHYSIOLOGY

Insulin is the primary hormone of blood glucose regulation. It is responsible for increasing peripheral glucose uptake and stopping hepatic gluconeogenesis. As blood glucose levels increase, counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) play reciprocal roles with insulin in attempts to maintain glucose homeostasis. DKA results from an absolute or relative deficiency of insulin and the resulting excess of counter-regulatory hormones. Absolute insulin deficiency occurs in new-onset T1DM as a result of pancreatic β-cell failure and in established diabetes as a result of insulin omission or insulin pump failure. Relative insulin deficiency can be attributable to insulin resistance or inadequate insulin dosing to balance the increased counter-regulatory hormone levels present during infection, trauma, or other physiologic stressors.

Medications such as high-dose glucocorticoids, atypical antipsychotics, and immunosuppressive drugs can also trigger DKA. Insulin deficiency leads to impaired glucose uptake and use by tissues. Counterregulatory hormone excess leads to increased glycogenolysis, gluconeogenesis, proteolysis (which creates more substrates for gluconeogenesis), and lipolysis. Lipolysis generates free fatty acids, which normally undergo β-oxidation to generate acetyl coenzyme A, an entry molecule for the citric acid cycle. In the absence of insulin, the significant lipolysis and fatty acid burden is diverted toward ketogenesis instead.

The two main ketones produced are acetoacetate and β-hydroxybutyrate, which dissociate fully at physiologic pH. Acetone is the least abundant product of ketogenesis but does not contribute to acidosis, as it does not dissociate to yield hydrogen ions. It is metabolized through the lung and produces the fruity breath characteristic of DKA. The ratio of β-hydroxybutyrate to acetoacetate, normally 1:1, increases to as high as 10:1 in DKA. Although ketones are weak acids, their severe overproduction overwhelms the buffering capacity of the body, which leads to an anion gap metabolic acidosis. Lactic acidosis and renal dysfunction are caused by prerenal azotemia and dehydration may also contribute to acidosis.

Respiratory compensation for this acidosis results in the classic shallow rapid breathing (Kussmaul respirations). Dehydration is a significant consequence of DKA and has several causes. Decreased glucose uptake and increased glucose production via glycogenolysis and gluconeogenesis lead to hyperglycemia, causing extracellular fluid and electrolyte shifts. An osmotic diuresis results when serum glucose levels increase above the renal threshold for glucose reabsorption. This causes free water, glucose, and electrolytes to be lost in urine. Ketone-induced nausea and vomiting, along with the insensible losses associated with Kussmaul respirations, compound fluid losses.

Multiple electrolyte abnormalities occur in the setting of DKA. Sodium, potassium, chloride, phosphorus, calcium, and magnesium are all affected. The most significant and imminently life-threatening electrolyte imbalance is hypokalemia. Potassium shifts out of the cells because of insulin deficiency and the exchange of hydrogen ions to compensate for acidosis. This can cause the serum potassium level to be normal or even increased, despite the total body depletion of potassium that results from osmotic diuresis, gastrointestinal losses, and volume depletion. Under these conditions, the renin-angiotensin-aldosterone system is activated, exacerbating renal potassium excretion via urine.

CLINICAL PRESENTATION

Diabetic ketoacidosis can develop quickly in patients with established diabetes, especially when it is related to insulin omission. However, when DKA acts as the first presentation of diabetes, the symptoms emerge over several days. Typical symptoms are the classic triad of polyuria, polydipsia, and weight loss with or without polyphagia. These symptoms are easy to miss in children who are wearing diapers and being fed by multiple caretakers. Abdominal pain, nausea, and vomiting are also common complaints. Dehydration and electrolyte derangements can lead to muscle pains and cramping. The abdominal pain can mimic an acute abdomen. It can also be an indication of an underlying cause, so further evaluation is warranted if the pain does not resolve with hydration and resolution of ketoacidosis.

Late findings include changes in mental status, Kussmaul respirations, and fruity, sweet, and ketotic breath. Because the presentation of DKA may vary and be subtle in children who may not have an established diagnosis of diabetes or be able to communicate their complaints verbally, a high degree of suspicion is needed to diagnose DKA in the pediatric population. Complaints of headache or changes in mental status are worrisome as indications of cerebral edema. Focal neurologic deficits can also be seen. Hemodynamic instability and shock are rare in children with DKA, but patients are often dehydrated to varying degrees as a result of fluid shifts, osmotic diuresis, gastrointestinal losses, and insensible losses.

DIAGNOSIS

The biochemical criteria for DKA are—hyperglycemia with blood glucose concentration >200 mg/dL (>11 mmol/L), venous pH <7.3, or bicarbonate concentration <15 mmol/L ketonuria and ketonemia. The severity of DKA can be categorized as follows:

- *Mild*: Venous pH <7.3, HCO_3 <15 mmol/L
- *Moderate*: Venous pH <7.2, HCO_3 <10 mmol/L
- *Severe*: Venous pH <7.1, HCO_3 <5 mmol/L

The basic *initial diagnostic tests* that should be obtained in all patients suspected of having DKA are listed in **Box 1**. Although hypotension is not common in straightforward DKA, but tachycardia can be present. Fever may occur in the setting of infection but is not caused by DKA inherently. Tachypnea is present in later compensatory stages of DKA. It is imperative to weigh all patients so that accurate medication and fluid doses can be calculated. The measurement of glucose levels in capillary blood samples with bedside meters provides information immediately and is adequate for monitoring changes during treatment. Values should be obtained at least every hour during acute management.

An *electrocardiogram* must be obtained if potassium measurement is not available immediately, such as via point-of-care testing, as early detection of arrhythmogenic electrolyte imbalances is crucial. U waves are suggestive of hypokalemia, whereas short QT intervals and peaked T waves may progress to prolonged PR intervals, widened QRS complexes, or a sine wave pattern in hyperkalemia. The complete blood count might show leukocytosis, which is not specific for infection in the setting of DKA and could be related to dehydration. An infectious workup should be initiated if the patient has a history of fever or other suggestive symptoms.

Serum chemistry is obtained for both the individual electrolyte values and to perform the calculations listed in **Box 1**. The serum sodium concentration is corrected to account for the dilutional effect of the degree of hyperglycemia. The anion gap, however, is calculated using the measured serum sodium level rather than a corrected sodium level because glucose is electrically neutral and does not contribute to the anion gap. The anion gap is determined by negatively charged ions and proteins such as albumin. Therefore, in the setting of albumin deficiency, the anion gap should be corrected, assuming a normal serum albumin concentration of 4 g/dL and an expected reduction in the anion gap by 2.5 mEq/L for every 1 g/dL decrease in serum albumin. Albumin levels should be obtained if there is a concern about nephrotic syndrome or severe malnutrition but not necessarily in a previously healthy child.

Venous Blood Gas Analysis

It is well-established that venous and arterial pH are well correlated in DKA. Consensus guidelines for management now include venous pH, rather than arterial pH, as part of the biochemical definition of DKA. This eliminates the added

BOX 1: Initial diagnostic workup for diabetic ketoacidosis patient.

- Vital signs
- Weight
- Capillary blood glucose
- Electrocardiogram
- *Serum Chemistry*: Glucose, sodium, potassium, chloride, blood urea nitrogen, creatinine, calcium magnesium, and phosphorus
- Complete blood count
- Venous blood gas
- β-hydroxybutyrate or urine ketones

Calculation using serum chemistry:

- Corrected sodium = serum sodium + 1.6 × [(serum glucose in mg/dL – 100)/100]
- Anion gap = serum sodium – (serum chloride + serum bicarbonate)
- Anion gap corrected for albumin = anion gap 2.5 × (4-serum albumin in g/dL)

risk of pain, hemorrhage, fistula formation, thrombosis, and infection when obtaining a sample for analysis of arterial blood gases. Although arterial blood gases used to be considered essential in the diagnosis of DKA, they have not been found to influence decision making in the emergency department when treating patients with DKA. Based on various studies, the mean difference between arterial and venous pH ranges from 0.015 to 0.05, and venous pH accurately measures the degree of acidosis in adult patients with DKA. Subtle differences are not likely to be clinically significant. Venous blood gas (VBG) electrolyte testing is a newer aspect of DKA diagnosis and monitoring that may allow the rapid assessment of essential data in a single test.

Ketone Testing

Although β-hydroxybutyrate is the predominant ketone produced in DKA, urine, and serum ketone assays typically use the nitroprusside reaction, which detects only acetone and acetoacetate and is semiquantitative using dilutions. During treatment with insulin therapy, β-hydroxybutyrate is oxidized to acetoacetate, causing β-hydroxybutyrate levels to decrease before acetoacetate levels. A ketone assay may give the false impression that the patient is not improving, when, actually, the overall quantity of ketones has decreased. Therefore, when interpreting ketone tests, both the time delay before the development of ketonemia and ketonuria must be considered in diagnosing DKA as well as the earlier clearance of β-hydroxybutyrate rather than urine ketones alone.

Urine ketone testing is affected by hydration status and urine stagnation in the bladder, and false-positive results can be encountered if patients are taking captopril, penicillamine, N-acetylcysteine, mesna, dimercaprol, or isopropyl alcohol. To more precisely measure ketone burden, a quantitative serum β-hydroxybutyrate test should be used.

The use of β-hydroxybutyrate testing has been proposed ahead of urine ketone testing as an end point to monitor resolution of ketosis and direct insulin infusion therapy. However, because serum β-hydroxybutyrate assays are not available at all institutions, the anion gap, pH, or bicarbonate can be used to direct DKA treatment.

EMERGENCY DEPARTMENT MANAGEMENT

First and foremost, pediatric resuscitation principles should be followed. Airway, breathing, and circulation should be secured. IV access must be obtained. Aspiration precautions should be taken if the patient has an altered level of consciousness. Continuous cardiac monitoring and pulse oximetry are imperative to assess for arrhythmias secondary to hyperkalemia or hypokalemia and to ensure adequate oxygenation. Frequent neurologic monitoring is also warranted. The best outcomes are achieved when children are monitored closely and continuously, with prompt attention to any changes. Additional hourly monitoring should include vital signs, neurologic checks, blood glucose, and accurate fluid intake and output. Frequent neurologic checks are particularly important in patients at greater risk for cerebral edema, such as those with new-onset diabetes, patients younger than 5 years old, and patients with greater degrees of acidosis, hypocapnia, or azotemia.

Capillary blood glucose levels should be confirmed with laboratory venous values. Initially, VBGs and chemistries should be checked every 2 hours, but depending on those initial values, may require more frequent monitoring. As previously mentioned, ketone testing should not guide treatment. The serum β-hydroxybutyrate concentration is ideal for monitoring progress; if that reading is not available, anion gap, pH, and bicarbonate can also be used as endpoints. Specific aspects of DKA management are—fluid resuscitation to rehydrate and improve tissue perfusion and glomerular filtration rate. Correction of ketoacidosis and hyperglycemia is acheived through inhibition of lipolysis and ketogenesis with insulin, restoration of electrolyte balance, and avoidance of complications, specifically cerebral edema.

Fluids

Intravenous fluids are administered for resuscitation and rehydration as well as to decrease the blood glucose level by improving the glomerular filtration rate and, thus, glucose and ketone clearance. Although adults tend to present with large volume deficits requiring aggressive fluid repletion, a more restrictive strategy must be used in the pediatric setting to avoid potential complications. The initial resuscitation of a pediatric patient in DKA calls for administration of an isotonic crystalloid solution as a bolus of 10–20 mL/kg over 1–2 hours. The dose can be repeated if the patient is hemodynamically unstable.

Children rarely present in hypovolemic shock caused by DKA alone. If a child does not respond to the initial resuscitation bolus, search for other causes of shock. To avoid increasing the risk of cerebral edema and herniation, resuscitation volumes should not exceed 40–50 mL/kg during the first 4 hours of treatment, unless the patient is in shock. After the initial bolus of IV fluid, the goal of rehydration is to administer the remainder of replacement fluids evenly over 24–48 hours with 0.45–0.9% saline.

Overzealous fluid resuscitation could lead to further complications, particularly cerebral edema, although no

data have demonstrated increased safety with rehydration over 48 hours. The rate of total fluid administration includes maintenance plus replacement of the fluid deficit based on the patient's estimated degree of dehydration (*see* section on degree of dehydration) and should not exceed two times the maintenance volume. Fluids that were administered before arrival should be accounted for in these calculations, but urinary losses should not.

Weight-based 24-hour maintenance fluid requirements can be calculated as follows:

- 100 mL/kg for the first 10 kg of body weight
- 50 mL/kg for the second 10 kg of body weight
- 20 mL/kg for each kilogram above 20 kg of body weight

Using the 4-2-1 rule, the requirements can be estimated as follows:

- 100 mL/kg/24 h = 4 mL/kg/h for the first 10 kg of body weight
- 50 mL/kg/24 h = 2 mL/kg/h for the second 10 kg of body weight
- 20 mL/kg/24 h = 1 mL/kg/h for each kilogram above 20 kg of body weight

Fluid Type

Normal saline (NS) (0.9% NaCl) is commonly used as the replacement fluid for patients with DKA and can be switched to half NS (0.45% NaCl) once the corrected sodium concentration normalizes (*see* section on sodium).

Recent evidence implicates the administration of large volumes of saline in the development of hyperchloremia with a nonanion gap metabolic acidosis, which increases with treatment duration and can mask the resolution of DKA if base deficit alone is being monitored as an endpoint for treatment. The clinical significance of hyperchloremia with acidosis is unclear, but concerns about possible deleterious effects from excessive saline administration have raised controversy with respect to fluid choice. A small blinded, randomized controlled trial failed to show any difference in time to normalization of pH and resolution of DKA between patients resuscitated using NS and others who received Ringer's lactate. Recent literature comparing noncalcium-containing balanced crystalloid such as Plasma-Lyte (Plasma-Lyte or Plasma-Lyte A, Baxter healthcare, Deerfield, IL) with NS administration to patients with DKA reported lower serum chloride levels and higher bicarbonate concentrations after resuscitation in the Plasma-Lyte group, consistent with prevention of hyperchloremia and acidosis. The effect of these changes on outcome and mortality rate is unknown. Chua and colleagues reported no difference in the rate of resolution of hyperglycemia, the duration or total dose of IV insulin administration, or length of ICU stay.

Further investigation is needed to determine whether the administration of a saline solution to patients with DKA carries any clinically significant risks; there is no evidence of associated morbidity. Currently, the use of saline remains the standard of care.

Rate of Rehydration

Because of conflicting theories on the underlying mechanism of cerebral edema in patients with DKA, arguments for both slower and faster rehydration have been put forth. If cerebral edema results from osmotic changes or vasogenic edema associated with a compromised blood-brain barrier, slower rehydration might limit edema. On the other hand, if ischemia and hypoperfusion are the major insults to the brain, then more rapid rehydration could rectify the problem sooner and prevent ischemia when intracellular fluid shifts during treatment with insulin. Unfortunately, little evidence is available to definitively guide the rapidity of fluid therapy.

Degree of Dehydration

The clinical assessment of dehydration such as reduced skin turgor, increased capillary refill time, dry tongue, and sunken eyes or fontanel, in assessing degree of dehydration, none of these parameters have been found to be accurate predictors of hydration status in DKA because they might not reflect only fluid losses. Acidosis can make a child seem more dehydrated because of the tachypnea of Kussmaul respirations, which results in dry mucous membranes, and vasoconstriction, which leads to cooler extremities. The ongoing lipolysis, proteolysis, and weight loss caused by insulin deficiency can also make a child seem clinically more dehydrated. On the other hand, hyperosmolarity tends to preserve intravascular volume (and thus pulses, blood pressure, and urine output) until extreme volume depletion and shock occur. Therefore, physical examination findings are often unreliable in estimating dehydration in the setting of DKA. Based on the available data, it might be excessive to estimate up to 10% dehydration in patients. Administration of maintenance fluids, based on an assumed 6% deficit, seems more reasonable.

Two-bag System

Because of rapid fluctuations in fluid, electrolyte, and dextrose requirements, patients with DKA require frequent adjustments in fluid and insulin administration. This system consists of two bags of fluids with identical electrolyte content but different dextrose concentrations (0% and 10%) that are administered simultaneously into the same IV line. The rate of fluid delivery is determined by the degree of dehydration and individual patient needs, whereas the concentration of dextrose depends on the patient's serum glucose level and its rate of decline during treatment. These factors can be manipulated independently, as different proportions of fluid from each bag are administered.

Initially, no dextrose is given; as hyperglycemia resolves with the infusion of insulin, dextrose is titrated up to control the rate of decrease in blood glucose while continuing the insulin infusion. The IV fluids can therefore be customized to meet the patient's individual glucose, fluid, and insulin needs by creating a fluid dextrose concentration that ranges between 0 and 10% to control the rate of blood glucose decline and prevent hypoglycemia. If >250 mg/dL (13.8 mmol/L), give NS alone, If <250 mg/dL (13.8 mmol/L), give half of the rate from each bag to make 5% dextrose (D5) NS. If <150 mg/dL (8.33 mmol/L), give 10% dextrose (D10) NS alone at a predetermined rate.

Studies have shown multiple advantages to the two-bag system. Rather than changing an individual IV fluid bag each time the dextrose concentration needs to be adjusted during correction of hyperglycemia and acidosis, which can take >30 minutes, the two-bag system allows rapid transitioning of fluids when necessary, taking as little as 1 minute.

The two-bag system is superior to the single-bag system with respect to flexibility, timeliness, and cost-effectiveness. The rate and dextrose concentration of the fluids can be adjusted independently, and the dextrose concentration can be changed quickly in response to updated serum glucose levels without discarding partially used bags of fluids. Studies have not yet demonstrated clinical benefit, but the two-bag system does not increase the risk of complications from DKA and could have clinical benefits in addition to its more practical advantages.

Insulin

Rehydration alone can decrease the blood glucose concentration, but insulin is required to suppress the lipolysis and ketogenesis that drive DKA. Insulin therapy is initiated after volume resuscitation has been started and after the serum potassium level is known. Low-dose insulin is the standard of care. Start and maintain a low-dose regular insulin IV infusion at 0.1 units/kg/h and continue until the ketoacidosis resolves or until the anion gap closes. Although still a point of contention in the management of adults with DKA, an initial bolus of insulin is not necessary in pediatric patients and may even be harmful by predisposing patients to hypoglycemia and increasing the risk of cerebral edema. Theoretically, rapid correction of hyperglycemia may shift osmolarity and lead to cerebral complications, but the rate of glucose correction has not been shown to increase the risk of cerebral edema or brainstem herniation.

Hyperglycemia usually resolves before the acidemia, but the insulin infusion must be continued to achieve full resolution of the ketoacidosis (pH >7.3, bicarbonate >15 mmol/L, β-hydroxybutyrate <1 mmol, and/or closure of anion gap). The target serum glucose level during treatment is approximately 200 mg/dL. To avoid hypoglycemia during insulin infusion, dextrose should be added to IV fluids when the blood glucose concentration reaches 250–300 mg/dL or if the decline in the blood glucose level exceeds 100 mg/dL/h (5.6 mmol/L/h). This practice is facilitated by the two-bag fluid system as described earlier. If hypoglycemia occurs on the maximum dextrose concentration of D10, then lower the insulin drip to no <0.05 units/kg/h, as rates less than this can prevent full resolution of the ketoacidosis.

The transition from IV to subcutaneous insulin should occur after ketoacidosis resolves. Subcutaneous insulin is given at least 30 minutes before discontinuing the insulin infusion to allow time for absorption and prevent rebound hyperglycemia. The patient must be able to tolerate oral fluids and should begin to eat at that time. Endpoints used to determine the transition from IV to subcutaneous insulin vary, mainly because no evidence-based guidelines have been established. Using a pH of 7.3 as a signal to make the transition might be inadequate, as patients have been found to be ketotic at this pH. Vanelli and colleagues used normalization of the β-hydroxybutyrate concentration as the signal to change the route of administration and reported financial savings and patient benefit stemming from a shorter ICU stay.

Route of administration IV insulin is indicated for patients with T1DM and moderate-to-severe DKA (pH <7.2 and bicarbonate <10 mmol/L) while mild DKA (pH 7.2–7.3 and bicarbonate 10–15 mmol/L) can be treated with either subcutaneous or IV insulin, depending on the clinical situation. Several studies have compared different dosages and schedules.

Sodium

The corrected sodium concentration should be calculated and monitored and should increase with treatment. A failure of the serum sodium level to increase or a decrease in the level despite treatment is associated with an increased risk of cerebral edema. In this situation, the sodium content of the fluid being administered may need to be increased.

Potassium

As previously mentioned, despite total body potassium depletion, serum potassium levels might be normal or even increased in response to transcellular shifts resulting from insulin deficiency and acidosis. Potassium levels quickly decrease with insulin therapy; therefore, to prevent fatal arrhythmias secondary to severe hypokalemia, insulin should not be given until an initial potassium level is obtained. If the serum potassium concentration cannot be measured immediately, an electrocardiogram should be obtained to assess for signs of hyperkalemia or hypokalemia. Potassium needs to be replaced depending on the initial serum concentration. The level must be checked at least hourly. If the initial serum potassium level is increased, give insulin without supplemental potassium until the patient's ability to urinate is ensured. If the initial serum potassium level is normal, give potassium (40 mEq/L) with IV fluids when insulin administration is started. If the initial serum potassium level is low, replete potassium when beginning volume resuscitation and before initiating insulin. IV potassium administration should not exceed a rate of 0.5 mEq/kg/h. If the serum potassium level remains low despite supplementation during insulin infusion, consider adding oral potassium supplementation or slightly decreasing the insulin infusion rate. Potassium can be given as potassium chloride, potassium phosphate, or potassium acetate. To avoid administering excess chloride and exacerbating hyperchloremia associated with saline administration, potassium can be replenished with half potassium phosphate and half potassium chloride or acetate, as long as serum calcium levels are monitored to avoid hypocalcemia resulting from phosphate administration.

Phosphate

Like potassium, phosphate is lost with osmotic diuresis. IV fluids decrease phosphate levels, and insulin exacerbates this change by causing the intracellular movement of phosphate. Symptoms of profound hypophosphatemia emerge with decreasing intracellular concentrations of adenosine triphosphate and 2,3-diphosphoglycerate, that is, when the plasma levels decrease to <0.32 mmol/L. Severe hypophosphatemia can occur in the setting of prolonged fasting (>24 hours). No data have demonstrated significant clinical benefits from phosphate repletion, and phosphate administration can result in hypocalcemia. However, if the patient has unexplained severe muscle weakness or decreased cardiac function, phosphate administration should be considered.

Magnesium

Serum magnesium levels can be low in patients with DKA, but they tend to normalize with resolution of the acidosis and with oral intake. There is no evidence supporting repletion of magnesium in the management of DKA.

Bicarbonate

Bicarbonate administration is not recommended or indicated in the management of DKA. Studies suggest that bicarbonate administration is associated with longer hospital stays for children, paradoxical worsening of ketosis in adults, and hypokalemia. Not only can bicarbonate exacerbate hypokalemia and decrease tissue perfusion by decreasing oxygen delivery but it has also been strongly associated with the development of cerebral edema in children. The mainstay of treatment of acidosis is fluid replacement and insulin. Fluids improve tissue perfusion and increase the glomerular filtration rate, enhancing the excretion of acid, and insulin inhibits the underlying ketone production.

COMPLICATIONS

The most common complications of DKA are hypokalemia and hypoglycemia, which occur in response to treatment. Thus, blood glucose and electrolyte concentrations must be monitored frequently throughout the course of DKA management. Cerebral edema, the most feared complication, is exclusive to pediatric patients with DKA.

Cerebral edema is a potentially devastating complication of pediatric DKA. It occurs in up to 1.5% of cases, with a mortality rate as high as 24%. Numerous factors have been implicated in the pathophysiology of DKA-related cerebral edema, but no single mechanism has been definitively proven as causative. Ischemic and cytotoxic edema secondary to acidosis decrease cerebral perfusion. Vasogenic edema that causes direct damage to cerebral vascular endothelium increases blood-brain permeability. Risk factors for DKA-induced cerebral edema are listed in **Box 2**. Typically, cerebral edema occurs within 4–12 hours after initiation of treatment, but its onset can be delayed up to 24–48 hours after initiation of treatment.

BOX 2: Risk factors for pediatric DKA-induced cerebral edema.

- New-onset diabetes
- Younger age
- Longer duration of DKA symptoms
- Degree of acidosis at presentation (pH 50 mL/kg in the first 4 h)
- Administration of insulin during the first hour of fluid resuscitation
- Higher blood urea nitrogen at presentation
- Slower increase in measured serum sodium concentration during treatment of DKA
- Bicarbonate treatment

Regular neurologic checks along with assessment of vital signs are crucial. Mental status changes, which can range from somnolence to irritability, are worrisome, as are focal neurologic deficits. Age-inappropriate incontinence can be a sign of cerebral edema. Complaints of headache should be considered seriously. The combination of hypertension, bradycardia, and irregular respiration (Cushing triad) is a sign of increased intracranial pressure. Hypoxemia can also result from compression of the brain's respiratory center, leading to impending brain herniation. When it is suspected based on clinical signs and symptoms, treatment should be initiated immediately. Treatment should never be postponed to wait for confirming computed tomography (CT) imaging; changes that indicate cerebral edema that can be seen on CT images occur late in its development.

Treatment includes elevation of the head of the bed and reduction of IV fluids by one-third. Mannitol should be administered at a dose of 0.5–1 g/kg IV over 20 minutes. This regimen can be repeated if there is no clinical response within 30–120 minutes. Mannitol decreases blood viscosity and thus improves cerebral blood flow acutely. Caution with its use is warranted, however, because mannitol can induce diuresis, thereby decreasing intravascular volume and causing hypokalemia. This may result in hypotension and, subsequently, decreased cerebral blood flow. Alternatively, 3% hypertonic saline can be given at a dosage of 5–10 mL/kg over 30 minutes, either instead of or along with mannitol. Hypertonic saline lowers intracranial pressure, increases intravascular volume, and increases mean arterial pressure. Patients might require intubation and mechanical ventilation to manage respiratory depression and avert impending respiratory failure. Patients with intracranial hypertension may be cautiously hyperventilated; however, hyperventilation to a PCO_2 <22 mm Hg should be avoided.

DISPOSITION

Established diabetics with mild DKA who are alert and tolerating oral fluids can be treated in the emergency department and discharged, provided they have close supervision at home, possess the proper medications and supplies, have been educated about insulin administration, have the ability to monitor their blood glucose level, and have access to close follow-up. Patients with new-onset diabetes must be admitted. Patients requiring IV rehydration over an extended period need to be admitted to a unit capable of hourly blood glucose measurement and frequent measurement of vital signs and neurologic checks. Patients with severe DKA should be admitted to the ICU, especially if they have had a long duration of symptoms, any hemodynamic instability, altered mental status, a high risk of cerebral edema [e.g., age <5 years low PCO_2 high blood urea nitrogen (BUN)].

SUMMARY

Despite advances in research and treatment, the incidence of pediatric-onset diabetes and DKA is increasing. Diabetes mellitus is one of the most common chronic pediatric illnesses

and, along with DKA, is associated with significant cost and morbidity. DKA is a complicated metabolic state hallmarked by dehydration and electrolyte disturbances. Treatment revolves around proper fluid resuscitation with insulin and electrolyte replacement under constant monitoring for cerebral edema, which is the deadliest complication. When DKA is recognized and treated immediately, the prognosis is excellent. However, when a patient has prolonged or multiple courses of DKA or if DKA is complicated by cerebral edema, the results can be devastating.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Pediatric Seizure

Devendra Richhariya

INTRODUCTION

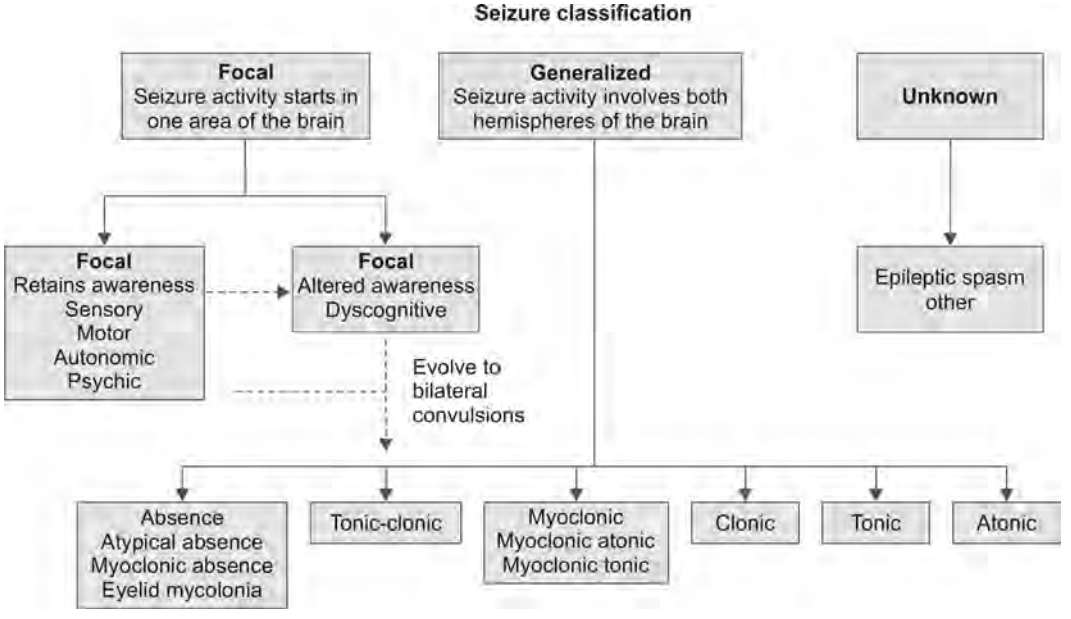
Seizure is paroxysmal involuntary motor activities, which cause changes in behavior, sensation, and/or consciousness due to abnormal electrical discharge in the brain. Seizures are most common neurologic emergency in pediatric age group. Seizures occur in approximately 1% of children up to 14 years of age. Incidence is highest in the first year of life (120 per 100,000). Seizure may be classified as focal and generalized (**Flowchart 1**). Seizure may range from subtle, nonconvulsive episodes to stereotypic movements to major generalized convulsions. Severity of seizures varies widely. It may be self-limited episodes with no hemodynamic compromise like febrile convulsions to prolonged events that may ultimately be fatal in as many as 3–4% of patients. Extensive evaluation and emergency management are essential in high-risk patients as in status epilepticus, neonatal seizures.

CAUSES

A seizure is a single event characterized by the abnormal excessive synchronized firing of cortical neurons that usually results in altered perception or behavior and recurrent unprovoked seizures labeled as epilepsy. Seizures could be multifactorial **Table 1**. A cause is identifiable in <20% of children with seizures. The most common etiology of neonatal seizures is hypoxic-ischemic encephalopathy (initial 48 h of life) and meningoencephalitis.

PATHOPHYSIOLOGY OF THE CONDITION

A seizure is a single event, which is characterized by the abnormal excessive synchronized firing of cortical neurons which causes involuntary muscle contractions with or without alteration in mental status. Focal seizure starts from unilateral



FLOWCHART 1: Classification of seizures.

area of brain (**Fig. 1**) while generalized seizures arise from both cerebral hemispheres at once. The manifestations of focal seizures depend on the area of the brain involved. Localized seizures may then spread to adjacent areas or to contralateral or other more distant regions through thalamocortical and interhemispheric pathways (**Fig. 2**), eventually resulting in secondarily generalized seizures. Aberrant electrical activity and subsequent manifestation of the seizure may range from subtle, nonconvulsive events to stereotypic movements to dramatic generalized convulsions. Neonatal seizures are typically subtler than seizures in older children and adults, in view of the immature nervous system of the neonates.

Benign febrile seizures (convulsions) are an inherited predisposition to developing a tonic-clonic seizure with a high fever (**Fig. 3**). The description is limited to convulsions associated with high fever in children under the age of 5 (usually between 6 and 36 months of age), with no cause for the seizure other than the fever. Benign febrile seizures are common, occurring in 3–5% of children under the age of 5. Most patients have only one or two seizures. Recent genetic analysis of families with febrile convulsions has defined specific associated gene defects.

TABLE 1: Causes of seizures.

Provoked seizures (seizure with an acute antecedent cause)	*Unprovoked seizures (no immediate provoking factor)*

• Hypoglycemia
• Toxic exposure
• CNS infection (meningitis, encephalitis)
• Head injury
• Other precipitating factors:
  ○ Fever
  ○ Immunization
	• Cryptogenic (no known cause)
	• Idiopathic (genetic)
	• Remote symptomatic (preexisting brain abnormality or insult):
	  ○ Hydrocephalus
	  ○ Disorders of brain development
	  ○ Neoplasms

Autonomic and Metabolic Changes due to Seizures

Patients of seizure may present with changes in autonomic system such as changes in pulse rate, sweating, salivation,

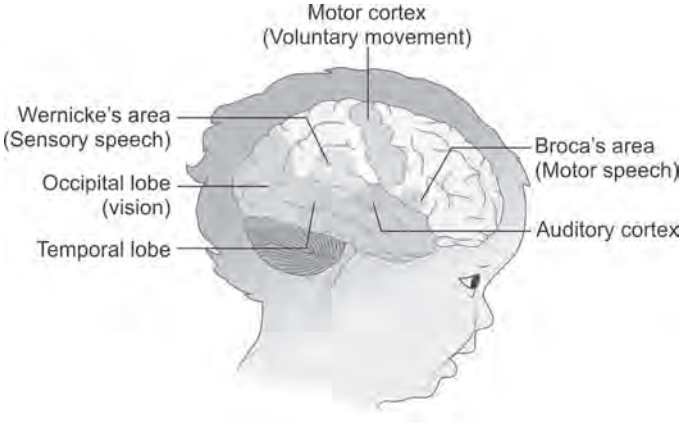


FIG. 1: Brain areas affected by Focal seizures.

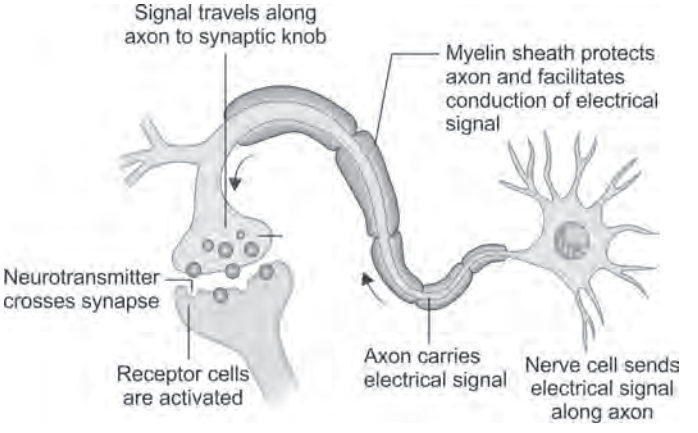


FIG. 2: Propagation of Focal seizures.

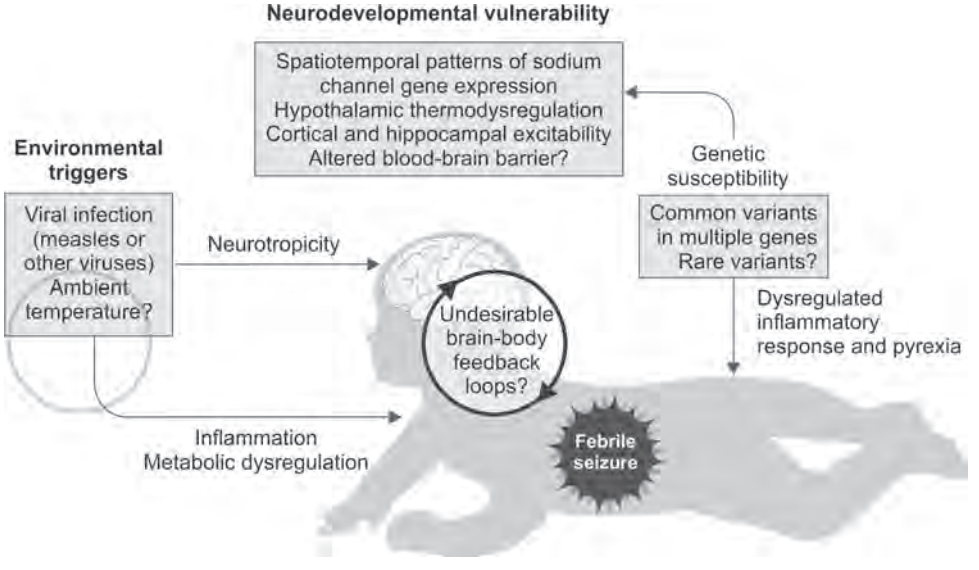


FIG. 3: Etiopathogenesis of the febrile seizure.

pupillary dilatation, and incontinence. And patient of generalized tonic-clonic seizures presents with an increase in blood pressure and pulse rate, increased autonomic nervous system activation, a metabolic acidosis, a drop in PO_2 and an increase in PCO_2 during the apneic tonic phase, and, rarely, hyperkalemia or rhabdomyolysis. Prolonged generalized tonic-clonic seizures may have serious consequences.

In seizure, following changes occur in blood. Blood flow to brain and glucose utilization increased. Increase in lactate, extracellular potassium, and serum prolactin, and a decrease in extracellular calcium are helpful in identifying true seizure. Prolactin also may be elevated after syncope and hence cannot differentiate seizures from syncope.

CLINICAL PRESENTATION

Depending upon the area in the brain where the seizure initiates and how it propagates symptoms could vary widely.

- Generalized seizures cause loss of consciousness along with purposeless full-body tonic (sustained)-clonic (interrupted) movements, atonia, and/or myoclonic jerking.
- Focal seizures can manifest as disturbances in motor/sensory/autonomic function, emotional state, cognition, behavior, or memory with or without alteration in consciousness
- At the cessation of seizure activity, the patient will enter the postictal period, characterized by confusion, fatigue, lethargy, and/or irritability.
- Neonatal seizures may present with subtle findings, such as ocular movement or lip smacking or abnormal vitals.
- Nonconvulsive status epilepticus can present as altered mental status, mild confusion, and subtle physical movements, inexplicable sudden changes in mental status or delayed recovery after a seizure.
- *Clinical features of concern (red flags) are* seizure in clinically unwell child, such as symptoms of infection, meningeal signs, dehydration, complex febrile seizure, altered level of consciousness, and additional risks for serious bacterial infection (age <6 months or >60 months with first febrile seizure, age <12 months with incomplete or unknown immunization history and febrile status epilepticus) and first nonfebrile seizure.

FEBRILE CONVULSION

Febrile convulsion is defined as seizure in neurologically normal child of 6 months–5 years with a temperature of >38°C (100.4°F) which has no identifiable cause or previous history of afebrile seizures. Febrile convulsion is the most common seizure disorder in childhood. It affects 2–5% of children between 6 months and 5 years age group, with peak incidence at 18 months. Around 6–15% occurs after 4 years, onset after 6 years is unusual. Febrile seizures generally occur during viral or bacterial infections. They sometimes occur after vaccinations such as measles, mumps, and rubella. Genetic and familial factors increase the susceptibility to febrile seizures. Febrile seizures usually take place during the initial rapid rise in body temperature, and mostly develop within 24 hours of fever onset. Typically, seizures are generalized; most are clonic, but some can manifest as periods of atonic or tonic posturing. Febrile seizures may be simple or complex:

- *Simple febrile seizures*:
  - Brief (<15-min) generalized seizures
  - Association with fever (temperature >38.0°C)
  - Predominantly generalized tonic-clonic seizure activity
  - Only one convulsion in a 24-hour period
  - Brief postictal period
  - Absence of preexisting neurological abnormality (intracranial infection, metabolic disturbance, or history of afebrile seizures)
- *Complex febrile seizures*:
  - Last ≥15 minutes continuously or with pauses
  - Have focal features
  - Recur within 24 hours

Febrile convulsion is established after exclusion of other possible causes. Fever may trigger seizures in a child with previous afebrile seizures and such events are not considered febrile seizures. >90% febrile seizures are simple. Routine testing is not required for simple febrile seizures other than to evaluate the source of the fever. Complex seizures, seizures with neurologic deficits, or signs of a serious underlying disorder (e.g., meningitis and metabolic disorders) warrant appropriate investigations.

- *Recurrence and subsequent epilepsy*: Recurrence rate of febrile seizures is nearly 35%. Risk of recurrence is higher if first seizure occurs in <1 year of age or history of febrile seizure is positive in first-degree relatives. Risk of developing an afebrile seizure disorder after having ≥1 simple febrile seizure is slightly higher (2–5%) than the baseline risk of developing epilepsy (2%). In children who have additional risk factors (e.g., complex febrile seizures, family history of seizures, and developmental delay); this risk is increased up to 10%. Prolonged febrile status epilepticus may be associated with damage to vulnerable parts of the brain such as the hippocampus.
- *Afebrile seizures*: A vast differential is to be considered in afebrile child with seizures. It could be a presentation of epilepsy or could be a symptom of another process, such as intracranial tumor or infection, metabolic derangement, toxic ingestion, neurocutaneous syndrome, or trauma.

STATUS EPILEPTICUS

Status epilepticus is a state of continuous seizures without return of normal neurologic function between them. Any of the classified seizures types may progress to status epilepticus. Status epilepticus can be convulsive or nonconvulsive. Convulsive status epilepticus is a medical emergency that can be produced by either primary generalized or secondary generalized tonic-clonic seizures. Nonconvulsive status epilepticus refers to either absence or complex partial status epilepticus. In either case, the patient does not have major motor seizures but is abnormal cognitively and may appear to be in a fugue state. Absence status appears to have no morbidity (unless injuries occur during the status), but complex partial status may lead to permanent cognitive deficits.

Status epilepticus is defined as—three or more seizures in an hour, a single prolonged seizure lasting at least 30 minutes with a motor component, and two or more convulsions without complete recovery of consciousness between seizures. Approximately 10% of children presenting with active seizure to the hospital are in status epilepticus. Nearly, one-third of them are related to fever, other etiologies include central nervous

system infections, ingestions and trauma, and antiepileptic drug withdrawal (most common cause in emergency department). Metabolic abnormalities, brain tumors, cerebral infarction, cerebral hemorrhages, and meningitis are the important causes of status epilepticus. Metabolic causes of status epilepticus are hypocalcemia, hyponatremia, hypoglycemia, liver failure, renal failure, and anoxia.

Open head trauma produced by bullets or shrapnel is associated with a 50% or greater chance of developing epilepsy. Closed head trauma, such as after automobile accidents or blunt injuries, carries a much lower risk (5% or less). Factors that predispose to the development of epilepsy after head trauma include a seizure within 2 weeks of injury, depressed skull fracture, loss of consciousness for longer than 24 hours, cerebral contusion, subdural hematoma, or subarachnoid blood, and age >65.

Nonconvulsive status epilepticus no convulsive status epilepticus can present as a continuous or fluctuating "epileptic twilight" state or as a prolonged postictal state. It must be considered in any child with altered mental state where no other cause could be diagnosed.

Neonatal seizures: The most common etiology of neonatal seizures is hypoxic-ischemic encephalopathy, usually manifesting within 48 hours of life. Still infection can be a significant trigger for seizures in neonates. So, possible meningoencephalitis is to be ruled out in this population.

EVALUATION

Most of the seizure activities stop before reaching emergency department so the detailed history usually is the guide to the diagnosis. In children presenting with seizure attack, a physical examination should address their cardiac, neurological, and mental status, and should include a developmental assessment where appropriate. Some findings are important in some specific conditions (**Box 1**).

Seizures can be partial (simple or complex partial, or partial with secondary generalization), generalized tonic-clonic, or tonic seizures. After stabilization of the child, it is important to determine if a seizure has occurred, and if so, if it is the child's first episode. Children can present with seizure-like symptoms that may not in fact represent actual seizures, but rather breath-holding spells, syncope, gastroesophageal reflux, pseudoseizures (psychogenic), and other nonepileptic events. The determination that a seizure has occurred is usually based on a detailed, careful history, and neurologic examination. Tests to exclude other disorders are determined clinically.

BOX 1: Evaluation of seizures.

History

- Age of child
- Onset, duration, progress and description of seizure activity
- History of trauma
- History of possible ingestion
- History of fever
- History of associated illness (vomiting or diarrhea)
- Feeding problems (especially in an infant)
- Changes in behavior
- Previous history of seizures and type of seizures
- Anticonvulsants dose and recent changes/missed doses
- Recent new medications (may alter metabolism of antiepileptic drugs)
- Allergies
- Other medical history
- Developmental history
- Family history of seizures
- Seizure-specific questions can be asked:
  - Was there a warning right before the convulsion (behavioral arrest, affective change)?
  - Did the head/eyes deviate upward or to one side?
  - Did the movements start unilaterally or bilaterally?
  - What was the child like immediately after and how long to recover to baseline?

Physical examination:

- *CNS infection*: Fever, headache, prolonged seizure, prolonged postictal state, Stiff neck, and confusion
- *Head trauma*: History, external evidence, and focal deficit
- *Brain tumor*: Headache, focal seizure, and focal deficits
- *Genetic syndromes and brain malformations*: Developmental delay and dysmorphism
- *Cerebral hemorrhage*: Trauma, family history of cerebral cavernous malformations, focal seizures, and focal deficits
- *Neurocutaneous disorders*: Birthmarks (hypopigmented macules, café au lait spots, etc.)

INVESTIGATIONS

- *Serum laboratory studies*: Serum glucose, sodium, calcium, magnesium, phosphorus, complete blood count, and liver and kidney function tests to rule out metabolic disorders if the history includes recent vomiting, diarrhea, or impaired fluid intake; if there are signs of dehydration or edema; or if a complex febrile seizure occurs. They are not required routinely in simple febrile seizures.
- *Electroencephalography (EEG)*: EEG should be performed within 24–48 hours only to support a diagnosis of epilepsy, in seizures with focal features, recurrent seizures, and first afebrile unprovoked seizures (**Fig. 4**). It is not recommended after an initial simple febrile seizure in children with a normal neurologic examination. When a standard EEG is not contributory, sleep EEG or long-term video or ambulatory EEG can be considered where appropriate. EEG and magnetic resonance imaging (MRI) are helpful in localizing the brain lesions (**Table 2**).
- *Neuroimaging computed tomography (CT)/MRI*: Neuroimaging should be used to identify underlying structural abnormalities that cause certain epilepsies. *MRI brain* is investigation of choice in children with epilepsies especially in these situations; epilepsies before the age of 2 years, signs of raised intracranial pressure, failure to control the seizures, and worsening of seizures. *CT brain is recommended* in suspected gross pathology, if MRI is unavailable or is contraindicated, in an acute emergency, CT can be used to determine whether a seizure has been due to acute neurological lesion or illness.

- *Lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis are indicated*—seizure in a child <6 months, persistent alteration of mental status of unknown cause or failure to return to baseline, seizure with suspected meningitis or meningitis or intracranial infection by history or examination, seizures after several days of febrile illness, and seizure with fever in those who are not fully immunized or taking antibiotics.

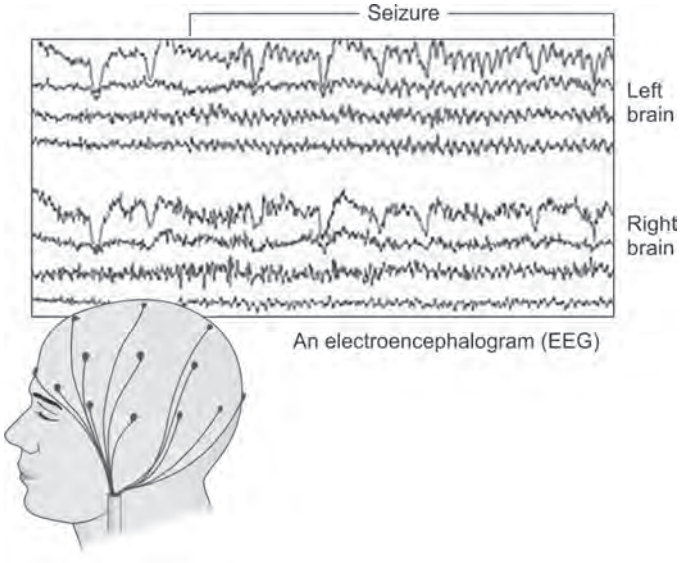


FIG. 4: EEG for localizing the seizure activity.

If increased intracranial pressure is suspected, the LP should be preceded by an imaging study of the head.
- *Other test like 12-lead electrocardiogram (ECG)* should be considered only in cases of diagnostic uncertainty in pediatric age group. *Neuropsychological assessment* is suggested in selected patients.

ANTIEPILEPTIC DRUGS

The choice of antiepileptic drugs is dictated by the types of seizures that the patient has (**Table 3**). If possible, monotherapy should be used. The selections are based on side effects as well as effectiveness. Phenobarbital and primidone are as efficacious as phenytoin and carbamazepine but are more likely to produce side effects. Tonic and atonic seizures are often resistant to therapy, and valproate seems to be most efficacious. Tonic and clonic seizures may be secondarily generalized, and phenytoin, carbamazepine, lamotrigine, topiramate, and felbamate can be helpful.

TREATMENT

There are limited data on pediatric seizures to lead to a consensus protocol. There are varieties of guidelines and algorithms endorsed by different organizations and institutions around the globe. Though they have variations, the essential management pathways are quite similar. Immediate measures for a seizing child in ED, should be taken and they are secure airway, give high-flow oxygen, assess breathing and circulation, assess vital signs, check blood glucose,

TABLE 2: EEG localization features and common causes of seizures.

Region	*Typical semiology*	*EEG*	*Etiology*
Frontal	Often nocturnal, occurs in clusters, often brief <30 sec. Other symptoms relate to subregion of frontal lobes (adversive turning). Complex motor automatisms such as bicycling, pelvic thrusting or other sexual gestures. Vocalizations common, minimal postictal symptoms	Frontal or anterior vertex epileptiform discharges. Occasionally frontal bisynchronous discharges	Trauma, malformations such as cortical dysplasia or cavernous angiomas, strokes, tumors, infections, and anoxia. Some genetic syndromes
Mesial temporal	*Auras common*: Olfactory, gustatory, rising epigastric sensation, déjà vu, experiential phenomenon behavioral arrest, automatisms of the mouth (oroalimentary), and ipsilateral hand (manual). Semipurposeful or repetitive stereotypical movements. Contralateral dystonic posturing. Significant postictal confusion	Temporal epileptiform discharges localized to anterior temporal region or sphenoidal electrodes, if used. Rhythmic theta activity	Mesial temporal sclerosis, postinfectious, and trauma
Lateral temporal	Auras more likely to be auditory, vertiginous, visual distortions, and early aphasia symptoms	Lateral temporal epileptiform discharges and rhythmic theta activity	Lateral cortical lesions and dysplasias. Cavernous angiomas. Genetic
Parietal	Rare. May reflect activity of association cortex activity and include elementary or unusual formed sensory phenomena, nausea/abdominal, dysphasia, or speech arrest	Parietal epileptiform discharges	Usually due to cortical lesions such as infarcts, cortical dysplasia, and malignancies
Occipital	Usually consists of unformed visual phenomena. May be negative visual symptoms	Occipital epileptiform discharges, unilateral, or bisynchronous	Cortical lesions such as infarcts, dysplasia, or malignancies, but also as an idiopathic epilepsy syndrome (benign epilepsy with occipital paroxysms)

TABLE 3: Choice of antiepileptic drugs for specific type of seizures.

	Seizures			*Epilepsies*	
	Partial seizures and localization-related seizures	***Tonic-clonic***	***Generalized absence***	***Myoclonic***	***Atonic/tonic***
First-line drugs	Carbamazepine, phenytoin lamotrigine, valproate, and oxcarbazepine	Valproate, lamotrigine, phenytoin, and carbamazepine	Ethosuximide and valproate	Valproate, lamotrigine, and topiramate	Valproate, lamotrigine, and topiramate
Second-line drugs	Primidone, phenobarbital, felbamate	Topiramate, primidone, phenobarbital, and felbamate	Topiramate, lamotrigine, and clonazepam	Primidone, phenobarbital, clonazepam, ethosuximide, and felbamate	Phenytoin, phenobarbital, primidone, clonazepam, and felbamate
Add-on drugs	Topiramate, levetiracetam, zonisamide, gabapentin, and tiagabine	Levetiracetam and zonisamide	Zonisamide	Levetiracetam and zonisamide	Levetiracetam and zonisamide

- *Decision regarding stopping the antiepileptic should be taken only after consulting the pediatric neurologist*
- *Recurrence of seizure* can occur when following abnormalities are present: neurologic abnormalities, mental retardation, complex partial seizures, and consistently abnormal EEGs

secure IV access in a large vein, place patient on full monitor, and followed by medications depending on seizure type and underlying cause.

Treatment of Febrile Seizure

Antipyretic therapy is to be given to relieve symptoms of associated febrile illness but they do not reduce seizure activity. Supportive therapy is usually sufficient for seizures lasting <15 minutes as most of the seizures are brief and self-limiting. Rectal diazepam can be used. Seizures lasting ≥15 minutes are treated in the line of status epilepticus. Maintenance drug therapy is usually not indicated.

Treatment of Neonatal Seizure

Maintain airway, breathing, circulation, and temperature. Collect blood for biochemistry. Check blood glucose immediately, correct glucose and calcium, and administer IV phenobarbitone 20 mg/kg. Repeat in 5 mg/kg boluses every 15 minutes, if seizure continues up to a maximum dose of 40 mg/kg. IV phenytoin 15-20 mg/kg diluted in same amount of normal saline at a maximum rate of 1 mg/kg/min over 35–40 minutes. IV lorazepam (0.05–0.1 mg/kg) or diazepam (0.25 mg/kg bolus or 0.5 mg/kg rectal) or IV midazolam as a continuous infusion an initial IV bolus of 0.15 mg/kg, followed by continuous infusion (1 μg/kg/min) increasing by 0.5–1 μg/kg/min every 2 minutes until a favorable response or a maximum of 18 μg/kg/min 100 mg pyridoxine IV or oral (if IV not available) should be given.

Treatment of Status Epilepticus

- *In the community*, prolonged (lasting 5 minutes or more) or repeated (3 or more in an hour) generalized, convulsive (tonic–clonic, tonic or clonic) seizures in the community should receive immediate emergency care. If history of previous episode of prolonged or serial convulsive seizures is present, buccal midazolam or rectal diazepam can be given. Care must be taken to secure airway and assess respiratory and cardiac function. *Patient in ED*—convulsive status epilepticus can lead to permanent neuronal injury. Majority of the seizures are brief and self-limiting. If a seizure activity lasts for >5 minutes, the chances are more that the seizure is likely to be prolonged. Keeping that in mind, all the status treatment protocols have used a 5-minute definition. Early treatment minimizes risk of seizures reaching 30 minutes and subsequent neuronal damage. Moreover, the adverse outcomes associated with needlessly intervening on brief, self-limited seizures are eliminated by avoiding aggressive therapy before 5 minutes.
- *Stabilization (0–5 minutes)*: Assess and stabilize patient's airway, breathing, and circulation. Give high-flow oxygen, if oxygenation is impaired. Consider intubation if assisted ventilation is required. Take quick history. Perform physical examination with stress on neurological examination. Check blood glucose and correct with IV dextrose if CBG <60 mg%. For children of ≤2 years: 4 mL/kg, for children >2 years: 25D 2 mL/kg 2 mL/h. Secure IV or IO access immediately. Collect blood for complete hemogram, electrolytes, toxicology screen, and antiepileptic drug levels where appropriate.
- *First-line therapy (5–20 minutes):* Benzodiazepines are the initial therapy of choice. Any one of the three benzodiazepines can be used: IM midazolam (10 mg for >40 kg, 5 mg for 13–40 kg, single dose) or IV lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once) or IV diazepam (0.15–0.2 mg/kg/dose, max: 10 mg/dose, one repeat dose can be given). If none of the above options are available, any one of the following drugs can be used:

IV phenobarbital (15 mg/kg/dose, single dose), rectal diazepam (0.2–0.5 mg/kg, max: 20 mg/dose, single dose), and intranasal/buccal midazolam.

- *Second-line therapy (20–40 minutes):* If there is a lack of response to the therapy administered in the previous phase, the following can be administered as a single dose: IV fosphenytoin (20 mg PE/kg, max: 1,500 mg PE/dose, single dose), IV valproic acid (40 mg/kg, max: 3,000 mg/dose, single dose), and intravenous levetiracetam (60 mg/kg, max: 4,500 mg/dose, single dose). If none of the above are available, intravenous phenobarbital (15 mg/kg, single dose), if not given already.
- *Third-line therapy (40–60 minutes):* At this juncture, no clear evidence is there to guide the therapy.
- If the seizure continues, second-line therapy can be repeated or anesthetic doses of thiopental, midazolam, pentobarbital, or propofol can be administered. EEG monitoring is necessary at this phase. Based on the cause and severity of the seizure, the second- of third-line therapy can be initiated at an earlier time, if necessary. If at any point the patient responds to therapy and is at baseline, symptomatic medical care should be initiated. Treatment of nonconvulsive status epilepticus is less well defined. Most forms are not life-threatening. Initial treatment is similar to generalized convulsive status epilepticus. Treatment of status epilepticus is summarized in **Table 4**.

TABLE 4: Protocol for treatment of status epilepticus.

0–5 min	• Provide for maintenance of vital signs. Maintain airway. Give oxygen. Observe and examine patient • Obtain 50 mL of blood for glucose, calcium, magnesium, electrolytes, blood urea nitrogen, liver functions, anticonvulsant levels, CBC, and toxicology screen. Begin normal saline IV and give 50 mL of 50% glucose and 100 mg of thiamine. Monitor EKG, blood pressure, and if possible, EEG
5–20 min	• Use intravenous lorazepam to stop seizures, 0.1 mg/kg at 1–2 mg/min • If seizures continue, load with phenytoin using fosphenytoin 20 mg phenytoin equivalents (PE)/kg at 150 mg PE/min. If cardiac arrhythmia or hypotension occurs, slow the infusion rate
20–40 min	If seizures persist 10–20 min after administration of phenytoin, give an additional 10 PE/kg. If seizures continue, intubate patient. Consider phenobarbital at a rate of 50–100 mg/min until seizures stop or 20 mg/kg is given. Alternatively move to anesthetic agents
40–60 min of status	Review laboratory results and correct abnormalities. Arrange for anesthesia, neuromuscular blockade, and EEG monitoring. Options include midazolam (0.15–0.2 mg/kg load, then 0.06–1.1 mg/kg/h) or propofol (1–2 mg/kg load, then 3–10 mg/kg/h), or barbiturate anesthesia (pentobarbital, 6–15 mg/kg loading dose, then 0.5–5 mg/kg/h). Pentobarbital often causes circulatory collapse, so be prepared to administer a pressor agent such as dopamine

(CBC: complete blood count; EEG: electroencephalogram; EKG: electrocardiogram)

SUMMARY

Admission should be considered for infants <6 months, children with complex features, seizures are uncontrolled or prolonged, and social concerns. Management of seizures includes airway, breathing, circulation, check glucose, stop seizures, prevent, or correct metabolic complications. Identify and treat underlying causes.

MULTIPLE CHOICE QUESTIONS

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173 CHAPTER

Pediatric Oral and Dental Emergencies

Trevor L Tredway

INTRODUCTION

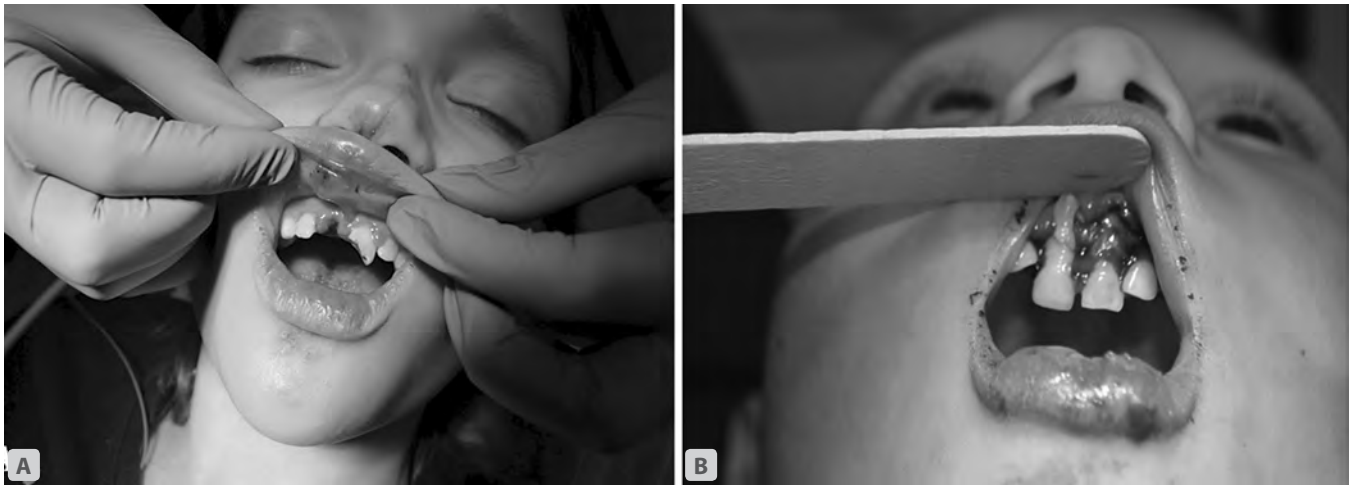
Oral injuries are a very common occurrence in childhood. It has been reported that traumatic dental injuries comprise 5% of the injuries for which people seek treatment. A child's oral cavity and teeth can be injured by accidental falls, motor vehicle accidents, or during sports activities. Trauma to the oral structures can involve the teeth and the surrounding tissues and supporting structures. A literature review in 2008 revealed that about 25% of all schoolchildren experience dental trauma and 33% of adults have had some type of dental injury to their permanent dentition usually by 19 years of age. Types of oral and dental injuries that may present to the emergency department (ED) are represented in **Figures 1A** and **B**. The majority of hospitals do not have dental services available to handle these types of traumatic injuries. Therefore, proper ED evaluation, diagnosis, treatment, and follow-up planning are warranted to ensure the best clinical outcome. The International Association of Dental Traumatology developed guidelines for evaluation and management of traumatic dental injuries.

Tooth Anatomy

Anatomically a tooth has a crown and root portion (**Fig. 2**). The external surface of the crown is covered by white enamel and the external surface of the root is covered by cementum. The cementoenamel junction (cervical line) is the point where the crown and root meet. The second layer of the tooth is composed of yellow/tan dentin, which makes up the majority of the tooth. The center of the tooth consists of the pulp tissue where the neurovascular supply is located. The pulp has a red to pink color when visible. Understanding the anatomy of the tooth enables the provider to evaluate the dental injury appropriately and determine the best course of action for treatment.

Pediatric Soft Tissue Injuries of the Oral Cavity

Pediatrics soft tissue injuries of the oral cavity can include abrasions, lacerations, and perforations. Soft tissue injuries may occur in isolation but they can also be associated with injuries to the dentition. Every assessment of oral soft tissue injuries must include adequate attention and examination of the dentition.



FIGS. 1A AND B: Pediatric oral and dental trauma. (A) 12 years of age female that fell while riding her bike and sustained oral/dental injuries. (B) 3 years of age male that fell onto a concrete sidewalk and sustained a dental injury. ***(For color version, see plate 29)***

- *Abrasions*: Superficial abrasions will usually heal without any complications and routinely do not require any intervention or repair in the ED. Abrasions can also be associated with other underlying injuries so as with contusions, careful examination and inspection of all adjacent structures are indicated.
- *Lacerations*: Intraoral lacerations are very common in children. Small intraoral lacerations with well-approximated margins do not require intervention or repair. Bleeding usually subsides spontaneously and healing takes place by itself. Children are often placed on soft diets with avoidance of salty or spicy foods until the wound has healed. Large lacerations with extensive tissue damage or uncontrolled bleeding will require careful examination and repair. Additionally, intraoral lacerations have communication between the intraoral surface and the outer skin surface ("through-and-through") will require surgical closure. This should be done in layers with the mucosal layer being closed first, then the muscle layer next and then finally the skin surface layer. Intraoral lacerations should always be investigated for possible foreign bodies but specifically those caused by tooth penetration.
- *Special lacerations*: Lacerations of the frenulum and the tongue tend to bleed profusely and can be very traumatizing to the patient and their parents. Hemostasis of frenulum lacerations can be achieved by direct pressure. These frenulum lacerations do not require any type of intervention or repair just parental reassurance (**Fig. 3**).

  Most tongue lacerations do not require repair and heal spontaneously. However, tongue lacerations with certain characteristics do require repair (**Figs. 4A** and **B**). These include bisecting lacerations, large flap-like lacerations, gaping lacerations, U-shaped lacerations, partial amputation type lacerations, or those lacerations where hemostasis cannot be achieved with direct pressure.

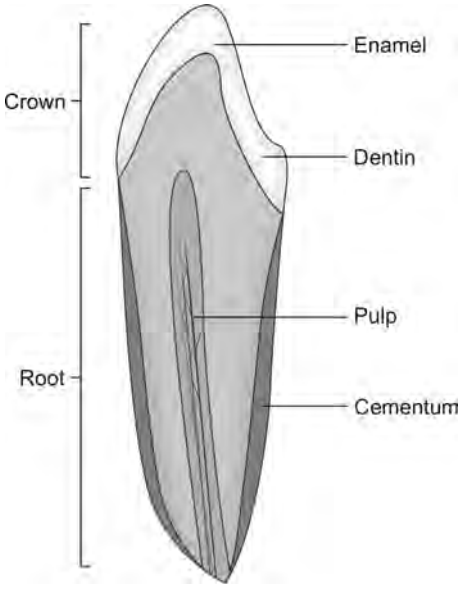


FIG. 2. Tooth diagram.

FIG. 3: Frenulum laceration. 18-month-old male that fell and sustained frenulum laceration. No intervention was required and he was discharged to home. ***(For color version, see plate 29)***

FIGS. 4A AND B: Tongue laceration. (A) 8 years of age male who sustained tongue laceration while jumping on a trampoline. (B) Laceration repaired with horizontal mattress sutures in the ED with procedural sedation. ***(For color version, see plate 29)***

- *Perforations*: These wounds are typically the result of a child falling with an object in their mouth. In these instances, the injury can be a small but deep perforation of the oral cavity or oropharynx. Careful inspection of the wound for any retained foreign body is important. When the perforation involves the posterolateral palate or a tonsillar pillar, one must also consider the possibility of damage to the large vessels residing in this region of the neck. A computed tomography scan of the region may be required to further evaluate the injury. In the majority of cases, no repair is needed for perforation injuries.

Pediatric Dental Trauma

Most hospitals do not have dental services available and thus the evaluation, diagnosis, and treatment of the patient fall on the providers in the ED. Most dental injuries that present do not require emergent intervention, however, to most parents any dental injury to their child seems emergent at the time. Providers that can adequately evaluate the patient with a dental injury can also provide reassurance to the parents. One resource that providers should have available in the ED is some form of dental splinting. This will allow them to stabilize an injured tooth initially until appropriate follow-up can be arranged. There are many commercial kits that involve acid etching of the tooth in conjunction with resin and/or soft arch wires that are available to splint the tooth until permanent repair. The specific management and treatment of the dental injury may differ depending on whether it involves the primary or permanent dentition.

CLASSIFICATION AND MANAGEMENT OF TRAUMATIC DENTAL INJURIES

- *Concussion*: It refers to minor traumatic injury to the tooth and supporting structures.
  - *Primary dentition*: No immediate intervention required, observation, soft diet × 1 week
  - *Permanent dentition*: No immediate intervention required, observation, soft diet × 1 week
- *Subluxation*: It refers to loosening of the tooth in its alveolar socket.
  - *Primary dentition*: No immediate intervention required, observation, soft diet × 1 week
  - *Permanent dentition*: No immediate intervention required, observation, soft diet × 1 week, consider dental radiograph to rule out fracture.
- *Lateral luxation*: It refers to loosening of the tooth in its alveolar socket with lateral displacement.
  - *Primary dentition*: Treatment by repositioning or extracting tooth, do not splint. Observation and soft diet × 1–2 weeks
  - *Permanent dentition*: Obtain dental radiograph, reposition, and splint tooth. Urgent dental consultation within 24–48 hours.
- *Extrusive luxation*: It refers to loosening of the tooth in its alveolar socket with vertical displacement.
  - *Primary dentition*: Treatment by repositioning or extracting tooth, do not splint. Observation and soft diet × 1–2 weeks
  - *Permanent dentition*: Obtain dental radiograph, reposition, and splint tooth. Urgent dental consultation within 24–48 hours
- *Intrusive luxation*: It refers to a tooth that has been forced up vertically into its alveolar socket. The tooth will appear shortened and in severe cases may appear as if it is missing.
  - *Primary dentition*: Obtain dental radiograph, observe, and allow to re-erupt. If alveolar plate is compromised, then tooth requires extraction. Routine dental follow-ups.
  - *Permanent dentition*: Obtain dental radiograph, urgent dental referral within 24–48 hours for surgical reduction. Permanent or secondary teeth do not re-erupt, thus reduction is indicated to prevent complications (i.e., root resorption).
- *Avulsion*: It refers to the complete displacement of the tooth from its alveolar socket. The periodontal ligament has been severed completely. The tooth may be completely removed or can remain attached to the gingival tissue.
  - *Primary dentition*: Do not replant, obtain dental radiograph if tooth is not located.
  - *Permanent dentition*: Tooth should be replaced in the socket as soon as possible. The root should not be handled or scrubbed. If tooth cannot be replaced within 30 minutes, it should be stored in a balanced salt solution or cold milk. In the ED you may obtain a dental radiograph to evaluate for alveolar fracture prior to reimplantation and splinting. Discharge home with soft diet, systemic antibiotics, and oral antiseptic rinse along with emergent dental referral within 24 hours.

CLASSIFICATION AND MANAGEMENT OF TOOTH FRACTURES

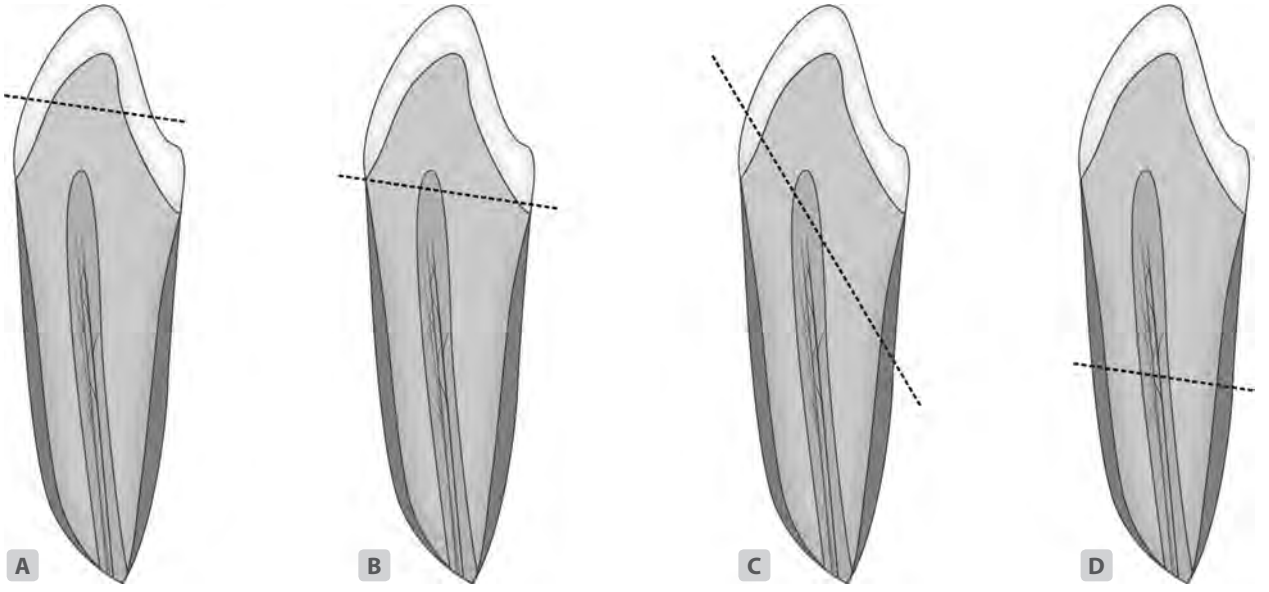
- *Uncomplicated crown fracture*: The fracture is limited to the enamel and dentin layers (**Fig. 5A**). Pain control is important to initiate as soon as possible. You may obtain a dental radiograph to rule out root fracture. These fractures may be associated with sharp edges thus dental referral within 24–48 hours is recommended for restoration or contouring to avoid further soft tissue injuries.
- *Complicated crown fracture*: The fracture involves the enamel and dentin layers along with exposure of the pulpal tissue (**Fig. 5B**). Initially, you may obtain dental radiograph to rule out root fracture. The exposed pulp is very sensitive to stimuli such as airflow and pressure. If available, calcium hydroxide can be used to place over the exposed pulp to ease the pain. Immediate dental referral within 24 hours is required. For younger children attempts to preserve the pulp vitality is important by pulp capping or partial pulpotomy. In older children, a root canal is commonly the treatment of choice.
- *Crown root fracture*: The fracture involves the enamel, dentin, and cementum. They may also include involvement of the pulpal tissue (**Fig. 5C**). Crown root fractures require dental referral within 24 hours. In the ED, radiographs to ascertain the fracture line and temporary stabilization of the tooth by splinting to the adjacent teeth can be performed.

- *Root fracture*: The fracture involves the cementum (**Fig. 5D**). The coronal segment of the tooth may be mobile and/or displaced and there is likely to be bleeding along the gingival sulcus. The initial ED treatment of root fracture involves repositioning of the tooth, if displaced and splinting to secure in place. These injuries require immediate referral to a dentist within 24 hours for a complete evaluation, treatment, and long-term follow-up/care.
- *Alveolar fracture*: The fracture involves the portion of the jawbone that carries the teeth. They are often combined with a luxation injury of the tooth. Alveolar fractures may cause malocclusion when the patient tries to close their mouth. These fractures result from significant facial trauma and thus one must consider possible injuries to other facial bones. A computed topography scan of the facial bones may be considered when there is concern for other injuries besides those to the dentition.

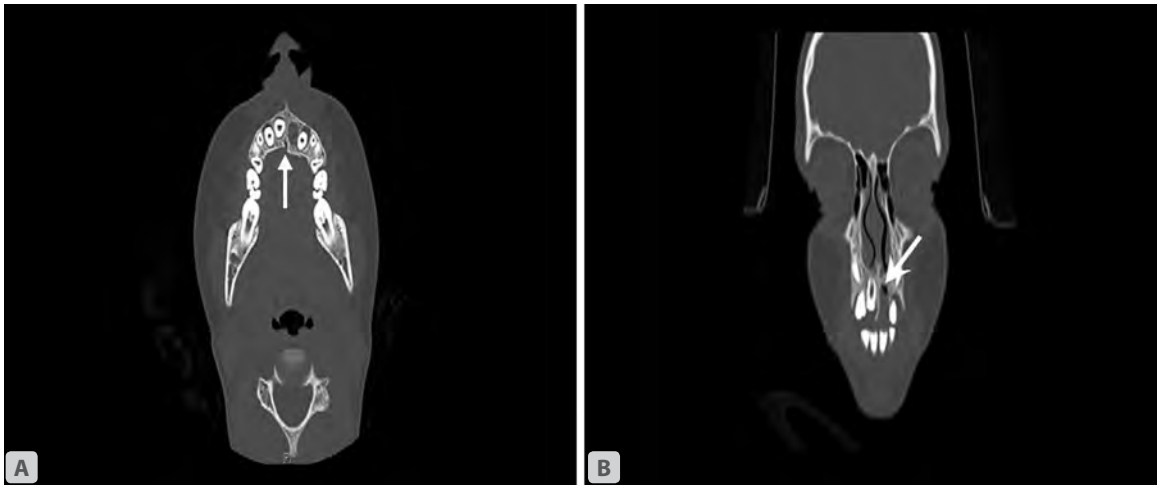
Figures 6A and **B** demonstrate a dental injury involving a tooth avulsion with an underlying alveolar fracture. Management of alveolar fractures is immediate referral to a dentist or oral surgeon following repositioning and splinting in the ED.

SUMMARY

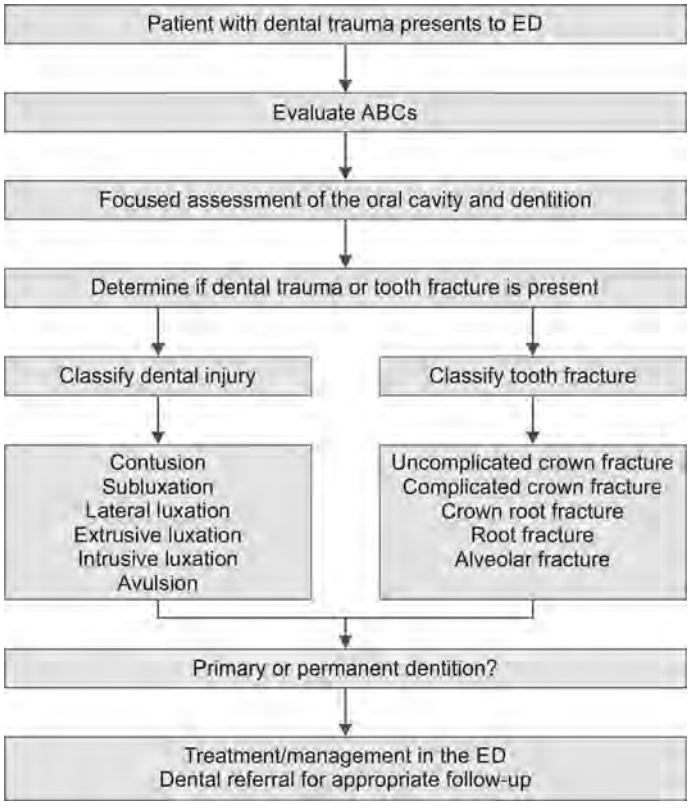
All healthcare providers need to be advocated for children in terms of good dental care. They can discuss proper dental hygiene as well as provide guidance to families about injury prevention and proper use of appropriate protective gear (i.e., mouth guards) during sports participation. However, when pediatric oral or dental injuries occur they can be very frightening to the patient and the parents. Having the knowledge to accurately diagnose and treat such injuries is essential to assure the best possible outcome for the patient (**Flowchart 1**).



FIGS. 5A TO D: Classification of tooth fractures. The solid black line represents the plane of the fracture.



FIGS. 6A AND B: Alveolar fracture. (A) 12 years of age female who fell while riding her bicycle and hit her face on the pavement. (A) Figure A shows the presence of an alveolar fracture (arrow). (B) Figure B shows the empty socket of an avulsed tooth (arrow) at the location of the alveolar fracture.



FLOWCHART 1: Approach to traumatic pediatric oral and dental injuries.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Rashes in Newborn and Infant

Nadeem Uddin Qureshi, Irene Oriaifo, Rekha Gadiparthi, Mohammed Moiz Qureshi

INTRODUCTION

Skin disorders in children necessitate careful observation and thorough assessment of the child's history. During examination, consider the appearance of the rash and the site and pattern of its development. Skin rashes in children are a very common sign and often very difficult to diagnose, as more than one skin disease may be involved. **Table 1** illustrates various criteria involved in successfully diagnosing a rash. Skin rashes in children require careful history taking and assessment and examination of the skin (**Table 2**). With the urgent need for adjustment to the extrauterine environment that the newborn faces, many different adaptive changes occur across all organ systems, including the skin occurs. Many of skin lesion/rashes are benign, but some usually are a cause of considerable concern for parents.

This article reviews rashes in pediatrics, with a step-by-step approach to the classification and identification of the rash.

TABLE 1: Classification of skin lesion according to clinical presentation.

Vesiculobullous skin lesion	*Pustular skin lesion*	*Papular skin lesion*
• Impetigo • Scalded skin syndrome • Herpes simplex virus • Eczema herpeticum • Erythema multiforme • Stevens–Johnson syndrome and toxic epidermal necrolysis • Varicella (chickenpox) • Insect bites and stings (e.g., mosquitoes and bees), burn wounds (second degree)	• Infantile acne • Neonatal pustulosis • Secondarily infected vesiculobullous rash • Acute generalized exanthematous pustulosis	• Scabies urticaria/serum sickness • Keratosis pilaris • Papular acrodermatitis • Molluscum contagiosum • Plane warts • Streptococcal infection (scarlet fever), rubella (German measles) • Measles (rubella)

Skin lesions should be differentiated on the basis of various aspects whether red rashes are with epidermal breakage or not, whether they blanch with pressure or not (**Table 3**). Skin lesion can also be differentiated as hypopigmented or hyperpigmented lesions (**Table 4**).

TABLE 2: Pediatric patient assessment with skin lesions/skin rashes.

Initial assessment of the rash	Is there any fluid-filled vesicles? Is the rash raised (papular) or flat (macular)? Is the rash red? Is the rash scaly? Is the rash itchy? When did the rash start? Where did the rash start, and how did it spread?
History—what is the past medical and drug history?	Did the patient present with other symptoms (e.g., fever and headache)? Has the patient been exposed to new topical applications (e.g., soap and lotions)? Has the patient ingested any unfamiliar foods? Has the patient had close contact with someone else with the same symptoms? Has the patient traveled recently?
General examination	If a systemic illness is expected, refer to a medical practitioner for further management.
Examination of the skin	Examine the whole skin, even if the rash seems localized. Ensure that the patient is comfortable, with a close caregiver nearby. A rash resulting from a topical application will be present in a specific area (e.g., underarms and nappy area). A rash resulting from a systemic cause will be generalized and symmetrical. Systemic illness may also present in the mouth (e.g., syphilis, drug reactions like Stevens–Johnson syndrome).

TABLE 3: Differentiating red skin lesions/rashes.	
Red rashes with epidermal breakage	Eczematous rashes atopic dermatitis (eczema)
Red rashes with/without epidermal breakage	• Papulosquamous rashes (red and scaly) • Seborrheic dermatitis • Psoriasis • Tinea corporis • Pityriasis rosea
Red rashes with blanching	• Erythematous rashes (red and blanching) • Fever and exanthem • Erythema infectiosum • Roseola infantum • Kawasaki disease
Red rashes without blanching	• Purpuric rashes • Enterovirus infection • Septicemia • Leukemia • Henoch–Schönlein purpura • Idiopathic thrombocytopenic purpura (ITP) • Vasomotor straining • Child abuse • Trauma

TABLE 4: Differentiating skin lesions on the basis of pigmentation	
Blue/black rash	• Vascular malformations • Hemangiomas • Mongolian spots • Blue nevi • Melanoma
Hypopigmented lesions	• Pityriasis alba • Pityriasis versicolor • Vitiligo • Postinflammatory • Hypopigmentation
Hyperpigmented lesions	• Congenital pigmented nevi • Acquired pigmented nevi • Postinflammatory • Hyperpigmentation

TERMINOLOGY OF PRIMARY LESIONS

- Macules are nonpalpable lesions ≤1 cm, patches are nonpalpable lesions >1 cm.
- Papules are palpable lesions ≤5 mm, plaques are palpable lesions >5 mm.
- Nodules are palpable lesions >5 mm in both width and depth.
- Telangiectasias are dilated superficial blood vessels, vesicles are clear fluid-filled lesions ≤5 mm.
- Bullae are clear fluid-filled lesions >5 mm, pustules are pus-filled lesions ≤ 5mm.
- *Nevus flammeus*, *port-wine stains*, when presents in the area innervated by the ophthalmic branch of the facial nerve, is associated with Sturge–Weber syndrome, a neurocutaneous disorder with vascular malformations of the brain and intractable seizures.
- Multiple or clustered capillary hemangiomas may be associated with deep tissue and parenchymal involvement, and further evaluation is necessary.
- Dermal melanocytosis or *Mongolian spots* are dark blue–gray patches of melanocytes located in the dermis. Mongolian spots should not be confused with bruising.
- Seborrheic dermatitis can be recognized clinically by the presence of greasy scales and erythematous plaques.
- Diaper dermatitis is usually caused by irritation of the skin from prolonged contact with feces and urine. Sparing of the skin folds is diagnostic.
- Atopic dermatitis is usually caused by dry skin, can be recognized by distribution.
- *Candida* skin or oral infections may be secondary to excessive use of oral antibiotics. Treatment includes antifungal agents such as nystatin, ketoconazole, or clotrimazole as well as consideration of probiotics and hygiene.
- Multiple café-au-lait spots of neurofibromatosis increase the risk for auditory and central nervous system (CNS) tumors.
- Vascular malformations in a "beard distribution" on the face are associated with airway hemangiomas.

BENIGN NEONATAL SKIN LESIONS

- *Milia* are tiny white-yellow discrete pearly papules, 1–2 mm, frequently occurring on the face and scalp. They are superficial inclusion cysts of the pilosebaceous units that contain laminated keratinized material of sebaceous origin. They are firm and unlike pustules are not easily denuded by pressure. Cause is unknown. The lesions resolve spontaneously and no treatment is necessary.
- *Miliaria rubra,* prickly heat, is caused by sweat duct obstruction deeper in the epidermal or dermal layers. Erythematous small papules are noted over face, neck, and upper trunk. It is common in infants and children during hot, humid weather (**Fig. 1**).

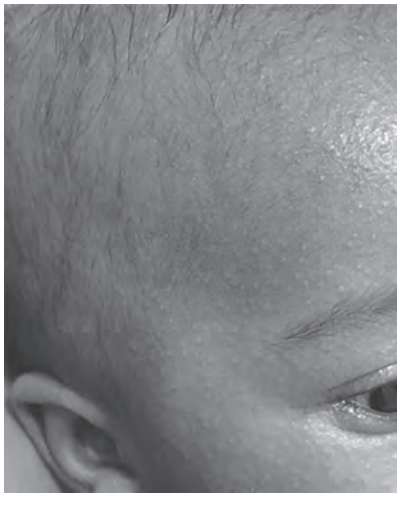

FIG. 1: Miliaria rubra. ***(For color version, see plate 30)***

- *Miliaria crystallina* is lesions caused by obstruction of eccrine sweat gland ducts located high in the outer layer of epidermis. Multiple thin-walled vesicles form over head, neck, and upper trunk.
- *Neonatal acne* is characterized by presence of open or closed comedones and papulopustules over cheeks and forehead. Thought to be due to placental transfer of maternal androgens, hyperactive neonatal adrenal glands or due to inflammatory response of skin to *Malassezia furfur* in severe cases. Treatment is not required as it is self-limiting, however, topical ketoconazole or hydrocortisone can be used in severe cases (**Fig. 2**).
- *Transient pustular melanosis* is a transient benign eruption seen in newborns at birth. It is more common in black infants. It presents as pustules which rupture to form fine scales and hyperpigmented macules. It may have all stages of lesions present anywhere on body but predominantly seen over forehead, neck, and lower back. A Wright stain of the contents will show a predominance of neutrophils, and absence of microorganisms **(Fig. 3)**.
- *Infantile acropustulosis* is a recurrent condition characterized by groups of pruritic vesiculopustular lesions on palms and soles. Lesions can occur on the dorsa of the feet, hand, fingers, ankles, and forearms. It can present from birth to 2 months of age. It resolves spontaneously by 2–3 years of age. Cause is unknown. Lesions start as tiny, red papules which evolve into vesicles and then pustules. Lesions appear similar to scabies. High-potency topical steroids and antihistamines may help relieve itching (**Fig. 4**).
- *Erythema toxicum* is a transient rash characterized by papules and pustules on an erythematous base. Usually, it is evident within first 48 hours of life and resolves spontaneously in 1–2 weeks without any sequelae. It can present as clumps of lesions in different areas or more diffuse, except palms and soles. Cause of this condition is unknown, thought to be secondary to an inflammatory reaction to microbial colonization at birth. Wright staining of the lesion contents will show collections of eosinophils with absence of infectious organisms (**Fig. 5**).
- *Seborrheic dermatitis* is common within the first 4 weeks of life. It is characterized by red scaling eruption predominantly over hair bearing areas and intertriginous areas such as scalp, eyebrows, eyelashes, perinasal, postauricular areas, neck, axilla, and groin. Scalp lesions consist of thick tenacious, salmon-colored scaly dermatitis, commonly known as "cradle cap" (**Fig. 6**). Pathogenesis is unknown although pityrosporum and *Candida* are

FIG. 2: Neonatal acne. ***(For color version, see plate 30)***

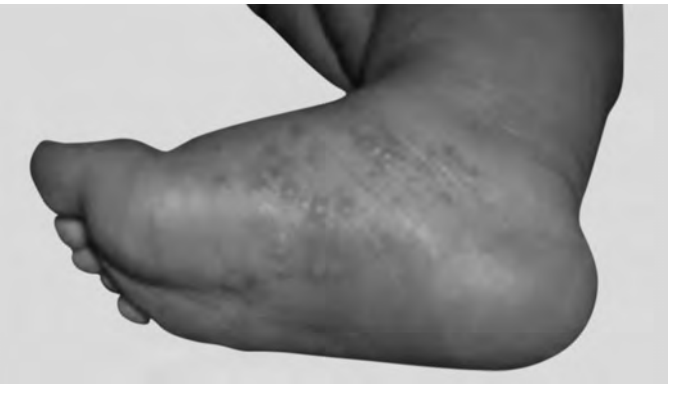

FIG. 4: Infantile acropustulosis. ***(For color version, see plate 30)***

FIG. 3: Transient pustular melanosis. ***(For color version, see plate 30)***

FIG. 5: Erythema toxicum. ***(For color version, see plate 30)***

implicated as causative agents. Seborrheic dermatitis is usually nonpruritic and responds well to low-potency topical corticosteroids and topical antifungal cream. Antiseborrheic shampoo and oatmeal baths often help.

- *Oral candidiasis* is also known as oral thrush or moniliasis. It is a superficial mucous membrane infection more common in premature infants. It can be seen in immunocompromised children or in those with underlying systemic diseases. *Candida albicans* is the most common cause. It is characterized by soft, creamy white plaques seen on tongue, palate, and buccal mucosa. Scrapping these lesions is difficult, and this differentiates from milk deposits. Scraping these lesions reveals erythematous base or punctate bleeding. Oral thrush can be asymptomatic but can cause pain, fussiness, and decreased feeding leading to dehydration and inadequate nutritional intake. Treatment includes topical application of nystatin over the affected sites. Recurrent infections can be treated with oral fluconazole for 10–14 days (**Fig. 7**).
- *Diaper dermatitis* encompasses all causes of skin irritation localized to the diaper area. Irritant dermatitis is the most common cause characterized by erythema, scaling, and excoriation sparing the intertriginous areas (**Fig. 8**). Failure to change diapers frequently and prolonged skin contact with urine and feces or from soaps and chemicals present in the diaper contribute to the rash. Absorbable disposable diapers have decreased the incidence of this problem. Secondary infection with *Candida* should be suspected when intertriginous areas are involved with the appearance of satellite lesions or diaper rash fails to respond to symptomatic treatment (**Fig. 9**). *Candida* skin or oral infections may also be secondary to excessive use of oral antibiotics. Treatment includes topical antifungal agents such as nystatin, ketoconazole, or clotrimazole as well as frequent change of diapers.
- *Drooling or spit-up rash* is common in newborn and infancy. Erythematous rash is seen on chin, cheeks, and neck creases. Usually it is caused due to prolonged contact with food or stomach acid that has been spit up. This rash comes and goes. It can be prevented by rinsing the face with water after all feedings or spit ups (**Fig. 10**).
- *Infantile scabies*: Scabies is highly contagious infestation caused by the mite *Acarus scabiei,* which burrows under the skin (**Figs. 11A** to **E**). The burrow which is produced by the female mite is pathognomonic sign for scabies. It consists of small scaly linear papule with pinpoint vesicles at the end. Infants are more likely to develop an intense and persistent nodular reaction to the mite. Lesions are characterized pruritic papules, pustules, and vesicles

FIG. 6: Seborrheic dermatitis. ***(For color version, see plate 30)***

FIG. 7: Oral candidiasis. ***(For color version, see plate 31)***

FIG. 8: Irritant diaper dermatitis. ***(For color version, see plate 31)***

FIG. 9: *Candida* diaper rash. ***(For color version, see plate 31)***

over the head, neck, trunk, palms, soles, lateral and instep portions of the feet, and lateral aspect of wrist. Eradication of scabies requires topical application of 5% permethrin cream to the patient, all household members, and close contacts. Thorough cleaning of all dirty clothing, towels, bedding, and car seat covers is essential. Two courses of treatment 1 week apart are necessary to kill the live mites and second to eliminate mites that had not hatched at the time of first application.

FIG. 10: Drool rash. ***(For color version, see plate 31)***

- *Infantile eczema* is also known as atopic dermatitis (**Fig. 12**). Usually, it begins between birth and 6 months of age and lasts about 2–3 years. Erythematous itchy papules and plaques that ooze and crust can occur over the cheeks, forehead, scalp, trunk, and extensor surfaces of the extremities. These patches are often symmetrical. Cause of atopic dermatitis remains elusive. Thought to be due to chronic elevation of IgE or aberrant cutaneous response to histamine and other mediators of inflammation. Atopic dermatitis can occur in families and in association with other atopic conditions such as asthma, allergic rhinitis, and food allergies. Children with eczema should be closely monitored for secondary bacterial and viral infections. Treatment includes adequate hydration and lubrication of skin, antipruritic agents to break itch-scratch cycle, and topical steroids to relieve itching and reduce inflammation.

FIGS. 11A TO E: Infantile scabies. ***(For color version, see plate 32)***

FIG. 12: Infantile eczema. ***(For color version, see plate 32)***

FIG. 13. Mongolian spot. ***(For color version, see plate 32)***

DISORDERS OF PIGMENTATION

- *Dermal melanosis, Mongolian spots* (**Fig. 13**), is single or multiple slate-gray or bluish-black irregular macules commonly seen over buttocks and lumbosacral area. It is more common in African- American and Asian infants. These are due to accumulation of melanocytes deep within dermis. Usually, self-resolve over years. Special variants of Mongolian spots, nevus of Ota (involving face and periocular area), and nevus of Ito (involving shoulder) may persist. Mongolian spots should not be confused with bruising.
- *Neurofibromatosis* is an autosomal dominant disorder characterized by multiple café-au-lait spots. Presence of six or more lesions measuring >5 mm in an infant, the presence of axillary freckling, optic glioma, iris hamartomas, or Lisch nodule is diagnostic (**Fig. 14**). These disorders are associated with a high incidence of optic gliomas, acoustic neuromas, and a variety of other CNS tumors. Neurofibromas are small, rubbery, and purplish lesions that usually appear during adolescence or pregnancy, but plexiform neurofibromas may be present at birth. The patient with neurofibromatosis who presents with headache or focal neurologic signs must be evaluated for an intracranial mass lesion. Other causes of café-au-lait spots include McCune–Albright syndrome, which is characterized by polyostotic fibrous dysplasia and multiple endocrine abnormalities.
- *Urticaria pigmentosa* can present at birth or first few months of life. It is characterized by multiple small reddish-brown papules or plaques over the trunk. These lesions are caused by vascular effects of histamine released from infiltrating mast cells in the cutaneous tissue. Development of a wheal and flare reaction after firm stroking of the lesion is a positive Darier sign (**Fig. 15**). Lesions are usually self-limited and resolve by adolescence. In infancy, these lesions can sometimes blister and widespread erosions can result in dehydration and sepsis. With temperature changes, metabolic insults, such as fever or viral illnesses, large numbers of degranulating lesions can produce flushing and systemic symptoms of histamine release. These patients should be counseled to avoid certain medications and iodinated contrast media.

FIG. 14: Neurofibromatosis with axillary freckling (Crowe sign). ***(For color version, see plate 33)***

FIG. 15: Darier sign for urticaria pigmentosa. ***(For color version, see plate 33)***

- *Incontinentia pigmenti* is an X-linked dominant disorder occurring in females and is usually present at birth (**Fig. 16**). It is a neurocutaneous syndrome characterized by four overlapping phases of skin presentation. The first stage usually within first 2 weeks of life manifested by inflammatory vesicles or bullae. The second stage presents usually before 6 months of age as the blisters evolve into

FIG. 16: Incontinentia pigmenti. ***(For color version, see plate 33)***

FIG. 17. Cutis marmorata. ***(For color version, see plate 33)***

warty plaques. As the plaques disappear, hyperpigmented whorls appear during stage 3. The final stage occurs later in adulthood with hypopigmentation and loss of hair and sweat glands. Approximately, 30% of patients will have seizures, CNS abnormalities, and mental retardation.

VASCULAR LESIONS OF INFANCY

- *Cutis marmorata* is a vascular phenomenon, characterized by reticulate reddish-blue mottling of the skin caused by transient vascular constriction and dilation (**Fig. 17**). It occurs symmetrically over trunk and extremities. It is a physiological response to cold temperature, and disappears on rewarming. When cutis marmorata is fixed, asymmetrical and does not disappear with rewarming, consider vascular malformation called cutis marmorata telangiectatica congenita.
- *Harlequin color change* is a benign transient color change, seen in approximately 10% of newborns (**Fig. 18**). Usually, it presents as well-demarcated color change with dependent half displaying erythema and the other half appears pale. It is thought to be due to temporary imbalance in the cutaneous blood vessel tone secondary to autonomic nervous system immaturity. It resolves spontaneously.
- *Vascular malformations* are common skin presentations at birth or in the first few months of life. They can be secondary to abnormalities of the capillary, venous, arterial, or lymphatic systems. Most are benign and self-limited, but a few may herald serious systemic consequences. The *salmon patch (nevus simplex or stork bite)* is a common capillary malformation may represent persistent fetal vessels, usually located on the forehead, upper eyelids, glabella, and posterior neck, and is present at birth. They become more apparent when baby cries or strains and usually resolve within 1–2 years, but if present on the back of the neck may persist for life.
- *Nevus flammeus*, *port-wine stains*, is persistent vascular malformations of deep dermal capillaries and postcapillary venules (**Fig. 19**). Mature capillaries infiltrate the deeper dermis and subcutaneous tissues causing purple red macules in newborn. They neither enlarge nor regress but become more hyperpigmented as the child grows.

FIG. 18: Harlequin color change. ***(For color version, see plate 33)***

FIG. 19: Nevus flammeus. ***(For color version, see plate 33)***

Most common over head and neck, when present in the distribution of ophthalmic branch of trigeminal nerve can be associated with Sturge–Weber syndrome, a neurocutaneous disorder with vascular malformations of the brain and intractable seizures.

FIG. 20: Strawberry hemangioma. ***(For color version, see plate 34)***

- *Simple capillary hemangiomas are* the most common vascular tumors in infancy. These are caused by proliferation of vascular endothelium and appear as small red telangiectasias that rapidly proliferate and protrude above skin to become the characteristic.
- *Strawberry hemangiomas* (**Fig. 20**) occur over the first year, then become stable, and involute by 5–9 years. Multiple or clustered capillary hemangiomas may be associated with deep tissue and parenchymal involvement, and further evaluation is necessary. Hemangiomas over the lower face, in an infant presenting with stridor or upper airway involvement suggest airway hemangiomas. Most of them will eventually involute; however, large lesions causing functional impairment may require steroids, pulsed-dye laser, or surgery. There are a number of hereditary and congenital conditions with vascular, hyper- and hypopigmented lesions, bulla, or ichthyotic scales that are beyond the scope of this text.

SUMMARY

Rashes are a very common occurrence in children, and often more than one skin condition may be present at the same time. The evaluation of skin conditions requires a systematic and holistic approach. A careful history is important to determine the origin of the rash. Referral is necessary if there are other systemic signs and symptoms.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Pediatric Antibiotic Prophylaxis

Veena Raghunathan, Devendra Richhariya

INTRODUCTION

In acute pediatric emergencies, the focus is mainly on identifying the problem and instituting rapid measures and conducting procedures to counter the same. While this approach is essential for the acutely sick child, an important aspect of holistic care is also prevention of infections or its complications in such children. This is relevant in scenarios such as trauma akin to a perioperative setting where antimicrobial prophylaxis is required. While administration of an antibiotic prior to planned surgery is usually protocolized and scheduled, it is not so in the emergency room (ER) where the emergency physician is responsible for initiating appropriate antibiotic prophylaxis. Antibiotics are mainly prescribed for two purposes in ER—firstly, for treatment for presumed infection and secondly for prophylaxis which is the focus of this chapter. *Common indications for antibiotic prophylaxis* include wound/trauma, animal bites, surgical prophylaxis, endocarditis prophylaxis, and others (exposure to meningococcal disease, needle stick injuries, etc.).

TRAUMATIC WOUNDS

In trauma, when the skin barrier is compromised, microorganisms can enter to cause infection. Wounds caused by trauma can be classified into low or high risk based on chance of infection.

Pathophysiology

Trauma leads to damage of local tissue. This causes cytokine release leading to swelling and erythema at the site of wound. Cytokines direct neutrophils and neutrophils to clear bacteria at the wound. Fibroblasts signal new tissue regeneration, thereby healing process occurs. Clearance of bacteria by above processes depends on mechanism of injury (e.g., puncture wound vs. laceration) and type of object causing injury. Prevention of wound infection requires thorough wound cleansing and appropriate closure, however inspite of this wound infection can occur. Antibiotic prescription is required for the wound where the bacterial load is difficult to clear spontaneously. For example, deep wounds, contaminated object causing injury, open fractures, immunocompromised host, and injury in relatively hypoperfused area. Antibiotic prophylaxis is essential to prevent development of a wound infection in such circumstances, similar to a presurgical prophylaxis. It should be administered as quickly as possible in the ER. Prophylaxis can be achieved with a single dose; whereas treatment for an established infected wound (not complicated by osteomyelitis or retained foreign body) requires 7–10-day administration. For contaminated wounds, duration of 3 days would usually suffice as prophylaxis.

Classification

Traumatic wounds are classified into low-risk and high-risk wounds depending on injury and host factors. A low-risk wound is a clean and minor wound in a healthy host. Such wounds do not benefit from antibiotic prophylaxis. A high-risk wound has one or more of the following features: deep puncture/penetrating wounds, retained foreign body/contaminated wounds, open fractures, crush injuries, bites, and immunocompromised host (on steroids, chemotherapy, diabetes, renal disease, etc.); and wounds involving tendons, joints, and cartilage (relatively avascular areas). It is difficult to predict which high-risk wounds will progress to develop infection; however, generally experts opine that antibiotic prophylaxis to such wounds may be beneficial. A high-risk wound requires antibiotic prophylaxis for at least 3–5 days. The anatomic site of the wound may be related to the risk of infection. The presence of devitalized tissue or collected blood acts as a bacterial growth medium encouraging establishment and spread of infection. Wounds on the foot get infected more than those on the head. Regional blood flow variation and degree of contamination (from exogenous/endogenous sources) probably explain this variability.

General Principles of Traumatic Wound Management

Goal for management of a wound is to achieve skin healing and functioning, similar to pretrauma state. High-pressure irrigation with tap water/saline helps to decrease bacterial load and should be done in all wounds. Both timing and technique of closure also matter. Delayed closure up to 18 hours after injury of clean wounds does not appear to be

associated with increased infection rate. Primary closure is not advisable for high-risk wounds which initially need open wound management along with antibiotic prophylaxis. The risk of wound infection generally decreases after 4 days of above management. Hence after initial debridement, clean dressing is done for the wound, and decision for closure can be taken by day 3–5 depending on wound condition.

Role of Topical Antibiotics

The utility of topical antibiotics in ER is not well studied. Topical antibiotics like mupirocin, neomycin can eradicate colonization and even independently treat infections in minor wounds. Use of topical antibiotics in daily dressing change of wounds has been suggested by some studies whereas other studies have not shown any significant reduction in infection rates with the same.

Tetanus Immunization

Tetanus immunization status should be reviewed in all cases of traumatic injuries. If >5 years have lapsed since the last tetanus booster in case of high-risk wounds or >10-year lapse in case of low-risk wounds, tetanus prophylaxis is needed. DTaP (diphtheria, tetanus, and pertussis vaccine) is recommended in children 6 weeks–6 years, Td can be given in children 7–10 years, and TT can be given in children >10 years.

Open Fractures

Open fracture is an emergency and carries a risk of osteomyelitis. Any skin break that can allow bacteria up to the bone is considered as an open fracture. Bone could be jutting out from the wound, which is an obvious case; however, more subtle presentations can occur, e.g., wound proximal to a fracture. A Cochrane database review of seven studies concluded that antibiotics decrease incidence of early infections in open fractures of the limbs. Prophylactic intravenous antibiotic should be administered as soon as possible in the ER, definitely within 6 hours. Cultures at treatment initiation are not very useful. Risk of infection depends on severity of fracture and extent of accompanying soft tissue damage. Open fractures are stratified as follows—type 1: <1 cm laceration, no extensive soft tissue damage; type 2: >1 cm laceration, no extensive soft tissue damage; and type 3: extensive accompanying soft tissue damage (with >10 cm soft tissue injury/requiring vascular repair/open >8 hours/amputations). The Eastern Association for the Surgery of Trauma guidelines recommend that a first-generation cephalosporin, e.g., cefazolin + methicillin-resistant *Staphylococcus aureus* (MRSA) coverage clindamycin/vancomycin/linezolid should be given for type 1 and 2 fractures and continued for 72 hours or till 24 hours after wound closure. For type 3 fracture, additional gram-negative coverage (aminoglycoside) is recommended. High-dose penicillin should be added to wounds with fecal/possible clostridial contamination.

Plantar Puncture Wounds

Plantar puncture wounds deserve a special mention, as they have potential for development of delayed osteomyelitis, which can occur sometimes months following injury. A common form of injury is a child stepping on a nail. Cellulitis can develop late and further evolution to osteomyelitis, osteochondritis, or septic arthritis may occur in few cases. Incrimination bacteria in postplantar puncture osteomyelitis are usually *Pseudomonas* and *Staphylococcus aureus*/*Streptococcus* species. The role of prophylactic antibiotics in plantar puncture injuries is controversial, as it may not help to prevent infection occurring later. Hence, prophylactic prescription is generally restricted to wounds distal to metatarsophalangeal joints or having higher infection risk (diabetic/immunocompromised patient, retained foreign body, etc). Antibiotics such as ceftazidime/cefepime or ciprofloxacin are good choices in such cases. Such wounds should be reassessed after 2–3 days of injury to assess for cellulitis. Radiographs are useful to identify any radio-opaque foreign bodies in addition to the fractures in the foot.

Penetrating Abdominal Wounds

These carry a high risk of infection due to possibility of spillage of intestinal contents into the peritoneum. Such patients are benefitted from antibiotic prophylaxis prior to surgery. Broad-spectrum antibiotic therapy (active against aerobic and anaerobic organisms) should be used. A single beta-lactam antibiotic is sufficient and as effective as combined therapy with aminoglycoside. Prophylaxis for 24 hours is sufficient; it helps to lower rates of postoperative peritonitis.

To summarize, the main aspects of care of a traumatic wound include the following:

- Thorough cleaning and irritation
- Examination for retained foreign bodies
- Antibiotic prophylaxis for high-risk wounds
- Radiographs to evaluate fractures/foreign bodies
- Consider/defer wound closure as appropriate
- Tetanus immunization status
- Reexamination of wound within 24–48 hours to assess for healing/development of infections/wound closure

BITE WOUNDS

Bite wounds are a common reason for ER visit. Bites are commonly due to dogs, cats, or occasionally other animals. Probability of infection depends on location, type of bite wound, type of biting animal, and underlying medical condition of the patient. A dog's bite is potentially dangerous and can lead to bad lacerations, crush injuries, fractures, skull puncture, or penetration of body cavities. Cats' bite generally leads to puncture wounds, due to their pointed sharp teeth. Infants and toddlers are prone to bites in head and neck area. Older children, especially >15 years, in contrast usually have bite injuries in the extremities. Hand bite injuries are highly susceptible to infection. Clenched fist injuries are usually forceful and can cause fractures, joint, and tendon damage. It can lead to cellulitis and deep-seated infections sometimes requiring hand amputation. All bite wounds must be carefully examined as they but can extend into deeper tissue (bone, blood vessels, tendons, etc.). Human bites also pose some risk for infection. Usually, infection related to animal or human bites develops within 12–24 hours after the injury. Initial cultures from wound site do not predict which ones will subsequently develop infection.

Management of Bite Wounds

All bite wounds should be well irrigated with large amounts of pressurized saline. This is vital for reducing bacterial load.

Concentrated povidone-iodine, hydrogen peroxide, and alcohol should not be used as these may cause further damage to tissues. Foreign matter should be removed from the wound along with debridement of devitalized tissue. Role of primary wound closure and prophylactic antibiotics in bite wounds is not standardized and controversial. Decision regarding them should be individualized after weighing all pros and cons and discussion with the caregiver.

Selected wounds in areas with rich blood supply, which carry lower infection risk and where cosmetic result matters, e.g., head and face wounds, primary closure may be advocated after thorough cleaning. Puncture wounds or open large lacerations should not be closed by primary suturing. Contaminated wounds will have increased infection risk if closed early. On the other hand, exposed bone/tendons can undergo dessication in a wound left open. Scarring is more when wound heals by secondary intention. Delayed primary closure is another option. In this, wound is initially cleaned and debrided and then reassessed 3–5 days later. If wound is clean, it can be sutured. The cosmetic result of delayed primary closure is better than healing by secondary intention.

Role of Antibiotic Prophylaxis

It is recommended for high-risk wounds including dog and cat bite, puncture wound, bites involving hand, foot, face, joint, tendon, ligament and for immunocompromised, diabetics, and asplenic individuals (**Table 1**). A Cochrane review supports antibiotic prophylaxis for hand bite wounds. For lower risk wounds, role of prophylaxis is unclear. Bite wounds tend to be polymicrobial, unlike traumatic wounds. They contain bacteria from oral flora of the biting animal. Anaerobes such as fusobacterium and bacteroides are usually present in addition to *Streptococcus* species. Appropriate choice of antibiotic is amoxicillin-clavulanate or penicillin + cephalexin. If penicillin allergy is present, moxifloxacin/ciprofloxacin + clindamycin/metronidazole may be used. Azithromycin is also an alternative in such a circumstance; however, it is less effective against anaerobes. Coverage for MRSA is not required in bite wounds, as it is an unlikely colonizer of oral cavity of animals/humans. Rodents can cause rat bite fever (due to *Streptobacillus moniliformis* or *Spirillum minus*) which is characterized by fever and rash and needs treatment with penicillin. However, prophylactic antibiotics are probably unwarranted for as rat bites have low propensity for infection. Macaque monkey bite can lead to potentially lethal herpesvirus simiae infection. Prevention against this is best achieved by aggressive bite wound irrigation. Acyclovir prophylaxis may be considered.

There is weak evidence for routine prophylactic antibiotic use in human bite wounds. Human bites pose risk of spread of hepatitis B, HIV, and hepatitis C. Whenever suspected, prophylaxis against these viral diseases should also be additionally administered.

Persons bitten by potentially rabid animals or unknown animals who cannot be tested/observed for 10 days should be advised rabies immune globulin (RIG) and rabies vaccination series according to the National Center for Disease Control (NCDC) guidelines. Intradermal regimen for vaccine involves administration of 0.1 mL each at two different sites (deltoid areas) on days 0, 3, 7, and 28. Intramuscular regimen is the administration of 5 injections (1 mL each) on days 0, 3, 7, 14, and 28 in deltoid or anterolateral aspects of thigh (in infants and toddlers).

TABLE 1: Antimicrobial therapy in high-risk traumatic wound

Traumatic conditions	*Antimicrobial therapy*
Human bites; dog or cat bites (where indicated)	• Amoxicillin/clavulanate 40 mg/kg/d PO divided BID (maximum dose 875 mg PO BID) • In penicillin, allergic patients—clindamycin 30 mg/kg/d PO divided q6 or q8 h plus trimethoprim/sulfamethoxazole 5 mg/kg PO BID
Open fractures	• First-generation cephalosporin MRSA therapy • Additional therapy for type III open fractures is gentamicin or amikacin
Plantar foot wounds distal to metatarsophalangeal joint and through shoe sole	Ciprofloxacin, ceftazidime, or cefepime
All other high-risk wounds	First-generation cephalosporin or dicloxacillin MRSA therapy

Methicillin-resistant Staphylococcus aureus (MRSA) therapy can be achieved with either oral clindamycin 30 mg/kg/day PO divided q6 or q8h or trimethoprim-sulfamethoxazole 5 mg/kg PO BID, or intravenous clindamycin, vancomycin, or linezolid depending on local resistance patterns. Alternatives for MRSA coverage in children 8 years include doxycycline and tetracycline. Anti-MRSA therapy should be individualized based on previous history of MRSA infections, colonization, and/or household contacts with MRSA

ENDOCARDITIS PROPHYLAXIS

The American Heart Association (AHA) recommends preprocedure antibiotic prophylaxis to the high-risk cardiac lesions. High risk includes prosthetic valves, cyanotic congenital heart lesions (not repaired), transplants with valvulopathy, and previous history of endocarditis. The procedures for which antibiotic prophylaxis should be given include dental work, procedures involving infected skin, subcutaneous, and musculoskeletal tissue (e.g., abscess drainage). Antibiotic such as antistaphylococcal penicillin or cephalosporin should be used. If community acquired (CA)-MRSA is present in the community, vancomycin/clindamycin depending on local susceptibility patterns should be used. No prophylaxis is required for clean noncontaminated wounds.

For low-risk procedures, antibiotic prophylaxis is not required. Foley catheter insertion, endotracheal intubation, joint aspiration, arthroscopy, local anesthetic administration, etc., do not require prophylaxis.

Risk of infection from an ER procedure for patients with orthopedic implants is low. Only high-risk category, i.e., in first 2 years after joint replacement, previous implant infection, and patients on immunosuppression, prophylaxis is indicated for procedures such as abscess drainage.

CHEST TUBE INSERTION

Chest tubes insertion is performed in ER in trauma for hemo-/pneumothorax. This may become a port of infection occasionally, especially if placed in an emergency as compared to placement in a sterile field like operating room by a scrub-bed surgeon. However, evidence for role of prophylactic antibiotics is conflicting, and it does not appear to decrease

incidence of infection. Hence, at present, prophylactic antibiotic use cannot be recommended in such circumstances.

MENINGOCOCCAL EXPOSURE

Meningococcal disease is a potentially fatal condition which spreads rapidly by droplet route. It should be considered strongly in patients with clinical symptoms (fever and purpuric vasculitis rash) along with presence of gram-negative diplococci/positive culture from a usually sterile site [cerebrospinal fluid (CSF) and synovial fluid). As close contacts of an index case are highly likely to be colonized (nasopharyngeal) and develop disease, postexposure prophylaxis is extremely important, despite previous vaccination status. This is because serogroup B disease is not prevented by vaccination. It should be initiated at the earliest, delay of >14 days is considered nonbeneficial. In children, first-line antibiotic for prophylaxis includes rifampin/ceftriaxone. Ciprofloxacin is an alternative, used in adults. Droplet precautions can be stopped after 24 hours of antibiotic initiation. High-risk contacts which need antibiotic prophylaxis include childcare/preschool contact anytime during 1 week preillness, close social contact, sharing eating utensils, same household contact, flight passenger seated next to index case >8 hours, and unprotected contact during endotracheal intubation. Low-risk contacts (casual contact, no direct exposure, healthcare personnel with no direct exposure to patient secretions, etc.), do not require prophylaxis (**Box 1**). **Table 2** summarizes antimicrobial therapy for close contacts and persons with meningococcal disease.

BOX 1: Risk categories and recommendations of chemoprophylaxis in meningococcal disease.

High risk: Chemoprophylaxis recommended (close contacts)

- Household contact, especially children younger than 2 years
- Child care or preschool contact at any time during 7 days before onset of illness
- Direct exposure to index patient's secretions through kissing or through sharing toothbrushes or eating utensils, markers of close social contact, at any time during 7 days before onset of illness
- Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation at any time 7 days before onset of illness
- Frequently slept in same dwelling as index patient during 7 days before onset of illness
- Passengers seated directly next to the index case during airline flights lasting >8 hours

Low risk: Chemoprophylaxis not recommended

- *Casual contact*: No history of direct exposure to index patient's oral secretions (e.g., school or work)
- *Indirect contact*: Only contact is with a high-risk contact, no direct contact with the index patient
- Healthcare personnel without direct exposure to patient's oral secretions

In outbreak or cluster

Chemoprophylaxis for people other than people at high risk should be administered only after consultation with local public health authorities

PERTUSSIS EXPOSURES

Pertussis is one of the most highly communicable diseases, with attack rates of 100% recorded in susceptible individuals. It is also known as "whooping cough," because of the pronounced inhalational whoop that is classically heard after a series of coughs. Infants and young children have the highest rates of acquisition, and young infants experience the most serious manifestations of illness. Although better vaccines and vaccine strategies are being pursued, physicians should remain vigilant to recognize, diagnose, and treat pertussis cases and their contacts. 2013 Advisory Committee on Immunization Practices (ACIP) recommends three doses of acellular pertussis vaccine at 2, 4, and 6 months of age, with a booster at 15–18 months, and a second booster at 4–6 years. An additional booster is recommended at 11–12 years. For adults, a one-time booster of acellular pertussis is recommended, but some experts argue that this should be repeated every 10 years, as protection is not lifelong. In October 2012, the ACIP recommended that all pregnant women receive one booster dose of tetanus/diphtheria/acellular pertussis (Tdap) for every pregnancy at 27–36 weeks' gestation regardless of previous Tdap history to maximize maternal antibody response and passive antibody transfer to the infant.

Pathophysiology

Pertussis disease is caused by *Bordetella pertussis* (95%) and less commonly by *Bordetella parapertussis*. A related organism, *Bordetella bronchiseptica,* is normally enzootic in animals and has been isolated from humans with cough-like illnesses. *Bordetella* is fimbriated gram-negative rod that expresses virulence factors, including filamentous hemagglutinin, periactin, and pertussis toxin, which cause a lymphocytic leukocytosis in unimmunized individuals. Transmission is presumably via droplets from a coughing patient that reach the upper respiratory tract of susceptible individuals.

Classification

Cases of pertussis fall into two categories—(1) Classic illness and (2) Mild illness. Pertussis that occurs as a primary infection in a previously unimmunized child is referred to as classic illness, whereas mild illness can occur in a previously vaccinated or unvaccinated host. Classic illness presents in three stages—(1) An initial stage with rhinorrhea, tearing, and mild cough; (2) A paroxysmal stage where cough increases

TABLE 2: Antimicrobial regimens for close contacts and persons with meningococcal disease.

Antimicrobials	*Age*	*Does*	*Duration*
Rifampin	<1 month	5 mg/kg PO q12h	2 days
	>1 month	10 mg/kg PO q12h (maximum 600 mg)	
Ceftriaxone	<15 years	125 mg IM	Single dose
	>15 years	250 mg IM	
Ciprofloxacin		20 mg/kg PO (maximum 500 mg)	Single dose

Rifampin is not recommended for use in pregnant women.

in frequency and number and when paroxysms of cough are interspersed with a significant inspiratory whoop that may be associated with post-tussive vomiting; and (3) A convalescent stage when coughing decreases in frequency and severity. Mild illness typically manifests as an indolent infection, and usually comes to medical attention because of chronic cough lasting 2 or more weeks in duration. Testing and presumptive treatment should be considered in infants with evidence of severe pertussis (e.g., white blood cell count >30,000/mL, tachycardia, and hyperventilation) and in those with a history of recent exposure to an index case. In adults, most have either been previously vaccinated and/or exposed to pertussis illness and thus may have some degree of immunity that can alter the initial clinical presentation to include only serial coughing, air hunger, and headaches.

Diagnosis

Laboratory testing to confirm pertussis disease includes culture on appropriate media, direct fluorescent antibody testing (DFA), or polymerase chain reaction (PCR). Nasopharyngeal specimens (swab, washing, or aspiration) are best for testing and are more likely to isolate the organism within the first 3 weeks of cough. DFA testing of secretions may be helpful in patients with symptoms for >3 weeks who may have negative culture or PCR testing, but these tests may cross-react with other antibodies to yield false-positive results or false-negative results in infants with pertussis disease due to limited antibody production.

Treatment

Treatment of those exposed to cases of pertussis includes a two-pronged approach of vaccination and chemoprophylaxis. Pertussis exposures should be evaluated for pertussis immunization status. Those not immunized or under-immunized should be vaccinated according to the recommended schedule. Special efforts should be made to give chemoprophylaxis to those at high risk for severe pertussis, including infants, pregnant women, and those in regular contact with these groups. First-line medications used for chemoprophylaxis include macrolide antibiotics—azithromycin, clarithromycin, and erythromycin. Azithromycin should be given to infants <6 months because of increased risk of hypertrophic pyloric stenosis associated with erythromycin use in this age-group. Alternative treatment can be given with trimethoprim-sulfamethoxazole in case of drug allergy or resistance to macrolides. A summary of chemoprophylactic regimens is outlined in **Table 3**. Side effects of macrolide antibiotics are typically related to the gastrointestinal system, including diarrhea, nausea, abdominal pain, and loose stool. Disposition all persons exposed to pertussis should be observed for 21 days after exposure to ensure they do not display signs or symptoms of pertussis. Those with symptoms or with confirmed pertussis should be excluded from day care, school, work, and other public settings until they have completed at least 5 days of antimicrobial therapy.

TABLE 3: Recommended antimicrobial therapy and postexposure prophylaxis for pertussis in infants, children, adolescents, and adults.

Azithromycin	<1 month	10 mg/kg/day as a single dose for 5 days
	1–5 month	10 mg/kg/day as a single dose for 5 days
	>6 month and children	10 mg/kg as a single dose on day 1 (maximum 500 mg), then 5 mg/kg as a single dose on days 2 through 5 (maximum 250 mg/day)
	Adolescents and adults	500 mg as a single dose on day 1, then 250 mg as a single dose on days 2 through 5
Erythromycin	<1 month	Only give if azithromycin is not available because of risk of pyloric stenosis: 40 mg/kg/day divided q6 h for 14 days
	1–5 month	40 mg/kg/day divided q6h for 14 days
	>6 month and children	40 mg/kg/day divided q6 h for 7–14 days (maximum 1–2 g/day)
	Adolescents and adults	2 g/day divided q6 h for 7–14 days
Clarithromycin	<1 month	Not recommended
	1–5 month	15 mg/kg/day divided BID for 7 days
	>6 month and children	15 mg/kg/day divided BID for 7 days (maximum 1 g/day)
	Adolescents and adults	1 g/day divided BID for 7 days
TMP-SMP	<1 month	Contraindicated in <2 months of age
	1–5 month	*>2 months of age*: TMP, 8 mg/kg/day; SMX, 40 mg/kg/day divided BID for 14 days
	>6 month and children	TMP, 8 mg/kg/day; SMX, 40 mg/kg/day divided BID for 14 days
	Adolescents and adults	TMP, 320 mg/day; SMX, 1,600 mg/day divided BID for 14 days

Complications

Complications of pertussis include pneumonia, apnea, seizures, encephalopathy, and cardiorespiratory failure. The death rate in young children who acquire disease is 1–2%. Pertussis can present with nonspecific signs of rhinitis and mild cough that fail to improve after 7–14 days. Other clinical signs include cough with or without paroxysms, whoop, and vomiting. Diagnosis relies on clinical suspicion, but disease manifestations can be elusive. Prompt diagnosis and antibiotic treatment limits spread to contacts and to the community. Transmission can be blocked if vaccine coverage rates are high and booster vaccines are given, but new vaccines with higher efficacy and additional control strategies are warranted. Acquisition of pertussis disease confers immunity, but similar to vaccine-induced immunity, this wanes over the time.

INFLUENZA EXPOSURES

Influenza viruses are RNA viruses and classified into three types—A, B, and C. Type A is the most common and is further subdivided based on surface antigens hemagglutinin and neuraminidase. Type B displays less genetic diversity compared with type A, and type C causes only mild disease in children. Influenza is spread by the respiratory route when large, virus-laden droplets are coughed or sneezed into the environment, or other contact with respiratory secretions. Transmission requires close contact, as large droplets can travel approximately 1 m and rapidly fall from the air after being expelled. The incubation period is from 1 to 4 days, with most cases occurring on day 2 postexposure. Although adults are deemed infectious from the day before symptom onset for the next 6–11 days, children transmit virus from several days before symptoms develop until up to 10 days after onset. Host immunity depends on underlying immune status and previous exposure to either naturally circulating virus or vaccine strains. As a result of limited host immunity, influenza disproportionately affects children <2 years, with the highest rates of hospitalization in children <6 months.

Diagnosis

Influenza is diagnosed using viral culture, PCR, or immunofluorescent or rapid diagnostic testing and is easiest to detect during the first 3 days of clinical symptoms when viral shedding is highest. Nasopharyngeal testing, using a swab, aspirate, or washing, is preferred. Influenza virus can be grown in culture within 2–6 days, a period after which antiviral medications may not provide maximal benefit reverse-transcriptase PCR (RT-PCR) testing is available in some settings, with more rapid results than culture while maintaining high sensitivity and specificity. Direct fluorescent and immunofluorescent testing can yield results in 3–6 hours, and can be used as a basis for treatment and prophylaxis of high-risk contacts. Both viral culture and RT-PCR methods are considered the gold standard for influenza testing.

A common influenza test used is rapid influenza diagnostic testing (RIDT). RIDTs are based on immunochromatographic lateral flow and membrane-based assays that are advantageous in their quick turnaround time and ease of use. Disadvantages include high false-negative rates during high influenza activity, high false-positive rates during low influenza activity, and some tests do not distinguish between influenza A and B or pandemic strains.

Chemoprophylaxis following influenza exposures should be considered in the following scenarios involving high-risk children; protection of unimmunized high-risk children or children who were immunized <2 weeks before influenza circulation, because adequate immune response develops 2 weeks after immunization; protection of children at increased risk of severe infection or complications, such as high-risk children for whom the vaccine is contraindicated; protection of unimmunized close contacts of high-risk children; protection of immunocompromised children who may not respond to vaccine; control of influenza outbreaks in a closed setting, such as an institution with unimmunized high-risk children; and protection of immunized high-risk children if the vaccine strain poorly matches circulating influenza strains.

TABLE 4: Recommended oseltamivir dose for influenza in pediatric age and adults.

Drug	*Age*	*Dose*
Oseltamivir	Neonate	1 mg/kg/dose BID (prophylactic dose—single dose)
	Infants (8–11 months)	3 mg/kg/dose BID for 5 days (prophylactic dose—single dose)
	≥12 months	• *<15 kg*: 30 mg BID • *15–23 kg*: 45 mg BID • 23–40 kg: 60 mg BID • *>40 kg*: 75 mg BID • Prophylactic dose—single dose
	Adults	75 mg BID (prophylactic dose—single dose)

Treatment

Drugs available in the United States for treatment or chemoprophylaxis of influenza exposures include the neuraminidase inhibitors oseltamivir and zanamivir, and the adamantanes amantadine and rimantadine. Neuraminidase inhibitors are active against both A and B strains, whereas the adamantanes are active only against A strains. Because of resistance of circulating A strains against the adamantanes, use of this class of drugs has not been recommended for use since 2005. Dosing of the neuraminidase inhibitors varies by age and weight and is summarized in **Table 4**. The duration of antiviral prophylaxis is for 7 days after exposure.

Optimal timing of initiation of antiviral therapy is as soon as possible after exposure has occurred for prophylaxis and within 48 hours of symptom onset for treatment. For those with compromised renal function, oseltamivir, amantadine, and rimantadine dosing should be adjusted. Only zanamivir does not require adjustment in renal insufficiency.

Complication

Potential complications of influenza illness include respiratory failure requiring mechanical ventilation and bacterial superinfection. Rare complications include encephalopathy, myocarditis, myositis, pericarditis, Reye syndrome, and transverse myelitis. Potential complications of antiviral medications used for treatment and prophylaxis include nausea and vomiting associated with oseltamivir and bronchospasm associated with zanamivir. Because of potential exacerbation of underlying conditions, such as asthma, zanamivir is contraindicated in people with underlying respiratory disease. Disposition education of patients and their caregivers regarding the need for prophylaxis and compliance with the prophylactic regimen is essential. For those who are not at increased risk or who refuse prophylaxis, physicians should offer anticipatory guidance to return for care and treatment should symptoms develop.

SUMMARY

To conclude, antibiotic prescribing in the ER for prophylaxis has specific indications. Broad usage should be avoided in ER to decrease unnecessary antibiotic usage. Overprescribing antibiotics carries the risk of increasing antibiotic resistance and adverse infections such as *Clostridium difficile*. Majority of antibiotics prescribed in ER are usually continued without any change after admission for 48 hours or so. Hence appropriate prescribing practices are very important in the ER setting.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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176 CHAPTER

Pediatric Gastrosurgical Emergencies

Meera Luthra, Apurva Arora

INTRODUCTION

This chapter covers common abdominal surgical emergencies in children that are often mistaken for benign self-limiting diseases. Most of the abdominal surgical emergencies in children present with pain abdomen, vomiting, distension, fever, and poor feeding. Due to the inherent difficulties involved in pediatric history taking and examination, the recognition of the urgency is often delayed. In 21.66% cases, cause of acute abdomen is congenital and acquired in 78.33%. A long list of pathologies presenting with broadly the same symptoms can confuse and/or delay the physician from ordering the ideal singular diagnostic investigation and making a timely diagnosis (**Table 1**). Morbidity and mortality in children vary by age and the condition.

TABLE 1: Nontraumatic cause of pediatric surgical abdomen.

Newborns: 0–1 months	• Duodenal Obstruction • NNEC • Intestinal malrotation • Volvulus • Anorectal malformation • Hirschsprung's disease
Infants and toddler: 1 month–2 years	• IHPS • Intussusception • Obstructed hernia • Foreign Body ingestion
Young children: 2–5 years	• Appendicitis • Meckel's causing • Intussusception • Foreign body ingestion • Intestinal obstruction? Band
Older children: 3 years and older	• Appendicitis • Cholecystitis • Pancreatitis • Abdominal cyst • Gonadal (ovarian/testicular torsion)

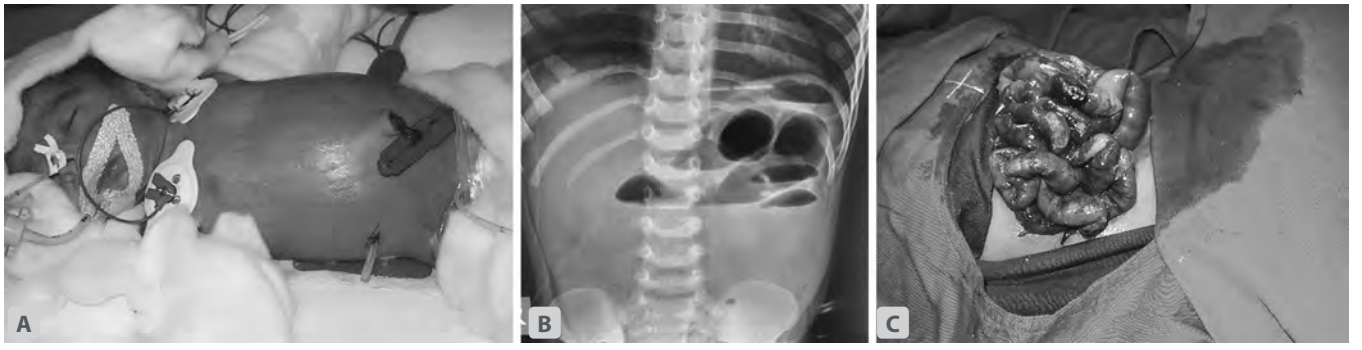
(IHPS: infantile hypertrophic pyloric stenosis; NNEC: neonatal necrotizing enterocolitis)

GENERAL APPROACH TO A SICK CHILD WITH ABDOMINAL SYMPTOMS

- Observe the child's behavior before you approach the patient directly wherever possible, because sometimes children can get scared or intimidated by the white coat. A child sitting or playing comfortably on the ER gurney can be quite reassuring.
- Rule out shock/dehydration/signs of sepsis apart from checking vitals and doing routine primary survey for airway and breathing.
- Due to lesser body weight and blood volume, children are more liable to dehydration—wide-bore intraosseous IV access is quite reliable in children.
- Consider surgical pathology early in the history and examination.
- Resuscitate while you evaluate/investigate.
- Have a low threshold for early imaging/specialist consult in children, especially for newborns and infants. Serial examinations are valuable if the diagnosis is not clear in the first instance.

NEONATAL NECROTIZING ENTEROCOLITIS

Typically, the baby is an NICU graduate, initially, there will be a mild abdominal distension, bilious vomiting, and lethargy. There is a drop in the mean blood pressure and often a drop in the platelet count. More often than not, these babies recover uneventfully on conservative management and antibiotics. A localized area of tenderness and a discoloration of the abdominal wall is a harbinger of intestinal gangrene. However, neonatal necrotizing enterocolitis (NNEC) is very deceiving and babies can deteriorate suddenly. Signs of sudden deterioration are sudden increase in the abdominal girth (**Fig. 1A**), suggestive of intestinal obstruction or perforation. A plain X-ray may show multiple air fluid levels (**Fig. 1B**). Surgical approach can vary from making a stoma with drainage of intraperitoneal collection to a resection and anastomosis (**Fig. 1C**).



FIGS. 1A TO C: (A) Clinical picture of neonatal necrotizing enterocolitis (NNEC); (B) X-ray abdomen showing multiple air fluid levels; (C) intestinal gangrene. ***(For color version, see plate 34)***

DUODENAL OBSTRUCTION

Congenital duodenal obstruction is amongst the most common anomaly in newborn. It affects one in 2,500–10,000 low births. Duodenal obstruction constitutes half of the cases of neonatal intestinal obstruction. They include duodenal atresia/stenosis (intrinsic) or malrotation and annular pancreas (extrinsic) obstruction. One-third of babies with duodenal obstruction have trisomy 21 or Down's syndrome. The baby presents with vomiting and later dehydration. The plain X-ray shows a double bubble appearance (**Fig. 2**). Resuscitation surgery is required and standard operation is a Kimura diamond-shaped duodenoduodenostomy.

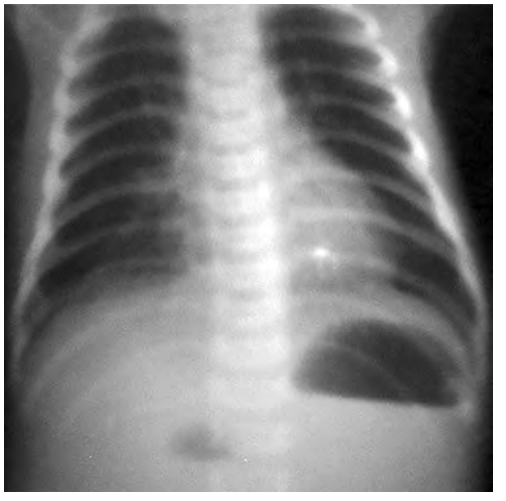


FIG. 2: Duodenal obstruction with double bubble appearance.

INTESTINAL MALROTATION AND VOLVULUS

Malrotation occurs due to incomplete rotation of the bowel with an abnormal fixation of the mesentery of the bowel. It is within this abnormal fixation that a volvulus occurs. Plain X-ray and ultrasound may be normal or show signs of obstruction. Barium upper GI series show that the gastroduodenal junction is to the right of the midline instead of the left. Ultrasound may show a "whirlpool sign" when the superior mesenteric vein (SMV) and mesentery wrap around the superior mesenteric artery (SMA) in a clock-wise direction. A baby with a malrotation presents with mild abdominal distention and failure to accept feeds. Usually, the baby is well on nasogastric aspiration and IV fluids, but as soon as baby is fed, the baby has obstructive symptoms.

It often takes a week after birth to diagnose a baby with the help of X-rays and a contrast study. Sometimes the baby with malrotation can go to puberty and adulthood without being diagnosed. Surgery is straightforward and these babies recover soon. The babies who have a volvulus have a very aggressive presentation. The neonates present with sudden onset of biliary emesis. Bleeding per rectum is another presentation and indicates a poor prognosis. Early surgery is the only choice of treatment in volvulus. At the same time, resuscitation before surgical intervention is mandatory. The outcome of babies with volvulus depends on a timely diagnosis, good preoperative preparation, and early surgery. It can vary from complete recovery to a disastrous outcome and/or intestinal failure in the event there is a volvulus with gangrene.

ANORECTAL MALFORMATION

The baby presents with an absent anal opening or a vestibular anus in the case of a female baby. A baby with anorectal malformation (ARM) may have a missed diagnosis, if the attending physician has not looked at the perineum. At times, in girls there is a vestibular anus and the absent anal opening goes unnoticed as the baby passes meconium after birth. Depending on the tightness of the anal opening in newborn, a stoma may be required for a high ARM or an anoplasty for a low ARM (**Fig. 3**).

HIRSCHSPRUNG'S DISEASE

Hirschsprung's disease is named after Harold Hirschsprung. It is also known as aganglionic megacolon due to the absence of parasympathetic ganglion cells of Auerbach's plexus in a variable portion of the distal intestine. The incidence 1: 15,000, it may be associated with other congenital anomalies. Babies with Hirschsprung's disease present at birth with delayed passage of meconium, abdominal distention, and vomiting. They may present later in childhood with milder symptoms. Rarely, a patient comes to emergency with abdominal distention and intestinal obstruction. Newborn with Hirschsprung's may present with intestinal perforation and is

very sick, lethargic, and has a tender abdomen. If the patient is stable, then a barium enema should be done the next day (**Fig. 4A**). However, an acute obstruction which fails to respond to nasogastric aspiration requires early surgery (**Fig. 4B**) and a stoma.

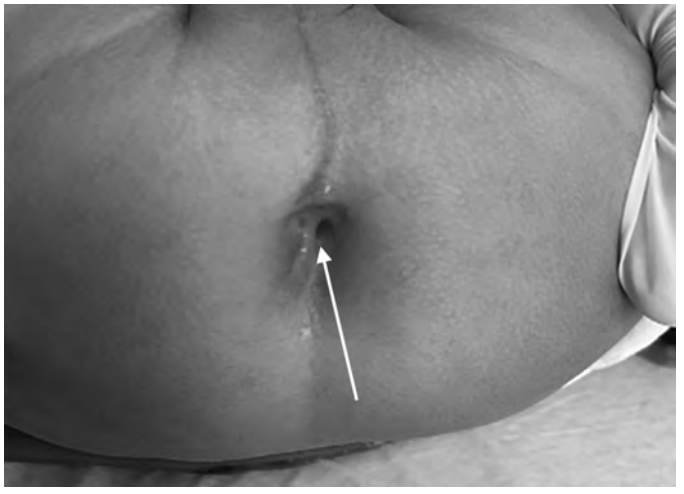


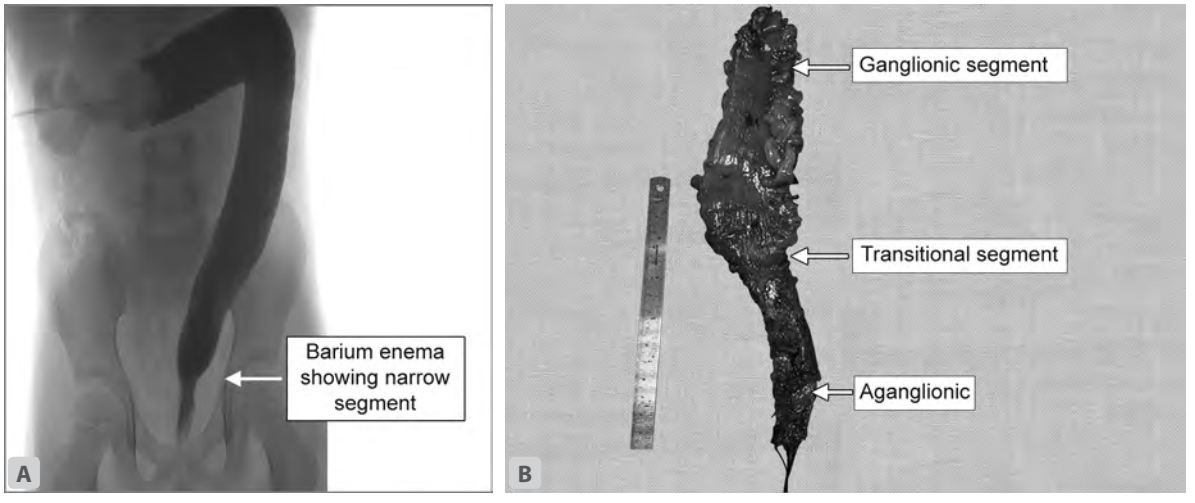
FIG. 3: Anal dimple—anorectal malformation (ARM). ***(For color version, see plate 34)***

INFANTILE HYPERTROPHIC PYLORIC STENOSIS

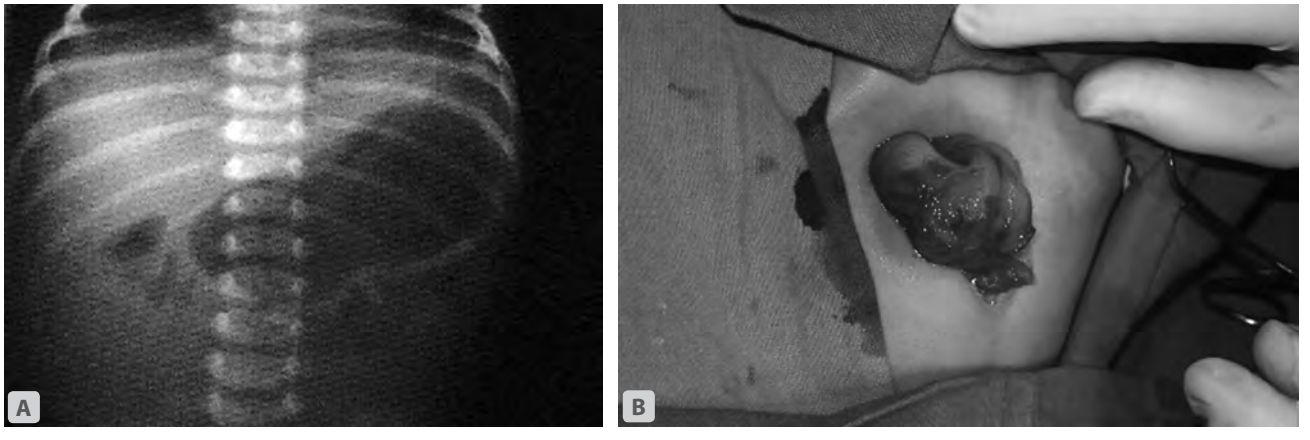
Classically, this is a first-born male baby. The incidence is 2–1,000 live births and male female ratio is 4:1. Early exposure to erythromycin in young infants has also be noted in babies with infantile hypertrophic pyloric stenosis (IHPS). Typically, the baby presents at 3 weeks of age with projectile, forceful vomiting, and an epigastric lump. The baby occasionally is dehydrated and sick due to excessive vomiting. A good clinical examination will reveal a pyloric tumor or an "olive". A plain X-ray abdomen is mostly nonspecific, but gastric dilatation with paucity of distal bowel gas is suggestive of IHPS (**Figs. 5A** and **B**). Gastric peristalsis may be seen as the "caterpillar sign". The baby has hypochloremic alkalosis due to loss of hydrochloric acid. Ultrasound shows >15 mm length and >3 mm width of the pyloric muscle. The surgery that follows is Ramstedt's pyloromyotomy which is the gold standard for this condition.

INTUSSUSCEPTION

The baby with intussusception is 3–9-month-old who is being weaned off from mother's milk and presents with incessant intermittent cry, with folding up of the legs, and



FIGS. 4A AND B: (A) Barium study in Hirschsprung's disease; (B) intraoperative Hirschsprung's specimen. ***(For color version, see plate 34)***



FIGS. 5A AND B: (A) X-ray pyloric stenosis; **(B)** intraoperative specimen pyloric stenosis. ***(For color version, see plate 35)***

bleeding per rectum. The baby with intussusception is usually a well-fed baby but gets sicker with increasing time. The baby starts to vomit and develops abdominal distention with current jelly stool. The intussusception is usually ileocolic and 90–95% are presumed to be the result of lymphoid hyperplasia. Diagnosis is made on a typical history and clinically an abdomen lump is felt. Early intussusceptions can be diagnosed and treated with ultrasound or fluoroscopic reduction. Ultrasound shows a target or "doughnut" sign. Fluoroscopy shows a typical meniscus sign or a filling defect. As time advances, the child becomes sicker lethargic and has altered sensorium. Adequate resuscitation, the baby requires surgical intervention. Surgical intervention varies from reduction of the intussusception with hydrostatic or fluoroscopic means to resection and anastomosis of the intussuscepted bowel which is gangrenous (**Figs. 6A** and **B**).

CONSTIPATION

A child with constipation presents with mild-to-severe abdominal pain sometimes mimicking appendicitis. A careful history and clinical examination will give the clue to the diagnosis. The child is typically one who has bottle feed through the day or someone who has junk food predominantly. A plain X-ray often shows impacted stools.

MESENTERIC LYMPHADENITIS

This condition can also mimic appendicitis. The pain is generalized and the white cell count is enlarged normal. The ultrasound shows multiple enlarged mesenteric lymph nodes. Most babies settle with pain killers but some require admission and IV fluids to give rest to the bowel.

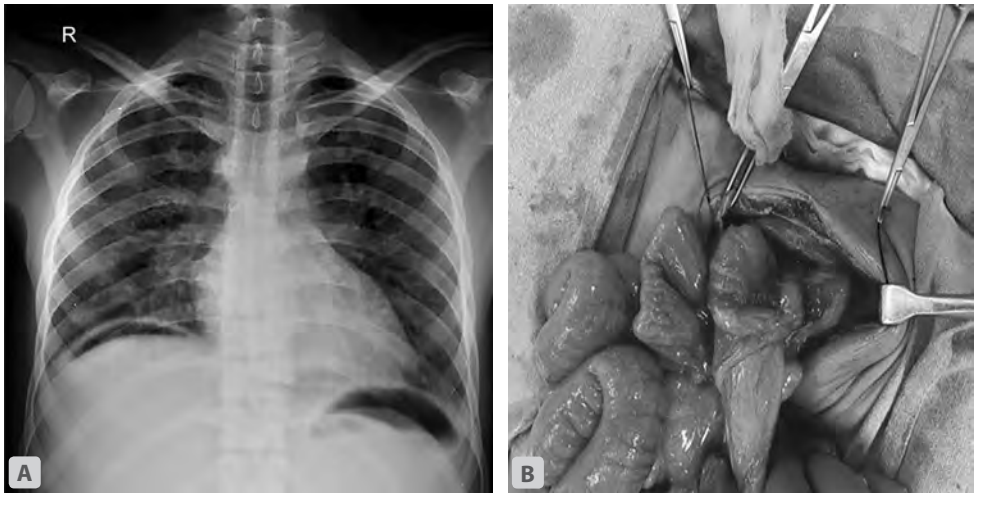
ABDOMINAL TRAUMA

Blunt trauma abdomen can present with an intestinal perforation (**Figs. 7A** and **B**) or mesenteric tear or omental torsion. Children sometimes hide the history of trauma when they present in emergency for fear that their parents may scold then. Any child with abdominal pain should be asked for history of trauma. Splenic and liver trauma may present with abdomen pain or distention. The child is pale and an ultrasound is diagnostic management of lower and splenic trauma response to conservative management along with blood transfusion, very few babies require surgery.

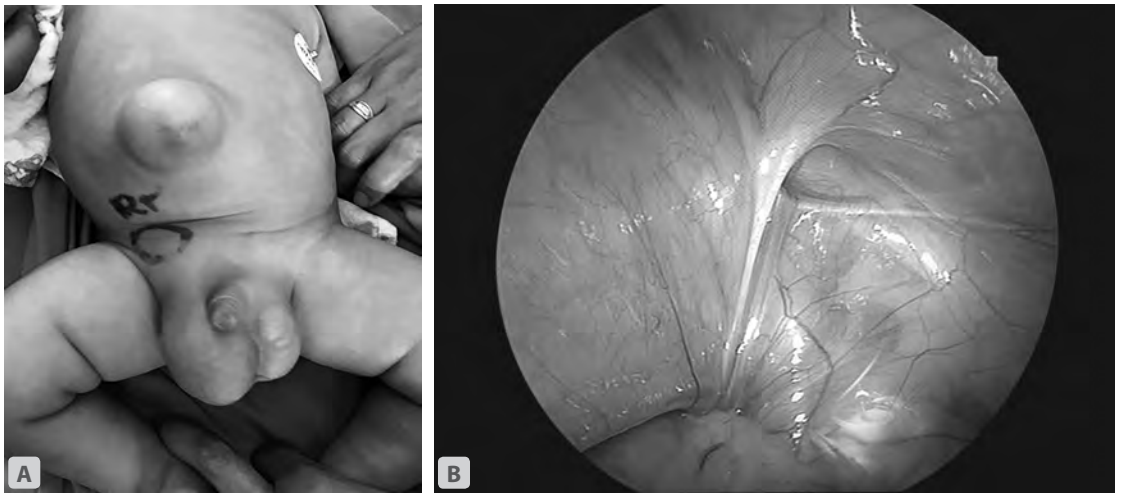
OBSTRUCTED HERNIA

The most common emergency is a child who presents with a swelling in the inguinal region which does not reduce. If

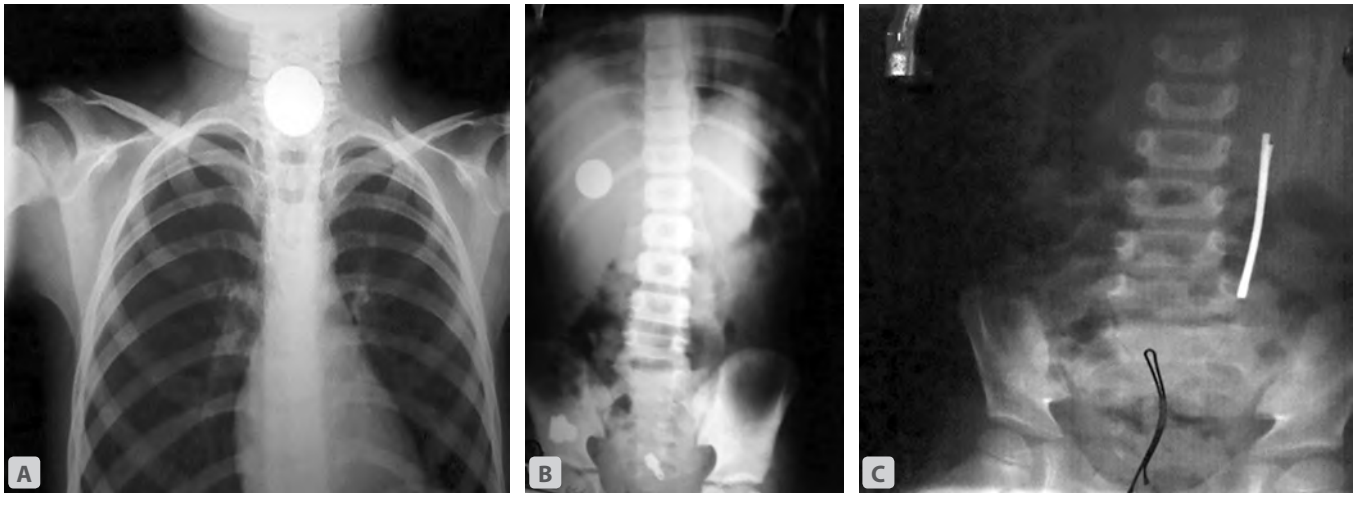
FIGS. 6A AND B: (A) Intussusception; (B) resected specimen. ***(For color version, see plate 35)***



FIGS. 7A AND B: (A) X-ray showing air under the diaphragm; (B) Intestinal perforation. ***(For color version, see plate 35)***



FIGS. 8A AND B: (A) Irreducible swelling right inguinal and umbilical hernia; (B) laparoscopic correction. ***(For color version, see plate 36)***



FIGS. 9A TO C: Foreign body ingestion—(A) coin in esophagus; (B) coin in abdomen; and (C) clip abdomen.

this swelling is irreducible (**Figs. 8A** and **B**), the child starts to vomit and develops distention of the abdomen. It cannot be overemphasized that any child who comes with abdominal pain must be examined with the pants pulled down to look for an obstructed hernia or a torsion testis. Occasionally, it could be an obstructed umbilical hernia. Early diagnosis is the way to early recovery. An attempt can be made to reduce the hernia and operate next morning. If it remains irreducible, then an emergency surgery must be carried out or else the bowel will become gangrenous.

FOREIGN BODY INGESTION

The average age of a baby who swallows a coin or aspirates a peanut is 1–2 years. The baby who swallows a coin is usually comfortable and has no physical finding except the history. A plain X-ray can be performed to locate the foreign body in cricopharyngeus or in the stomach (**Figs. 9A** to **C**). It can be taken out by a Magill forceps in the child in ER itself. However, button batteries are notorious. If history of button battery is present, and the X-ray confirms the battery, then emergency endoscopy must be done to extract the foreign body. Foreign bodies in the laryngotracheal tree are dangerous as the baby comes with mild-to-severe respiratory symptoms of sudden duration. The culprit is usually a vegetable foreign body such as a peanut, a screw, a whistle, or a pen tip. A good history and clinical will clinch the diagnosis. Unilateral decreased breath sound or noisy breathing may be present. The patient may be admitted to the ward or pediatric intensive care unit (PICU) depending on his clinical condition. Rigid bronchoscopy is the way forward. The reason we mention it here is that it is sometimes difficult to differentiate a foreign body in the esophagus versus the trachea.

APPENDICITIS

Appendicitis is common after 5 years of age and the child usually presents with central abdominal pain and right iliac fossa tenderness with rebound tenderness. The male-to-female ratio is 1.4:1. The child may be dehydrated with poor appetite for a day or so. The white cell count is raised with neutrophilia and the clinical diagnosis is confirmed by ultrasound. If the history is longer than the child is sicker and the abdomen may be tense and tender all over suggestive of a perforated appendix with peritonitis. There are various clinical prediction rules (CPRS) and various scores such as Alvarado score/MANTRELS

(Migration, Anorexia, Nausea/vomiting tenderness, relend pain, Elongation of temperature, Leukocytosis), and pediatric appendicitis score (PAS). Treatment consists of stabilizing the child followed by appendectomy; open/laparoscopy (**Fig. 10**). Computed tomography (CT) scan is only done in case of a diagnostic dilemma. Sensitivity and specificity for CT are 94% and 95%, respectively, over USG, 88% and 94% (Doria 2006).

MECKEL'S DIVERTICULUM

Meckel's diverticulum presents with painless bleeding per rectum. Meckel's diverticulum can also cause intussusceptions and intestinal obstruction. Painless bleeding from the heterotrophic gastric mucosa of a Meckel's is diagnosed by a technetium scan. If the diagnosis is still in doubt, an ultrasound and CT should be done. The choice of treatment is surgical resection of the Meckel's and an anastomosis of the small bowel (**Figs. 11A** and **B**).

CHOLECYSTITIS

The child presents with epigastric pain which later shifts to the right hypochondrium. The child may have fever, symptoms of dyspepsia, and tenderness in the right hypochondrium. The white cell count is raised and an ultrasound shows a thickened gallbladder (GB) wall or GB calculus (**Fig. 12**). An acalculous cholecystitis can occur in a child with enteric fever. Although, rare such patients are sicker and may need surgical intervention. Management consists of conservative management with an elective cholecystectomy 6 weeks later. If there is evidence, if perforation, then an emergency cholecystectomy is warranted.

PANCREATITIS

Pancreatitis is rare in children, although seen from time to time. The child presents with acute epigastric or central abdominal pain which is radiating to the back. On examination, there may be tenderness in the epigastric region. Serum amylase and serum lipase are often raised. An ultrasound may show GB stones. The pancreas is best seen on the CT scan (**Fig. 13**). Pancreatitis responds to rest to the GI tract by inserting a nasogastric tube and IV fluids. Once the child has recovered, a magnetic resonance cholangiopancreatography (MRCP) is done to evaluation the biliary tract, surgery is only indicated in cases of pseudocyst of the pancreas or an anatomical anomaly in the biliary or pancreatic duct.

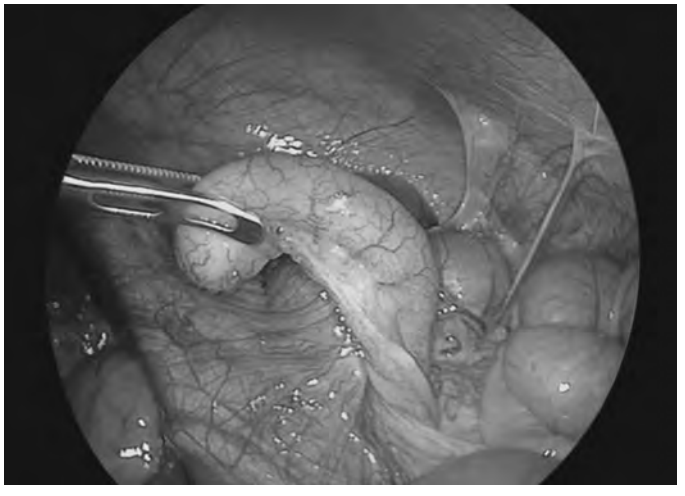
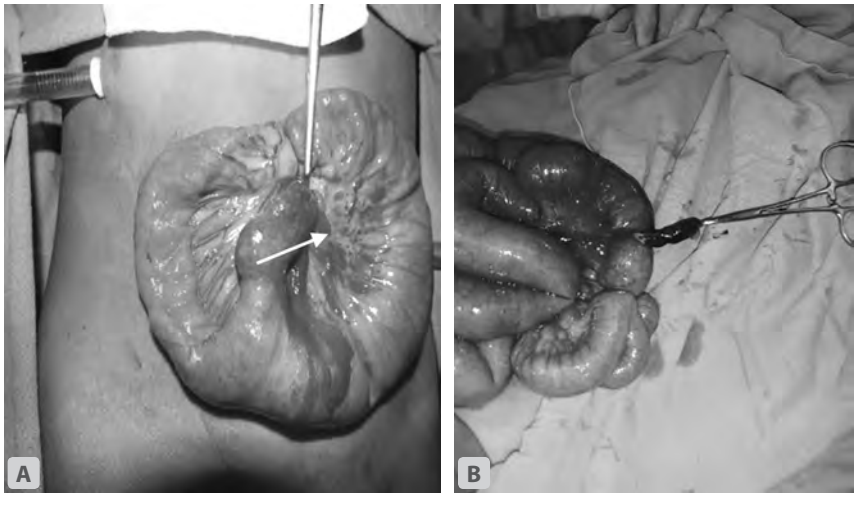


FIG. 10: Appendix (laparoscopic view). ***(For color version, see plate 36)***

FIG. 12: Gallstones. ***(For color version, see plate 37)***



FIGS. 11A AND B: (A) Meckel's diverticulum; (B) Meckel's gangrenous. ***(For color version, see plate 36)***

FIG. 13: Pancreatitis on computed tomography.

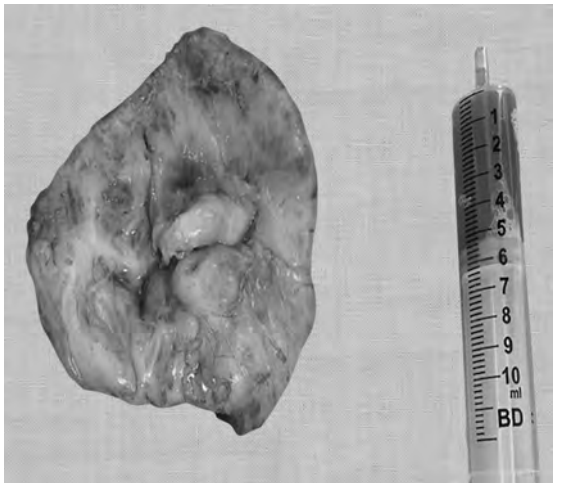


FIG. 14: Mesenteric cyst. ***(For color version, see plate 37)***

ABDOMINAL CYST

Abdomen or mesenteric cyst is often congenital acute abdominal pain occurs usually when the cyst is twisted. The child may present with increasing abdomen girth. Ultrasound is diagnostic and, in some cases, CT scan may be required. Management consists of surgical intervention (**Fig. 14**).

FEATURES OF CONCERN

Signs, symptoms, or radiological findings that prompt urgent surgical intervention.

- *Red flag symptoms*: Bilious vomiting/persistent nonbilious vomiting, inability to tolerate feeds, incessant cry, abdominal distension with vomiting, and bleeding per rectal with unstable vital signs
- *Red flag signs*: A lethargic child with pallor/dehydration, labored shallow fast breathing or grunting, abdominal distension visible loops/visible peristalsis, distended abdomen with tenderness/rebound tenderness, and hypothermia (in neonates). Radiology features which are suggestive of serious pathology are X-ray abdomen—pneumoperitoneum, multiple air fluid levels, fixed localized dilatation of loops, paucity of bowel gas in abdomen, paucity of bowel gas in pelvis and dilated proximal loops, pneumatosis intestinalis, and portal venous gas. Ultrasound abdomen findings suggestive of serious pathology are free fluid, target sign of intussusception and acute appendicitis. Color Doppler finding which suggestive of serious pathology are superior mesentric artery (SMA) and superior mesentric vein (SMV) axis reversal, decreased or absent flow to a gonad.

POSTOPERATIVE COMPLICATIONS

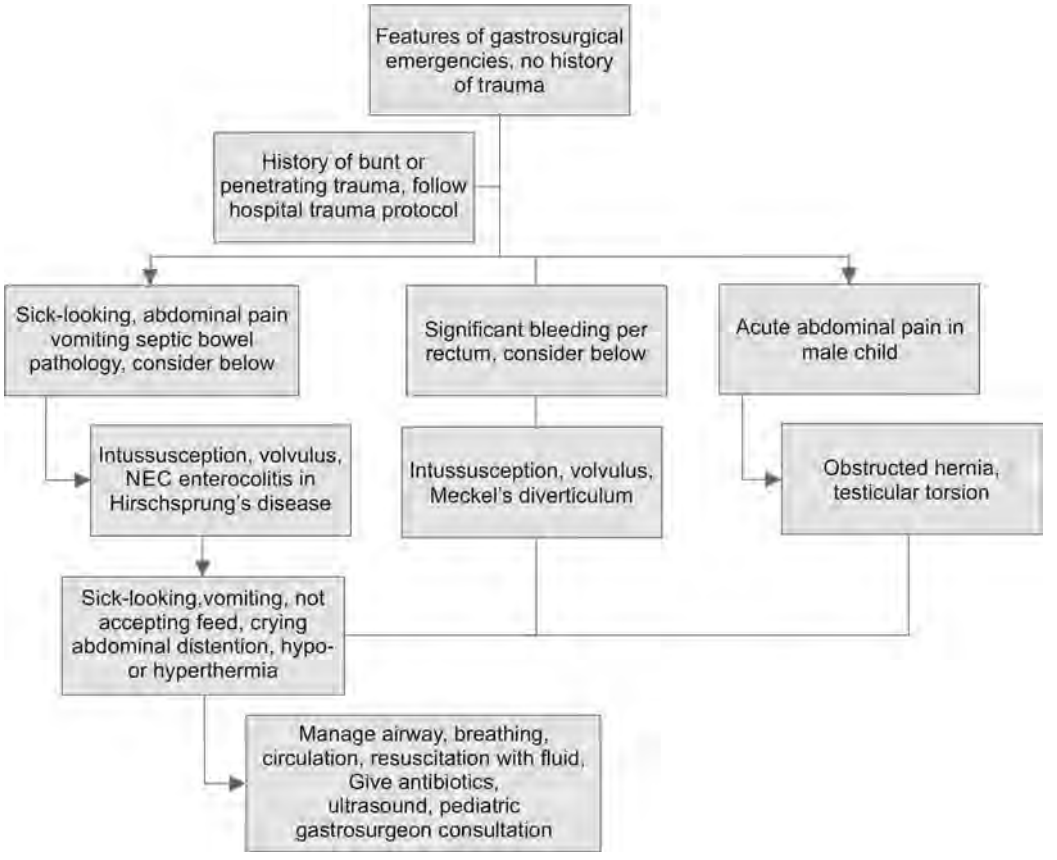
Patients operated for pediatric gastrointestinal emergencies may develop the various complications in postoperative periods, e.g., mild-to-moderate wound infections, leak from intestinal anastomosis, residual abscess and bleeding and postoperative adhesive obstruction. All these complications can be anticipated and addressed from the time the patient enters the emergency by a vigilant emergency physician. Early antibiotics and early diagnosis followed by good resuscitations will warrant early surgery. Intestinal perforation and severe abdomen pain with grossly distended abdomen which do not respond to nasogastric aspiration demand early surgery.

MANAGEMENT

Management consists of fluid resuscitation, placement of appropriate size nasogastric tube and continuous drainage, hospitalization, serial examination, and treatment of underlying cause. If pediatric patient with acute abdominal symptoms rule out any history of blunt or penetrating trauma (follow hospital trauma protocol if trauma). Sick looking children with abdominal pain and vomiting have septic bowel pathology unless proven otherwise, e.g., volvulus, intussusception, NEC, and enterocolitis in Hirschsprung's disease. Bilious vomiting is an indication of a high bowel obstruction, warrants immediate surgical consultation. Significant bleeding per rectum with unstable vital signs can be seen in intussusception, Meckel's diverticulum, and volvulus. Examination of genitalia is imperative in children with acute abdominal signs, especially boys, to pick up obstructed hernias and testicular torsions. On examination, if child is sick appearance, lethargic, inability to accept feeds orally, vomiting, hyper-/hypothermia, abdominal distension, and low urine output incessant cry; start the resuscitative measures: Perform primary survey, check oxygen saturation, temperature, and dehydration signs, start resuscitation with intravenous fluid, start broad spectrum antibiotics, warm the babies if hypothermic, place the nasogastric tube and aspirate if indicated. Perform initial investigations, e.g., venous blood gas, blood glucose, blood group and typing, X-ray chest and ultrasound abdomen if indicated and arrange early neonatologist and pediatric surgeon consult. Management approach of gastrosurgical emergencies is summarized in **Flowchart 1**.

SUMMARY

Abdominal pain is one of the most common presenting complaints in the pediatric emergency department. Early recognition of any life-threatening conditions requires high indices of suspicion and also rewarding. The diagnosis of pediatric abdominal emergencies remains challenging despite advances in research and treatment and can be associated with high cost and morbidity. Management often includes appropriate fluid resuscitation, electrolyte repletion, obtaining advanced imaging, and prompt surgical consultation.


Features of gastrosurgical emergencies, no history of trauma
History of bunt or penetrating trauma, follow hospital trauma protocol
Sick-looking, abdominal pain vomiting septic bowel pathology, consider below
Significant bleeding per rectum, consider below
Acute abdominal pain in male child
Intussusception, volvulus, NEC enterocolitis in Hirschsprung's disease
Intussusception, volvulus, Meckel's diverticulum
Obstructed hernia, testicular torsion
Sick-looking,vomiting, not accepting feed, crying abdominal distention, hypo- or hyperthermia
Manage airway, breathing, circulation, resuscitation with fluid, Give antibiotics, ultrasound, pediatric gastrosurgeon consultation

FLOWCHART 1: Management approach for gastrosurgical emergencies.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Geriatric Emergency Department

Don Melady, Thom Ringer

INTRODUCTION

Most medical specialties define themselves by the organ system in which they are an expert. By contrast, Dr Judith Tintinalli, a preeminent emergency physician leader, has described emergency medicine (EM) as "a population-based specialty." By this, she means a group of clinicians who must provide every form of care—preventive, primary, urgent, and critical—to anyone and everyone in the community they serve, particularly its most vulnerable members. More so than any other specialty, every aspect of EM practice is heavily determined by the characteristics of that population.

There is no more universal and striking feature of the world's population than its rapid aging. Worldwide, the number of persons aged 80 years or over is expected to triple between 2017 and 2050. In India, a comparatively young nation by global standards, the number of adults aged 65 years or older is expected to rise from 83 million in 2019 to 227 million by 2050. Moreover, in much of the world, the increase in emergency department (ED) visits by older adults outpaces the rate of growth of this population.

These trends have enormous implications for the vast majority of EDs that already struggle with funding, staffing, and space. American data reveal that on an average, an older patient stays in the ED for 20% longer and uses 50% more laboratory and imaging services than younger counterparts. Moreover, frail (medically and psychosocially vulnerable) older adults are at a high risk of prolonged hospitalization, functional dependence after discharge, healthcare-related harm, and death.

Equally, though, care of older adults is uniquely rewarding and an opportunity to return to the compassionate heart of medicine. Harkening back to Tintinalli's paradigm of a *population-based specialty*, the International Federation of Emergency Medicine has challenged EM practitioners and institutions to "recognize that older people are *a core population of service users,* not defined merely by chronological age but by the complex interactions of physical, psychological and social frailty, disease, and access to care."

Despite a tendency among EM clinicians and bodies to see care of older adults as resting outside of the specialty's core responsibilities, geriatric EM (GEM) advocates have been successful in:

- Creating and promoting best practices for the design and operation of geriatric EDs
- Developing robust research to support evidence-based care of older adults
- Advocating for more attention to geriatric topics in medical education

In this chapter, we focus on creating and promoting best practices in the geriatric ED.

WHAT IS A GERIATRIC EMERGENCY DEPARTMENT?

Creating a geriatric ED does *not* require a purpose-built space, radical redesign, or even changes apparent to the naked eye. Rather, the GEM pioneer Dr Ula Hwang and her colleagues simply *define a geriatric ED as one that provides:*

- Better education in GEM care for all clinicians, including physicians, nurses, and allied health professionals
- Evidence-based protocols for common geriatric syndromes
- Appropriate structural modifications

In 2013, the American College of Emergency Physicians (ACEP), the Society for Academic Emergency Medicine, the American Geriatrics Society (AGS), and the Emergency Nurses Association developed and published practice guidelines designed to "effectively improve the care of the geriatric population and which [are] feasible to implement in the ED." In 2018, on the basis of these guidelines, the ACEP began accrediting geriatric EDs. In the culmination of nearly a decade of innovative work, the ACEP Geriatric ED Accreditation Criteria (GEDA Criteria) are a structured and rigorous framework to help put into practice the tenets articulated by Hwang et al. By 2020, 166 EDs, including international ones, had achieved one of the three levels of accreditation.

Formal accreditation may not be the goal of all EDs which want to improve the care of older ED patients. They may simply

want a framework to organize those changes. As such, we offer a practical, minimalist approach to *three key elements of the geriatric ED*:

1. People
2. Education
3. Processes

A PRACTICAL APPROACH TO GERIATRIC EMERGENCY DEPARTMENT OPTIMIZATION

People

Creating Leadership

Ideally, a geriatric ED will have one physician and one nurse manager with joint responsibility for the oversight of the geriatric ED initiatives and processes. These professionals should have some minimal geriatrics training and/or experience—or strong interest in cultivating such expertise—and continually develop their geriatrics knowledge and skill base. The ACEP GEDA Standards, for instance, recommend 8 hours of geriatric-appropriate continuing education every 2 years.

Involving Multiple Disciplines

Geriatrics-informed ED care requires attention to the interplay of medical, physical, psychological, and social vulnerabilities. While EM physicians can and should recognize the presence of these last three factors in their patients, they are not trained or best positioned to evaluate and address all of them. As such, it is essential to involve nursing staff as well as physiotherapists, social workers, occupational therapists, and other allied health professionals from the outset of any geriatric ED initiative. Most EDs do not have those professionals as a regular part of the ED team. It is helpful to establish a process with them that allows for targeted assessments of the selected older patients in a timely manner.

In departments without allied health support, other options include focused training for nurses in gait and falls risk assessment and creating a binder (real or electronic) of information about community resources available for older adults. In their advocacy at the departmental and institutional levels, the geriatric leads should prioritize an access to an interdisciplinary team ahead of education and supplies. Nothing has shown more positive impact on patient outcomes for older adults than multidisciplinary care.

Engaging Patients and Caregivers

In most societies, family members provide a substantial amount of care for older adults. In many cases, particularly where the older adult is cognitively impaired or does not speak the language in which medical care is provided, caregivers are responsible for carrying out discharge instructions, following up on referrals and results, and managing medication changes. This experience offers them invaluable insights into the practical aspects of care, both within the ED and after discharge. Involving patients and caregivers in the development and governance of geriatric ED initiatives helps to capture those perspectives and use them to improve care.

Education

The GEDA Criteria observe that "the success of (a geriatric ED program) rests largely on the education of a multidisciplinary staff directed toward the needs of the geriatric population." Molnar and colleagues' *"5M" model* summarizes the care issues that clinicians need to address to provide optimal care to older adults in any setting (**Table 1**).

Effective Interdisciplinary Education

Given that geriatric ED care is a team sport, it follows that the teams that provide care together should learn together. While the design of effective educational programs is beyond the scope of this chapter, a comprehensive review by Hammick and colleagues of the evidence around interprofessional education highlights certain key principles which are as follows:

- Staff should fully participate in the development and delivery of educational programs.
- Programs should be continuously improved based on the learner reactions.
- Curricula must reflect as much as possible the actual practice environment, including its limitations, rather than an abstract ideal state.
- Teaching should be structured with an understanding that staff are adult learners in professional practice with little dedicated educational time, as opposed to preclinical students whose main focus is didactic learning.
- Like any change program, education should be evaluated in real and simulated practice settings for its impact on attitudes and behavior.

Ways of Delivering Education

The GEDA Criteria recommend considering a broad range of educational methods, including didactic lectures, case

TABLE 1: 5M model for geriatric patient care in an emergency department.

Category	*Description*
Mind	• Mentation • Dementia • Delirium • Depression
Mobility	• Impaired gait and balance • Fall injury prevention
Medications	• Polypharmacy • Optimal prescribing • Adverse medication effects and medication burden
Multicomplexity	• Multimorbidity (the presence of multiple overlapping and interacting medical conditions) • Complex biopsychosocial situations
Matters most	Each individual's own meaningful health outcome goals and care preferences, going well beyond the most basic issue of so-called code status

conferences, simulations, journal clubs, coaching, and online modules. Simulation and case-based learning, though resource-intensive, are preferred by learners. In addition, studies demonstrate that they are particularly well suited to promoting interdisciplinary collaboration and teaching learners to untangle the complexity of geriatric ED scenarios using a variety of perspectives.

It is also important to provide training to all staff whose work involves providing care to the older ED patient. In most systems, EM physicians and nurses play a large role in educating prehospital ambulance and emergency medical services (EMSs) personnel. Despite having the direct contact with older adults in the community, prehospital clinicians consistently receive limited geriatric training. Community paramedicine, which gives EMS an expanded role in delivering public health, primary and preventive care to older adults where they live, is one of the most promising geriatric ED innovations.

Processes

Patient's Journey

Depending on their acuity, all ED patients go through certain steps in their journey through the department, e.g., transport/arrival, triage, transfer to another area of the department, initial assessment by a nurse, physician assessment, treatment, reassessment or consultation, and disposition. The geriatric ED is the one in which all of these steps have been examined and improved using geriatric principles. Physician leaders have a natural tendency to pay the most attention to what they know best and focus exclusively on medical decision-making (e.g., simply encouraging physicians to broaden their differentials or consider the harms of treatment). However, this approach neglects all the other interactions that affect care.

One simple exercise, common to all quality improvement initiatives, is to collaborate with ED staff to draw a map of the typical patient journey and then consider what unique challenges older adults face at each stage. Examples include:

- *The waiting room*: Is the "front door" of the ED accessible to older adults who use canes or walkers? Are signs readable to people with visual impairment? Can people with cognitive impairment understand where they are supposed to go?
- *Triage*: Are caregivers encouraged to participate, even if by phone, in the triage process so that ED personnel can get the whole story? Is there an opportunity for triage personnel to look for signs that a patient might be physically or socially frail? Can they flag older adults whose chronological age does not match up with their "medical age" (level of morbidity or functional impairment)? Might they screen for cognitive impairment and ask about and document living situation and medications?
- *Discharge*: Does preparation for discharge involve more than simply establishing a diagnosis? Is safety for discharge assessed? Are caregivers notified when an older adult is being discharged home? If a discharge prescription is provided, does someone ask how the patient will fill it and know how to take it? If there are concerns about cognitive impairment, are follow-up and return-to-care instructions clearly documented and communicated to someone who can ensure that they are followed?

Medical Directives and Preprinted Order Sets

In many geriatric EDs, triage and/or nursing personnel are permitted by medical directive to initiate certain orders before the patient is seen by a physician. These include measures to prevent falls, and delirium prevention orders through effective management of factors, such as pain, disorientation, and constipation. Many EDs also have preprinted order sets that allow physicians to quickly and conveniently activate these measures even when they are not extensively trained in taking care of older adults.

Policies and Protocols

Though labor- and time-intensive, the GEDA Criteria strongly recommend a full review of all the departmental and institutional policies and procedures with the potential to affect care *of* older adults. These should be analyzed using a 5M lens to optimize them for geriatric patients. Examples of pertinent policies include:

- Standardized screening for delirium and cognitive impairment using validated tools
- A medication review by a pharmacist as part of the ED process
- Screening of an elder for abuse and neglect
- A standardized approach to fall assessment to identify the cause and modifiable risk factors and modifications for safe discharge
- Pain assessment and control
- Goals of care (e.g., do not resuscitate/allow natural death, palliative care)
- Clear evidence-based guidelines for urinary catheter placement

SUMMARY

Populations of older people are increasing globally. They are among the core users of ED services. A successful ED in the 21st century will acknowledge that reality and will start making changes—large and small—to its structure and processes. This may involve a long-planned and expensive complete change of the physical environment if time and resources are unlimited. But more importantly, it should involve small incremental changes, implemented one at a time—enhanced education of caregivers about issues specific to older patients, creating opportunities for enhanced assessment beyond those that are purely medical, or changing the workflow to permit screening for important geriatric conditions, such as delirium and cognitive impairment and abuse/neglect.

Early research suggests that implementing these changes has a beneficial return on investment. While hiring a new geriatric nurse case manager may be expensive, it may well lead to a significant decrease in ED length of stay, in avoidable admissions, and in unnecessary early ED returns. Similarly, implementing a process that ensures early identification or prevention of a delirium can pay substantial human and financial dividends in decreased morbidity and hospital expenses. Building a system that allows ED physicians and nurses to provide the best possible care to older patients will create conditions for better recruitment and retention and instill a sense of pride that they are fulfilling the EM mission, best articulated by Dr Tintinalli, of being an essential resource to all members of the community they serve.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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178 CHAPTER

Comprehensive Geriatric Assessment

Lorraine Lau, Rebecca Schonnop

INTRODUCTION

Older people often have multiple comorbidities, polypharmacy, and atypical presentations. Unlike younger patients, they rarely present to the emergency department (ED) with an isolated medical issue. They require a comprehensive approach for evaluation, management, and disposition planning. Multiple domains need to be considered including medical, psychological, functional, and social and environmental factors. Physicians often focus on the medical assessment, but other domains are equally important to care of in the ED and will largely influence the assessment and disposition plans. To capture these multiple important domains in the geriatric care, a comprehensive geriatric assessment (CGA) was developed by geriatricians. A CGA is a multidimensional interdisciplinary approach toward older persons to help develop a complete holistic care plan. Completion of a CGA in the ED has been associated with reduced functional decline and a decrease in repeat ED visits. However, it is time consuming and is not intended to be used by emergency physicians for episodic assessment of patients with acute presentations. In this chapter, the CGA framework (**Fig. 1**) will be used to outline how to apply an acute comprehensive assessment for older patients in the ED setting, categorizing these components within the medical, psychological, functional, and social and environmental domains.

MEDICAL ASSESSMENT

Older people often present to the ED with atypical clinical presentations, physical findings, and investigation results due to age-related physiologic and anatomic changes. These changes can result in vague or delayed complaints with absence of typical findings, confounded by polymorbidity and polypharmacy with drugs that may cause or mask disease symptoms.

Generalized symptoms—such as weakness, dizziness, fatigue, and malaise—are easy to dismiss, but these may be due to multiple serious causes. They require cautious evaluation as these patients are at increased risk for bad outcomes. Falls are a common ED presentation for older patients; they should be thought of, not as an event, but as a symptom. They may be the presenting complaint for underlying illness and pathology, such as acute coronary syndrome, sepsis, adverse drug effects, and intra-abdominal pathology. Older people often lack the typical presentation of illnesses, such as pain or fever. A review of past medical history, medications, and a thorough physical examination are components of this medical assessment. This section will highlight some principal differences in the clinical presentation and physical examination that should be considered for older patients.

Vital Signs

Due to age-associated changes, interpreting vital signs in older patients requires enhanced knowledge and skills of physicians. These changes lead to loss of regulatory and adaptive mechanisms. Older people also have a lower core body temperature and altered thermoregulatory responses.

FIG. 1: Comprehensive geriatric assessment framework.

Compensatory tachycardia may not be observed as maximal heart rate decreases and the cardiovascular system is less adrenergically responsive with age. Hypotension can be a later clinical sign due to stiff peripheral vasculature and loss of responsiveness to sympathetic stimuli. Furthermore, dysregulation of autonomic sensitivity can lead to orthostatic hypotension. Assessing orthostatic vitals can be helpful in patients presenting with dizziness or syncope.

Neurologic System

A complete neurologic exam may sometimes be difficult because of cognitive or sensory impairment. On physical exam, look for signs of head injury, neurologic deficits, impaired speech, and impaired cognition. As part of the neurological assessment, physicians should also screen older people for delirium. Delirium is reported in 7–20% of older patients in the ED, and older ED patients are at the highest risk for delirium. Delirium is associated with increased morbidity and mortality, reinforcing the need for routine screening and early recognition. Numerous screening tools have been validated or tested for diagnostic accuracy for use in the ED, including variations of the confusion assessment method (CAM), such as brief confusion assessment method for the (bCAM), modified confusion assessment method for the emergency department (mCAM-ED), and confusion assessment method for the intensive care unit (CAM-ICU). The fundamental components of delirium guided by CAM are outlined in **Figure 2**. To accurately complete a delirium screen, one must know the patient's baseline status, acquired through collateral history.

Cardiovascular System

With age, a weakening cardiovascular system leads to increased risk of diseases including coronary artery disease, dissection, heart failure, valvulopathies, and other comorbidities. Silent or unrecognized infarctions account for 25% of all myocardial infarctions (MIs) but account for up to 60% in patients over the age of 85 years. For acute coronary syndrome patients, those over the age of 85 years are more likely to present with heart failure and have different symptoms, such as dyspnea, diaphoresis, nausea and vomiting, and syncope compared to younger patients. On physical examination, evaluate for existing or new murmurs, irregular and nonequal pulses, and signs of heart failure.

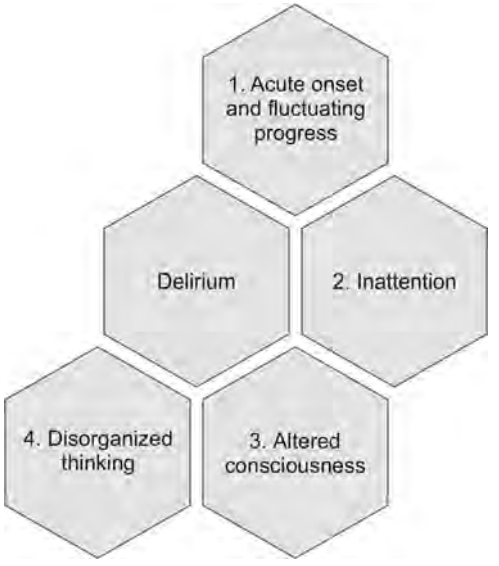

FIG. 2: Components of delirium based on confusion assessment method: Delirium = 1 + 2 + either 3 or 4.

Respiratory System

Pulmonary function decreases with age, and cardiopulmonary disease can further decrease respiratory reserve. On exam, assess for respiratory distress, auscultate for adventitious sounds, and take into consideration baseline respiratory function [e.g., history of chronic obstructive pulmonary disease (COPD)]. For ambulating older patients, consider performing a walk test in the ED while monitoring oxygen saturation to look for desaturation with exertion.

Gastrointestinal System

Compared to younger patients, older patients with intra-abdominal infections tend to present atypically or delayed which are associated with increased likelihood of surgical intervention, morbidity, and mortality. The abdomen should be examined fully, noting previous scars, pain, distension, organomegaly, masses, or ecchymoses. In older patients, abdominal musculature is often thin, which may lead to limited guarding and rigidity in the presence of peritonitis. Localization of pain is also impaired due to fewer peripheral sensory nerve cells.

Genitourinary System

Urinary tract infections (UTIs) are commonly overdiagnosed, largely due to the high prevalence of asymptomatic bacteriuria in older people (up to 19% in community-dwelling older people). According to Canadian and American guidelines, urinary symptoms include urinary frequency, urgency, dysuria, suprapubic tenderness, costovertebral tenderness, changed urinary incontinence, and gross hematuria. New confusion, decreased appetite, falls, wandering, or aggression alone are not indications for investigations of a UTI.

Musculoskeletal System

Given the increased prevalence of osteoporosis in older patients, even minor trauma such as a fall from standing height can lead to fractures. Approximately 10% of falls among older adults result in a fracture. Hip fractures, for example, are associated with a significant increased risk of mortality and morbidity. In geriatric trauma, special considerations include spine fractures, rib fractures, pelvic fractures, and long bone fractures. Assess for neurological deficits, respiratory distress in cases of associated pneumothorax, hip pain, and bone deformities.

Integumentary Examination

Aging skin loses elastin and collagen, the epidermis becomes thin, and there is decreased subcutaneous support. As such, older adults have fragile skin and are more prone to soft-tissue injuries. With immobilization, pressure ulcers may develop in as little as 4–6 hours and become a potential source of infection. On exam, it is important to assess the patient's back and sacral region and look thoroughly for ulcers, skin breakdown, and cellulitis.

Medications

Polypharmacy increases with advanced age. Due to physiological changes with aging, pharmacokinetics (what the body does to a drug) and pharmacodynamics (what a drug does to the body) are different in older patients. A thorough review of a patient's medications is important, including both prescription and over-the-counter drugs. In addition to obtaining an accurate list, physicians should inquire about how the patient manages his/her medications. Identify if the patient requires observation and assistance with medication administration, and if the medications are stored in bottles, pill organizers, or blister packs. A habit history of recreational substances including cigarettes, alcohol, and cannabis consumption should also be documented. This accurate and complete medication history is imperative to prescribe safely in the ED, to discern if presenting symptoms may be attributable to adverse medication effects, and to continue important home medications while the patient is in the ED.

PSYCHOLOGICAL ASSESSMENT

Older adults can present to the ED with cognitive impairment, agitation, and behavioral changes. This can include acute delirium, behavioral and psychological symptoms of dementia, and mood disorders. Delirium should be assessed as part of the acute neurological examination, described above. Cognitive and mood assessments should be considered for older people in the ED as indicated by their presenting issues.

Cognitive Assessment in the Emergency Department

The ED visit is a unique opportunity to identify underlying neurocognitive disorders which may have a significant impact on the patient's ability to function in the community and may have an impact on the ED assessment. A patient with underlying cognitive impairment may not be able to give an accurate history, to participate in the entire physical examination, or to understand and follow through with disposition planning. While there are several validated cognitive assessments available, such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Rowland Universal Dementia Assessment Scale (RUDAS), they have limited applicability in the ED because of time constraints. The three step Mini-Cog instrument is a screening tool that can be completed quickly in the ED to aid in identifying cognitive impairment. This short test involves a three-item recall component for memory and a clock drawing test. A score of 3 or greater indicates a lower likelihood of dementia but does not rule out mild cognitive impairment. Collateral information from family, friends, or caregivers can aid in understanding the patient's baseline cognitive status prior to ED presentation. If a cognitive disorder is suspected, this may alter your assessment and disposition instructions in the ED. It should certainly be communicated to the primary care provider in the community for follow-up.

Assessment of Mood Disorders

Major depression is a prevalent health disorder in older adults. Compared to younger patients who may present with primarily low mood, older people with depression more commonly have irritability, anxiety, and physical/somatic symptoms. There are short, validated tools that can be used in older persons, including the ED Depression Screening Instrument (ED-DSI) and the Patient Health Questionnaire-2 (PHQ-2). If a patient screens positive for depression, this should prompt a safety assessment to inquire about suicidality, including protective and risk factors. It is important to arrange follow-up in the community and communicate mood or safety concerns with the primary care provider when the patient is safe for discharge.

FUNCTIONAL ASSESSMENT

Beyond diagnosing and treating older patients' medical issues in the ED, it is especially important to evaluate their functional status. This includes their ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs refer to self-care tasks: transferring (i.e., between a bed and chair), toileting, bathing, dressing, feeding, and continence. IADLs refer to activities that are needed to live independently: shopping, preparing meals, housekeeping, managing medications, driving or using public transportation, managing finances, and using a telephone/technology. Identifying in the ED the patient's baseline function can clarify the clinical presentation and guide disposition planning. Inquiring about current help and services at home (i.e., primary caregiver, personal support worker, community services) is important for a safety assessment. It may prompt a suggestion for additional home support.

Gait assessment is a vital component of the functional assessment. Provide patients with an appropriate mobility aid for evaluation. The timed up and go (TUG) test is a simple test that can be used in the ED for assessing mobility, static, and dynamic balance. The patient stands up from sitting position on a chair, walks for 3 meters, turns around, walks back, and sits back down. If the test takes longer than 20 seconds, it indicates that the person may need assistance and further evaluation. If it takes 30 seconds or more, it suggests that the person is prone to falls. However, it is important to note that no single screening method used in isolation, including the TUG, has been demonstrated to be accurate for predicting the risk of falls.

Allied healthcare professionals play an essential role in the functional assessment of patients. If available in the ED, interdisciplinary team members can help with more detailed evaluations that can help optimize discharge planning. These professionals include occupational therapists, physical therapists, social workers, and dedicated geriatric ED nurse case managers.

SOCIAL AND ENVIRONMENTAL ASSESSMENT

Assessing the patient's socioenvironmental circumstances is vital in organizing an appropriate discharge plan. This domain includes understanding the patient's social support network (i.e., spouse, family, caregiver, roommate), available support resources (i.e., family, community services), and environmental/home safety (i.e., ability to perform usual ADLs/IADLs in the physical environment). Home safety also encompasses the physical and social environment. Screening for elder abuse and/or neglect is an important part of the

assessment. Correcting a patient's acute medical illness without considering social and environmental factors can quickly break down a discharge plan, resulting in an unsafe discharge, or a prompt return ED visit. For example, discharging a patient home with a wrist fracture splinted in a cast may not be appropriate if the patient lives alone, has limited social support, and uses a walker for ambulation. If available, use your allied health workers, including social workers and geriatric ED nurse case managers, to help facilitate this assessment and liaise with community support services. Occupational therapists in the community can also help with assessing the patient's home environment, identifying safety risks, and recommending assistive devices or environmental modifications.

Advanced Care Planning

In the face of potentially life-threatening circumstances, early goals of care discussion in the ED ensure patient-centered care. Have the discussion with the patient if they are competent and the situation is appropriate, identify the person who has the power of attorney, and look for official documents such as a Do Not Resuscitate Confirmation Form. Online tools are available for physicians interested in developing skills for discussion on advanced care planning and end of life, such as the Center to Advance Palliative Care (CAPC) website (https://www.capc.org/).

SUMMARY

Older people present to the ED with complex clinical presentations that can make the diagnosis, management, and safe disposition challenging. An ED-based CGA, similar to a formal CGA, enhances care of the older patient by considering the medical, psychological, functional, and social and environmental domains of the patient's presentation. It is essential to factor these contributing aspects into disposition planning and to utilize an interdisciplinary team approach to deliver high-quality care to older patients in the ED.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Geriatric Syndromes

Devendra Richhariya

INTRODUCTION

With increasing age, physiological degeneration of various organs occurs as a normal biological process and requires no treatment, termed physical aging. With improvement in the accessibility of the healthcare system to most, people are living longer; the prevention of disability in elderly is the basis of healthy aging. A geriatric syndrome is a condition of "multifactorial health conditions with impairment of multiple systems in an older person vulnerable to situational changes." The geriatric syndrome is a unique feature of common health problems in older people with multifactorial and multiorgan systems involvement. These syndromes do not limit to one organ system or discipline-based boundaries, because of their multifactorial nature. For example, an elderly patient may present to the emergency room with delirium and altered cognitive and neural functions if they have urinary tract infection (UTI). The geriatric syndrome-defining criteria include: (1) disorders related to age, (2) age-related functional decline, (3) multiple systems involvement, (4) complex multifactorial etiology, (5) usually poor outcome if not diagnosed early and treated, and (6) usually treatable.

Five major geriatric syndromes are as follows: (1) falls, (2) urinary incontinence (UI), (3) pressure ulcers, (4) delirium, and (5) functional decline. The common risk factors of these giants of the geriatric syndromes include age, cognitive impairment, functional impairment, and impaired mobility. Frailty is the common entity of these geriatric syndromes. The main feature of frailty—after a stressful and destabilizing event—is the reduced ability to regain physiological homeostasis. With the decline in physiological reserve and function of multiple organ systems with increasing age, elderly are often unable to cope up with the acute stresses. Frailty in turn may further intensify the shared risk factors and the geriatric syndromes.

FALLS

A fall is considered as an unintentional event when a person attempts to rest on the lower surface. Falls can be divided into three phases. The first phase includes initiating events which involve extrinsic risk factors, such as environmental hazards, and intrinsic risk factors, such as joints problems, weakness of muscles, and slow postural reflexes. The second phase is considered when systems which maintain upright posture fail to detect and correct any displacement in time to avoid a fall. These are individual and intrinsic factors related to body, such as loss of sensory function, impaired central processing, and muscle weakness. The third phase includes body impact on environmental surfaces, usually the floor or ground, which results in the transmission of forces to body tissue and organs. This is followed by sequelae phases, with disabling prospects which may be physical, psychological, or social. Falls are extremely common among older adults. Each year, about one out of three elderly people who live in the community falls; this rate increases with advanced age and is higher among people who live in institutional settings. Falls cause considerable mortality and morbidity. The risk factors for falls include: (1) *Intrinsic risk factors*: gait and balance impairment, peripheral neuropathy, vestibular dysfunction, muscle weakness, vision impairment, medical illness, advanced age, impaired activities of daily living (ADLs), orthostasis, dementia, and drugs and (2) *Extrinsic risk factors*: Environmental hazards, poor footwear, and restraints.

Assessment for Falls

The most important predictors of falls can be assessed by taking the history of previous falls, gait/balance impairment, use of psychoactive medication, and decreased muscle strength. The assessment of fall includes detailed history of fall to find out a specific etiology or to narrow down the differential diagnosis. This includes history of orthostatic hypotension or slip gait, balance or vision disturbance, vertebrobasilar insufficiency, arterial or carotid sinus compression, and loss of consciousness (history of syncope or seizure). History should also be taken for assessment of risk factors including polypharmacy and functional and environmental assessments. Physical examination should include assessment of gait, assessment of hearing and vision (sensory assessment), measurement of orthostatic vital signs, and neurologic and musculoskeletal assessment, as well as depression and cognitive impairment screening. The examination should also include an appropriateness of footwear and gait aid. Depending on the results of this risk assessment, appropriate multifactorial interventions may be undertaken for preventing ambulatory falls, such as home assessment and modification

for high-risk individuals; exercise programs that include strength, gait, and balance exercises, such as physiotherapy; vitamin D supplementation in doses greater than 700 IU/d; review medications, minimizing psychoactive medications and reducing the total number of medications; management of postural hypotension; expedition of cataract surgery on the first affected eye; and considering pacing in cardioinhibitory carotid sinus hypersensitivity and recurrent falls. Manage foot problems and recommend use of antislip shoe devices for the outdoors. The patient and the caregiver should be educated regarding specific environmental improvement.

URINARY INCONTINENCE

Urinary incontinence is a troublesome and common disorder among geriatric patients that leads to a social or hygienic problem. UI is an involuntary loss of urine that is objectively demonstrable and many older frail persons require assistance by a caregiver. The urinary continence is maintained due to the integrity of the lower urinary tract (LUT), the nervous system, the visceral supporting mechanism (pelvic floor), and the urine production mechanism. With aging, the LUT undergoes a series of morphological and functional changes, which alter the functions, such as bladder overactivity and urgency, impaired bladder contractility, increased residual urine, and decreased functional bladder capacity. UI and LUT symptoms may be caused by prostatic hypertrophy—benign or malignant. In women, an increased incidence of atrophic vaginitis and related symptoms occurs due to estrogen deficiency, which increases the incidence of recurrent UTIs, and also UI. A practical approach to incontinence in an elderly patient depends on its duration (acute or chronic).

Acute or transient incontinence: This includes cases of short-duration incontinence (lasting <4 weeks), including functional, without any associated structural disorder. The causes for these include: *D*—delirium, dementia, diabetes; *R*—restricted mobility, retention; *I*—infection, inflammation, impaction of stool; *P*—pharmaceutical agents and psychological causes.

Chronic or established incontinence: These cases are commonly associated with structural disorders, either in the urinary tract or outside of it (e.g., nervous system). The incontinence lasts longer than 4 weeks. This established incontinence might be further classified depending on the etiopathogenesis. Urge incontinence presents as urgency, frequency, and nocturia. Elderly may present with strong urge to void, caused by an overactive detrusor muscle causing excessive involuntary bladder contraction. Various neurological conditions including stroke, spinal cord lesions, dementias, and Parkinson's disease are associated with UI. Coughing, sneezing, bending, lifting, or laughing increase intra-abdominal pressure which gives rise to conditions known as stress incontinence. The cause is pelvic muscular weakness causing urethral hypermobility, multiparity, hypoestrogenism, obesity, and pelvic surgical procedures, such as prostatic resection. Overflow incontinence occurs when the bladder muscle is overdistended. The patient may present with stress or urge symptoms. Functional incontinence is considered when in spite of a competent urinary system, physical or psychological impairment impedes continence status. A mixed type of incontinence, including features of more than one aforementioned type, may also occur.

Assessment for Urinary Incontinence

History-taking should include the questions about UI onset, frequency, volume, timing, and associated factors or events. Cognitive and functional assessments along with potential comorbid conditions associated with UI should be evaluated under physical examination. Perform rectal examination to assess masses, tone, and prostate nodules or firmness in men (not size). The neurologic assessment should be done to evaluate sacral cord integrity with perineal sensation. Examination of vaginal mucosa should be done for severe atrophy, and the pelvic examination should include evaluation for pelvic organ prolapse (cystocele, rectocele, uterine prolapse) with straining. Urine analysis is important for hematuria, pyuria and/or bacteriuria, dysuria, associated with fever, or other signs of UTI, especially if UI is not acute. Ultrasound or catheterization is used to look for postvoid retention, especially in frail elderly with recurrent UTIs and neurological concerns. A clinical stress test (single vigorous cough relaxed patient) may be helpful in documenting stress UI. When etiology is questionable and intervention is required, cystoscopy and urodynamic studies may be used.

Treatment

Correction of contributing factors and reversible causes is an important part of treatment. Nonmedical interventions, such as lifestyle and behavioral changes, are beneficial; these include avoiding excess of fluid intake, especially in the evening to avoid nocturia, less intake of caffeinated beverages, and alcohol; and smoking cessation. Bladder training and pelvic muscle exercises, both of which are effective for urge, mixed, and stress UI and are often used in combination, are two main behavioral therapies for UI. Pharmacologic treatment is largely limited to antimuscarinic agents for urge UI, overactive bladder, and mixed UI. Of these, oxybutynin (immediate and extended release, and topical patch), tolterodine (immediate and extended release), solifenacin, darifenacin, and trospium have been used widely. Women who have stress or urge UI are exacerbated by bladder or uterine prolapse, and pessaries may benefit them. Duloxetine is used for moderate-to-severe stress UI, especially in women. Alpha-blockers are beneficial in men with LUT symptoms, use cautiously due to hemodynamic effects. Desmopressin should be avoided in elderly UI because it can precipitate hyponatremia. In the cases of chronic urinary retention or bladder-impaired contractility, in which the patient keeps high postvoid residual urine, catheterization may be required. Minimally invasive therapies helpful for patient with urge UI refractory to antimuscarinics include botulinum toxin injection into the bladder wall and sacral neuromodulation. In refractory cases, especially in women with stress incontinence, surgery may be beneficial.

PRESSURE ULCERS

Pressure ulcers are developed when an area of skin and the tissues which get placed under pressure result in impairment of their blood supply and leads to their damage. Pressure sores, bedsores, and decubitus ulcers are the other different names of the pressure ulcers. Pressure ulcers exert deep impact on both patients and the healthcare system. These lead to severe or intolerable pain, are prone to infection, and are associated with high mortality rates.

National Pressure Ulcer Advisory Panel (NPUAP)/European Pressure Ulcer Advisory Panel (EPUAP) international classification of pressure ulcers:

Stage I: Intact skin and nonblanchable erythema.

Stage II: Partial-thickness skin, loss of the epidermis or dermis, presentation of lesions as an abrasion, blister, or superficial ulcer.

Stage III: Full-thickness skin loss that may extend up to the fascia but does not penetrate the fascia; the ulcer may be undermined.

Stage IV: Full-thickness skin loss with involvement of deeper structures, such as muscle, bone, or joint structures.

Unstageable ulcer (depth unknown): Full-thickness tissue loss in which the base of the ulcer is covered by slough and/or eschar in the wound bed.

Suspected deep tissue injury (depth unknown): Discolored intact skin, with purple or maroon localized area, or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear.

Risk factors for pressure ulcers' development are either intrinsic or extrinsic. The intrinsic risk factors responsible for pressure ulcers are reduced mobility and poor nutrition. Less subcutaneous fat, decreased dermal thickness, and decreased sensory perception in elderly persons make them prone to more rapid tissue injury and delayed healing. In some studies, incontinence, diabetes mellitus, stroke, white race, skin abnormalities, and male sex are also documented as rick factors for pressure sore. The extrinsic factors responsible for pressure ulcers are pressure, friction, shear stress, and moisture. Out of these, pressure is the most significant predictor of pressure sores. Sacrum, heels, ischial tuberosities, greater trochanters, and lateral malleoli are the most common sites for pressure ulcers. Friction can damage superficial skin, as well as deeper vessels, leading to increased ischemia. Moisture is also the independent risk factor for pressure ulcer and associated infections as well.

Assessment for Pressure Ulcers

Thorough clinical examination is critical to the identification of pressure ulcers that may serve as an occult focus for infection. Look for signs of soft-tissue involvement, such as warmth, erythema, local tenderness, purulent discharge, and presence of foul odor. Systemic signs, such as fever and leukocytosis, may be minimal or absent, and even local signs of inflammation may not be obvious because of associated comorbidities and advanced age. One should assess for the presence of exudate, odor, sinus tracts, necrosis or eschar formation, tunneling, undermining, infection, healing (granulation and epithelialization), and wound margins. As patients who are malnourished have more bony prominences and are therefore at a greater risk for pressure ulcers, nutritional assessment is important. Microbiological evaluation should be done with an aim to distinguish between bacterial invasion and colonization. Blood cultures or cultures of deep tissue biopsy specimens are more clinically important than the cultures of superficial swab or aspiration of the pressure ulcer. Imaging studies in cases of pressure ulcer are helpful in the assessment and determination of the presence of osteomyelitis and to find out the extent of deep-tissue involvement. It includes plain radiography, CT and MRI, and radionuclide scintigraphy.

Management of Pressure Ulcers

Reduction of extrinsic factors—in particular, pressure relief—is a cornerstone of therapy. This may be done with the use of pressure-reducing devices, such as low-air loss or air-fluidized bed, or static devices, such as foam or fluid-filled mattresses or supports, in patients who can change positions independently. Debriding of necrotic tissue, cleansing the wound, managing bacterial load and colonization, and selecting a wound dressing are other important components of ulcer management. Appropriate antibiotic therapy is instituted in infected pressure ulcers. In an elderly frail patient who is susceptible to develop pressure ulcers, prevention is the most important aspect. Risk factor assessment on hospital visit and application of appropriate preventive measures, such as improving general health, minimizing external forces, and promoting educational programs about pressure ulcers to caregivers, are the keystones. The emphasis on quality nursing care is important in this regard.

DELIRIUM

Delirium is considered as an acute, fluctuating syndrome of altered mental status, unawareness to surroundings, and cognition precipitated by an underlying condition or event, in vulnerable persons. It is frequently described by using terms, such as altered mental status, acute confusional state, sundowning, encephalopathy, and acute organic brain syndrome. An episode of delirium can initiate a cascade of deleterious clinical events, in older adults and serious complications including prolonged hospitalization, loss of functional independence, reduced cognitive function, and death. History from various sources (family members, caregivers, etc.) and bedside observations are helpful in diagnosing the delirium. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for delirium include:*

A. A disturbance in attention (i.e., inability to direct, difficulties in focus, unable to sustain, and shift attention) and unawareness (reduced orientation to the environment).
B. The delirium develops over a short period of time (usually hours to a few days); baseline attention and awareness changes and fluctuation of severity occur during the course of a day.
C. Cognition disturbance (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D. Criteria A and C changes are not explained by another preexisting, neurocognitive disorder and not explained in the context of a severely reduced level of arousal, such as coma.
E. History, physical examination, or laboratory findings confirm that the disturbances are due to multiple etiologies and as a result of direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or a medication), or exposure to a toxin.

Multiple risk factors give rise to development of delirium. The risk factors are of two types: (1) predisposing factors (patient arrives with) and (2) precipitating factors (iatrogenic factors). In older people, dementia is the most prominent risk

factor and present in up to two-thirds of all cases of delirium. Severe medical illnesses; comorbid psychiatric disorder; such as depression, alcoholism, poor functional status, inactivity, malnutrition, male gender, hearing or vision impairment; and social isolation are the other predisposing factors. Common drugs which precipitate delirium are sedative hypnotics, narcotics, anticholinergic drugs, corticosteroids, and other psychoactive medications. Besides infection (urinary tract, lungs, skin, blood), metabolic disturbances (fluid, electrolytes, nutrition), polypharmacy, structural upsets (surgery, trauma, cardiac ischemia, central nervous system and pulmonary insults), and retention problems (fecal impaction, constipation) may be involved.

Assessment for Delirium

Clinically, in delirium, patients may be hyperactive (agitation, restlessness, hypervigilance), or hypoactive (apathetic, lethargic) or mixed. Delirium in the geriatric age group presents with subtle manifestations, such as incontinence (new onset), falls, immobilization, dysphagia, dysarthria, mild disorientation, and slowing in the speed of mental processing. The detailed history is important in assessing the delirium which should include the mental status change and search for potential predisposing, precipitating, or perpetuating factors, e.g., recent medication changes or signs of medical illnesses. For identifying the delirium the *confusion assessment method* is the most effective tool. A comprehensive physical examination of cardiorespiratory and neurologic systems is required to find out infectious diseases.

Treatment

Diagnosis and treatment of the underlying conditions remain the mainstay of managing the delirium in elderly. Whenever possible, medications, such as psychotropic, narcotic, and anticholinergic medications, should be reduced or discontinued. Physical illnesses should be treated on an urgent basis. Nonpharmacological measures are of great help in managing the delirium in older people, measures such as noise reduction; provision of soft lighting, clocks, and calendars; orienting the patient to time and place; appropriate powered eyeglasses and hearing aids are helpful in correcting sensory deficits and increasing the patient's sense of control which may reduce symptoms.

FUNCTIONAL DECLINE

The functional status of an elderly is determined by the ability to perform ADLs—self-care activities that a person performs daily, such as eating, dressing, bathing, ambulating, and toileting—and instrumental activities of daily living, which a person performs to live independently, such as shopping for groceries, meal preparation, housework, getting to places beyond walking distance, managing medications, managing finances, and using a telephone. Cardiopulmonary diseases, neurologic conditions, diabetes mellitus, cancer, obesity, dementia, affective disorders, ophthalmologic and auditory disorders, and fractures are the common health problems in the elderly, which cause a functional decline. In geriatric population, the active presence of various health issues (e.g., arthritis, stroke, heart disease) may have a more disabling effect than predicted in the day-to-day life and hampers the self-care also. An elderly patient commonly experiences reduced mobility and activity levels during hospitalization. Functional decline, including changes in physical status and mobility, has been identified as the leading complication of hospitalization for the elderly.

Assessment of Functional Status

History taking, with the emphasis on characterization of the functional disability itself and focusing on the course of functional decline, associated symptoms, and specific tasks that have been affected by the disability, including basic ADLs is important. An assessment of the existing comorbid conditions should be done, such as cognition, mood disorders, pain, poor nutrition, adverse medication reactions, sensory impairments, and muscular weakness. Contextual factors, including social support, financial resources, and environmental factors, should be assessed by the physician.

Treatment

Medical and surgical interventions should be undertaken promptly, if needed. These interventions typically increase the capacity and improve the quality-of-life (e.g., cataract surgery, hip replacement, oxygen supplementation, medications to improve cardiac output). Also, exercise, nutritional supplements, and prosthetic devices (e.g., hearing aids) greatly improve the overall functional status. Early mobilization protocols, timely removal of catheters, and reorientation programs should be undertaken during hospital stay itself before discharging the patient.

SUMMARY

With improvement in accessibility of healthcare to most of the population, people have started living longer; the prevention of disability in the elderly is the basis of healthy aging. Geriatric syndrome is a condition of "multifactorial health conditions with impairment of multiple systems in an older person vulnerable to situational changes." A geriatric syndrome comprises unique features of common health problems in older people with multifactorial and multiorgan systems involvement. These syndromes do not limit to one organ system or discipline-based boundaries, along with their multifactorial nature. Good history-taking, comprehensive physical examination, and specific management are necessary for assessing geriatric syndrome.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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180 CHAPTER

Abuse or Neglect in Geriatric Population

M Sai Surendar

INTRODUCTION

Is there elder abuse in India? Elder abuse is not a problem in India. Our culture is respectful and supportive toward elders, hence protecting elders against the scourge of abuse. Old age has never been a problem for India as a value-based family system prevails in our country. *Role of elderly in society*: *Elderly* people have substantive experience throughout their lives. They play an important role in contributing to the knowledge capital of the society, emotional-spiritual guidance to a community. *What has sidelined the elderly*? The wisdom of elderly has been sidelined in the age of digital world. Techno smarts have eclipsed the wisdom of age and experience of the elderly population. Now it seems that the information held by most experienced members of the society is now uploaded into the cloud, easily googled with a few strokes on the keyboard. We need to understand the risk factors of mistreatment with the elderly (**Table 1**). The risk factors for the abuse can be divided into victims related, perpetrators related, relation based, and community based. The risk factors can be high or low. Understanding the risk factors of abuse will be helpful in taking preventing measures.

DEFINITION: ELDER ABUSE

The World Health Organization, 2002, defines elder abuse as "A single, or repeated act, or lack of an appropriate action occurring within any relationship where there is an expectation of trust, which causes harm or distress to an older person." This broader definition includes abuse by any person, including strangers.

Action: Harming a person or his/her property or assets—*abuse.*

Not acting: Not providing care or assistance when a person should have—also called *neglect.*

Mistreatment can be a single one-time action or continuous and repeated acts over a period of time. The issue is always the impact on the older person. Ask yourself, was the older adult hurt in some way? Elder abuse comes various forms, such as psychological, chemical, financial, sexual, spiritual, confinement, and neglect (**Fig. 1**).

TABLE 1: Risk factors for abuse.

	Risk factors	***Risk level***
Individual (victim)	• Functional dependence/disability	High
	• Poor physical health	High
	• Cognitive impairment	High
	• Poor mental health	High
	• Low income/financial dependence	High
Individual (perpetrator)	• Mental illness	High
	• Abuser dependency	High
	• Substance abuse	High
	• Victim–perpetrator relationship	Potential
	• Marital status	Potential

Physical Abuse

Inflicting physical pain or injury by hitting, slapping, shoving, burning, and forceful restrain comprise physical abuse. We may not often witness an elderly person get hit. What we are more likely to notice is the injury (bruises, broken bones, physical pain), or an older adult's fear of an abusive person. In a caregiving context, being unnecessarily rough or forceful is physical abuse. For example, shoving or pulling a person into a room, dressing a person by yanking his/her limbs into clothes, or roughly transferring a person from a bed to a chair or toilet. In each of these instances, the caregiver could be gentle with the person.

Chemical Abuse

Overmedicating a person, denying needed medication, or making medication decisions without consulting a doctor comprise chemical abuse. Chemical abuse is medication abuse. Too much or not enough medication can cause harm. When medication decisions are not for the well-being of an older person or when medication decisions are made without the consent of the person who needs the medicine or the legal substitute-decision-maker, then that is abuse. Medication abuse is most common when older adults have health problems that make it impossible or difficult for them to take care of themselves, fill prescriptions, or understand medical information. For example, denying an expensive medication to save money for inheritance could be mistreatment. On the

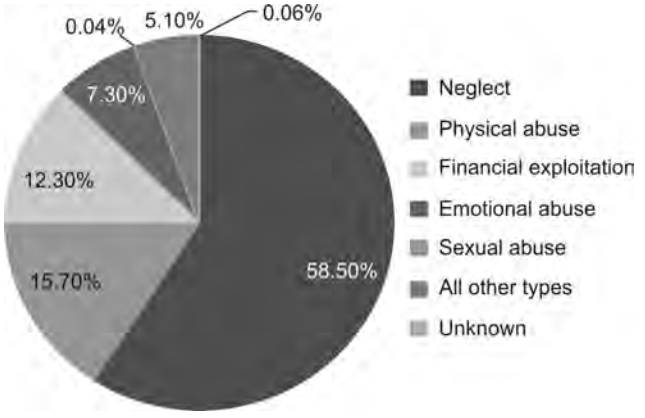

FIG. 1: Types of elder abuse.

flip side, giving them a higher dose of the medicine so that they become more docile and make fewer demands is also abuse.

Spiritual Abuse

Preventing a person from practicing his or her faith or forcing a person to participate in a spiritual ritual or to practice a religion comprises spiritual abuse. Our faith is an important part of who we are as people. When someone prevents an older person from practicing his or her faith and seeing people in a chosen faith community, then it is mistreatment. Prohibiting a person from going to church, mosque, or any other place of worship or from being involved in spiritual or religious practices of choice or forcing to practice a different religion or forcing a nonbeliever to follow a faith and its institutions can also be abusive. Forcing a person to participate in any religious or spiritual ceremony, event, or ritual could be elder abuse. Requiring a person to receive any form of spiritual-based healing would be abuse. Spiritual abuse is mentioned in very few laws, but it can go hand in hand with psychological abuse and can have a devastating effect on an older person.

Combinations

Emotional abuse often accompanies physical abuse or financial exploitation. Physical abuse often accompanies financial abuse.

NEGLECT

Neglect means failure to carry out a care-giving responsibility. *Passive neglect*: Unintentional failure. *Active neglect*: Intentional failure to provide care. Neglect is a complex idea. Basically, if a person depends on another person for care or assistance, and that person does not take proper care of the older person, that could be neglect. Assistance could be with food and nutrition, mobility, medication and medical appointments, and intimate activities, such as bathing and toileting. In some cases, assistance can mean finding a different helper if providing help is too difficult or time consuming for an individual.

STATISTICS OF GROUND REALITY

103.84 million people out of India's 1.21 billion population (census 2011) are senior citizens. Elder abuse is a silent pandemic. One in nine Americans over 60 years of age has experienced abuse, but only 1 in 23 cases of elder abuse in the US is reported. Most nations report that they still do not have a formal action plan to address elder abuse. A recent survey of 133 countries found that only 40% had national plans and only 17% had a national survey.

Reporting of abuse (WHO): Only 4% of elder abuse is reported. Elderly fear retaliation or worry about getting the abuser into trouble. Most of the elderly are mentally incapable and feel ashamed and embarrassed. Also, many countries do not have a proper system or have limited system where older people can turn for help. Most cases involve more than one form of abuse—79% involve psychological abuse, 54% financial abuse, 19% physical abuse, 17% neglect, and 1% sexual abuse. Major contributors of elder abuse are son (32.39%), relative (23%), daughter (14.5%), spouse (13.5%), stranger (7.04%), friend (5.16%), and neighbor (4.69). The perpetrators are often a family member—adult child or grandchild who is unemployed, addicted to alcohol and drugs and is mentally ill, or a socially irresponsible citizen. 67.3% of elder abuse victims are females as per the National Centre on Elder Abuse, Bureau of Justice.

Status in India: According to a rough estimate, nearly 40% of older population living with their families are reportedly facing abuse of one of the kind or other, but only 1 in 6 cases are reported. *Forms of abuse*: Disrespect—55%, verbal abuse—39%, economic exploitation—23%. Maintaining confidentiality of family matters is the main reason behind 45% of elders not reporting the abuse. Up to 23% of elders did not report abuse as they did not know how to deal with the problem. Up to 58% of elders experienced abuse in Madurai. 61% of them lived with family (HelpAge India report).

IDENTIFY ELEDR ABUSE IN THE EMERGENCY DEPARTMENT

A victim may be unable or unwilling to tell you that abuse is occurring in view of relationship to, or fear of, the abuser, which may affect the victim's willingness to pursue arrest. It is very important that an emergency physician recognizes signs of abuse in the victim. Inadequately explained bruises, cuts, burns, dehydration, and malnutrition could be some of the signs.

Overly medicated or sedated, unusual confinement, lack of grooming, fear of speaking for oneself, shame, fear, embarrassment, inadequate medical supplies leads to worsening health despite a treatment plan. Behavioral signs of abuse or neglect also need to be looked for. During the physical examination, note the size, shape, and location of all injuries. Photographing the injuries is helpful for forensic documentation.

PREVENTION OF ELDER ABUSE

Avoid living with a person with a history of abuse or violence. Beware of financial motifs of the family members. Elder should take appropriate measures (**Fig. 2**). They should stay social, expand their friend network, invite friends and relatives at home, and try new activities to make new friends. They should keep in touch with old friends and neighbors if a case of relocation is involved. They should be careful while signing any documents and take the help of a trusted one. They should not interfere with the lives of the younger generation and unnecessarily instruct them.

Caregiver interventions: This is a promising approach to prevent elder abuse, thus assisting them in housekeeping, meal preparation, education, and day care, which should be promoted as abuse-prevention strategies.

Stay social and expand friend circle
Do not interfere in lives of younger. Do not instruct or complain unnecessarily
Invite friend and relatives at home. Try new activities
What the elderly should do?
Do not sign any paper unless reviewed by trusted one
Keep in touch with old friends and neighbors

FIG. 2: Measures to prevent abuse.

Emergency shelter: Providing emergency shelter to battered elderly especially women is a hallmark intervention. However, shelter homes are not designed to accommodate older women with physical health problems or dementia. These shelter homes offer temporary relocation for victims, providing not only a safe environment but also a medically appropriate one.

Money management program: This is offered to individuals with financial exploitation. Assistance is given in paying bills, making bank deposits, and paying home care personnel. This intervention is promising, as the preventive potential is high and targeted to groups at high risk for financial exploitation and in particular individuals with some degree of cognitive impairment and who are socially isolated. Since this program is carried out by well-trained and accredited money managers, the risks of adverse outcomes are low.

Helplines

Telephonic helplines is one of the most widely effective interventions, which allow individuals to seek advice and assistance regarding elder abuse. Helplines are typically staffed by trained volunteers or professionals and facilitate early intervention that can prevent mistreatment.

Helplines have the advantage of in that that callers remain anonymous if they choose to because many elders experience shame about the abusive situation.

Multidisciplinary Teams

Multidisciplinary teams, including criminal justice, healthcare, mental healthcare, victim services, civil legal services, adult protective services, financial services, and long-term care, are helpful in proxy decision-making, coordinating care and reducing fragmentation, leveraging resources, increasing professional knowledge, and improving outcomes.

LEGAL FRAMEWORK

Hindu Personal Law: "The statutory provision for maintenance of parents under Hindu personal law is contained in Sec 20 of the Hindu Adoption and Maintenance Act, 1956."

Muslim Personal Law: "Children in easy circumstances are bound to maintain their parents even if they are able to earn."

The Code of Criminal Procedure (CrPC): "CrPC 1973 is a secular law and governs persons belonging to all religions and communities." "Daughters, including married daughters, also have a duty to maintain their parents." "Maintenance and Welfare of Parents and Senior Citizens Act, 2007, has also been there to provide legal assistance and help to senior citizens of our country."

SUMMARY

Older persons should be able to live with dignity and security and should be free from exploitation and mental and physical abuse. Every geriatric patient gives us an opportunity to look for abuse and to create awareness in the patient and his/her family about abuse. Resuscitation studies document no difference in the percentage of successful outcomes across the age spectrum. Elderly patients who survive are no more likely to sustain irreversible brain injury than younger patients. Unless there is a well-defined advance directive, there should be no discrimination based on age in resuscitating elderly patients in cardiac arrest.

MULTIPLE CHOICE QUESTIONS

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181 CHAPTER

Drug Therapy in a Geriatric Patient

Phraewa Thatphet

INTRODUCTION

The progression of medical technology and innovation makes human lives longer. The global proportion of the aging group of people increases every year as well as in the emergency department (ED). Geriatric patients account for up to one fourth of emergency patients. Unfortunately, research reveals that physicians still cannot treat this group of patients appropriately. Using drugs with potential adverse effects, polypharmacy, and adverse drug events (ADEs) are common problems in the elderly. These misconceptions of drug use in the elderly have caused many adverse effects and complications. This chapter aims to provide the principle of appropriate drug use in the elderly to enhance their good care taking. This chapter will highlight common and preventable clinical issues, which are prescribing inappropriate medication, polypharmacy, and ADE.

PHYSIOLOGIC CHANGES

Physiological changes due to aging affect both pharmacokinetics and pharmacodynamics. Understanding these processes will help physicians to optimize the choice of drugs, route, and dose in elderly patients.

Pharmacokinetics

The pharmacokinetic of drugs is divided into four main categories: (1) Absorption, (2) Distribution, (3) Metabolization, and (4) Excretion.

Absorption

The older adult will have decreasing gastrointestinal blood flow and motility, increasing gastric pH, and decreasing gastric acid secretion. But overall absorption function is not significantly changed in the elderly.

Distribution

The elderly has less lean body mass compared to the younger adult. This may affect the drug that binds to the muscle, for example, digoxin which can enhance toxicity even in a dose lower than expected. Older people also increase total body fat and decrease total body water. These affect the distribution of the drug. The hydrophilic drugs, for example, lithium, digoxin, and aminoglycosides, may decrease the volume of distribution and have higher initial serum concentration. On the other hand, lipophilic drugs, for instance, benzodiazepines, phenytoin, and propranolol may increase the volume of distribution and increase accumulation and prolong half-life. Aging people also decrease in plasma protein binding which leads to increase in free fractions of protein-binding drugs, for example, warfarin, diazepam, and furosemide. Older adults with malnutrition or having liver disease may affect albumin levels leading to decreased volume distribution and higher serum concentration in drugs with high protein binding. For example, ceftriaxone, furosemide, phenytoin, diazepam, ibuprofen, digoxin, and warfarin can lead to toxicity.

Metabolization

The liver is the main organ for metabolization in many drugs. Advanced age associated with decrease hepatic mass and blood flow. Decreasing blood flow affects metabolization with the first-pass mechanism and leads to increased bioavailability of the drug. Some of the drugs in this group that are commonly used in the elderly are calcium channel blockers, beta-blockers, nitrates, a tricyclic antidepressant, and hydralazine. Decreasing hepatic mass and number of functional hepatocytes slow down the metabolization of drugs and increase half-lives, for instance, acetaminophen, diazepam, nifedipine, and theophylline. The hepatic function of enzymes usually does not significantly change, but it can be affected with the co-congestion of multiple drugs that are metabolized with the same enzymes or with the consumption of a large amount of one type of drug. Cytochrome P450 is one of the enzymes that has a major role in drug metabolization, and it changes in the oxidative phase in an older adult which affect many drugs, for example, diazepam, amitriptyline, and alprazolam.

Excretion

The renal system is responsible for the excretion function. Unfortunately, renal function decreases with age even in the normal adult. The glomerular filtration rate (GFR) declines by about 8 mL/min/1.73 m^2 per decade after 40 years of age. Using serum creatinine alone is not reliable to estimate renal function

in older adults since it was affected by decreased muscle mass and muscle wasting. The Cockcroft–Gault formula is a useful tool to calculate GFR in an older adult as it uses the age, weight, and gender of the patient in the calculation. Even if a study showed that the Cockcroft–Gault equation overestimated GFR by 16%, it still remains handy and is a useful tool to use in the ED. In older age group, decrease in renal functions and clearance ability resulting the drug accumulation and toxicity of many drugs, e.g., aminoglycoside, lithium, morphine and ketorolac. Many drugs should be avoided in the elderly patients who have declined creatinine clearance, for example, ciprofloxacin, apixaban, dabigatran, enoxaparin, fondaparinux, rivaroxaban, gabapentin, pregabalin, tramadol, ranitidine, and colchicine.

Pharmacodynamics

The change in pharmacodynamics in an older adult can be explained from the decrease in the number of receptors or affinity or changes in postreceptor response which leads to a decrease or increase in sensitivity; another reason behind the change in pharmacodynamics is that physiologic and homeostatic mechanisms impairment with age. Patient can develop increase or decrease in sensitivity for a partcular drug. For beta-agonists, beta-blockers, furosemide, and various vaccines, the sensitivity decreases with advance age; on the other hand, benzodiazepines, dopaminergic agents, H1 antihistamines, metoclopramide, neuroleptics drugs, opioids, and warfarin have more sensitivity with aging.

Moreover, older people with malnutrition have some chance to alter the absorption and bioavailability of drugs as well as increase the toxicity of some drugs from dehydration and electrolyte imbalance.

COMMON PROBLEMS OF DRUG USE IN AN OLDER ADULT

Since there are many changes in the older adult, it leads to problems associated with aging change. There are many problems or ADEs related to medication use in the elderly, for example, polypharmacy, adverse drug reaction (ADR), medication nonadherence, over-the-counter drug, herb and remedies usage, drug treatment failure, medication error, prescribing inappropriate drug, inappropriate dosage, inappropriate medical handling, adverse drug withdrawal event, drug–drug interaction, drug–food interaction, untreated indication, and treatment without indication. The problems can be categorized into problems due to medical provider–related factors, drug-related factors, and patient-related factors. Some problem related to these factors are shown in **Figure 1**.

PRESCRIBING INAPPROPRIATE MEDICATIONS

Prescribing inappropriate medication (PIM) is a crucial issue for geriatric care. There was an estimate that half of the elderly patients were prescribed at least one potentially inappropriate medication with increasing prevalence during the past decade. Due to physiological changes listed above, the physician should bear in mind that the effect of medications used in a younger adult might not have the same effect as in the older people and sometimes can cause the risks. Using inappropriate medication in an elderly adult is associated with higher costs, ADEs, poorer health-related quality-of-life, falling, readmission to the ED, hospitalization, and even death. *Many tools are being used to assess inappropriate medications. Two of the most validated and practical tools for use in the ED are Beers and STOPP/START (Screening Tool of Older Persons' Prescriptions/ Screening Tool to Alert to Right Treatment) criteria, respectively.*

Beers Criteria

Beers criteria were developed by the American Geriatrics Society. The latest version was revised and launched in 2019. It contains the information about medications that are potentially inappropriate in most older adults, those that should typically be avoided in older adults with certain conditions, drugs to use with caution, drug–drug interactions, and drug–dose adjustment based on kidney function. **Table 1** lists some of the potentially inappropriate medication use in older adults that are frequently used in the ED.

Moreover, some medications have drug–disease or drug–syndrome interactions which should be avoided in patients with specific underlying conditions. Commonly used drugs have been listed in **Table 2**.

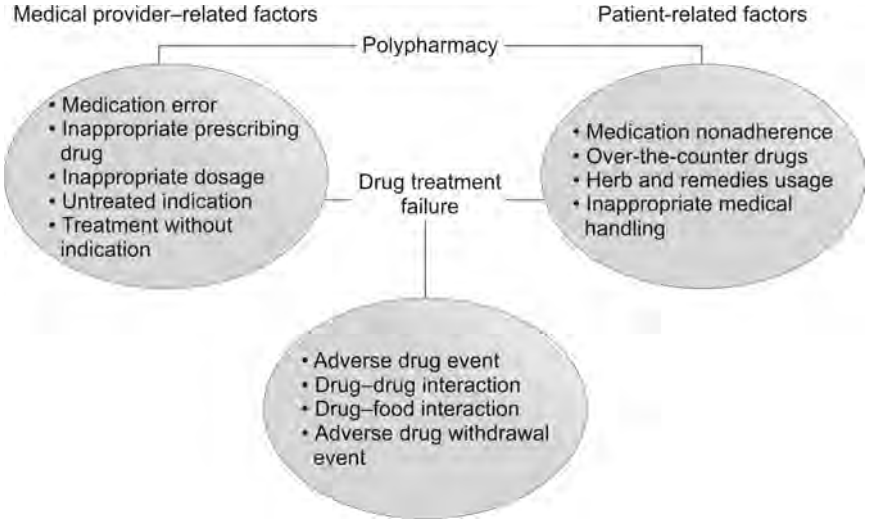

FIG: 1: Problems related to medication use in the elderly.

TABLE 1: Potentially inappropriate medications commonly used in older adults which should be avoided.

Drugs	*Recommendation*
• Anticholinergics First-generation antihistamines: ○ Chlorpheniramine ○ Cyproheptadine ○ Dimenhydrinate ○ Diphenhydramine (oral)	Avoid
Antiparkinsonian agents: Benztropine (oral)	Avoid
Antispasmodics: Hyoscyamine	Avoid
Cardiovascular: Digoxin	Avoid this rate control agent as first-line therapy for AF and HF
Amiodarone	Avoid as first-line therapy for AF unless the patient has HF or substantial LVH
• Central nervous system Antidepressants, alone or in combination: ○ Amitriptyline ○ Nortriptyline	Avoid
Antipsychotics, first (conventional) and second (atypical) generations	Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy
Barbiturates: Phenobarbital	Avoid
• *Benzodiazepines* • *Short and intermediate acting:* ○ Alprazolam ○ Lorazepam • *Long acting:* ○ Clonazepam ○ Diazepam	Avoid
Endocrine: Insulin, sliding scale	Avoid
Sulfonylureas, long-acting: Glyburide (Glibenclamide)	Avoid
Gastrointestinal: Metoclopramide	Avoid, unless for gastroparesis with the duration of use not to exceed 12 weeks
Proton-pump inhibitors	Avoid scheduled use for >8 weeks unless for high-risk patients
Pain medications: Meperidine	Avoid
• *Noncyclooxygenase-selective NSAIDs, oral:* ○ Aspirin > 325 mg/day ○ Diclofenac ○ Ibuprofen ○ Mefenamic acid ○ Naproxen	Avoid chronic use, unless other alternatives are not effective and the patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)
Indomethacin *Ketorolac*	Avoid
Skeletal muscle relaxants: Orphenadrine	Avoid

(AF: atrial fibrillation; HF: heart failure; LVH: left ventricular hypertrophy; NSAIDs: nonsteroidal anti-inflammatory drug)

Besides the previous list of drugs, some medications should be used with caution in the older adult, for instance, aspirin (for primary prevention of cardiovascular disease and colorectal cancer), dabigatran, rivaroxaban, prasugrel antipsychotics, carbamazepine, diuretics, SNRIs, SSRIs, TCAs, tramadol, dextromethorphan/quinidine, and trimethoprim-sulfamethoxazole.

Elderly people tend to have more diseases and need more medication groups of treatment. BEERS criteria also list potentially clinically important drug–drug interactions that should be avoided in older adults. Some of the common drugs are listed in **Table 3**.

Avoid using drugs in the same class because most of the ADEs are dose dependent.

Beers criteria also pay attention to drugs with strong anticholinergic properties that can cause serious adverse effects in the elderly, for example, delirium, falls, hospitalization, and death. Common uses of drugs in this group are amitriptyline, nortriptyline, promethazine, antihistamines (first generation), hyoscyamine, benztropine, chlorpromazine, and orphenadrine.

STOPP/START Criteria

STOPP/START criteria were developed by the European multidisciplinary specialists. These were adapted from the Beers criteria by aiming at avoidance of medications that cause or contribute to adverse effects and hospitalization in older adults. The criteria updated the medications commonly used in Europe and have been last revised in 2015. STOPP contains the list of medications that have drug–drug and drug–disease interactions, drugs that increase the risk of falls, and drugs which duplicate therapy. Some examples of drugs listed in STOPP criteria which are frequently prescribed in the ED are listed in **Box 1**.

STOPP criteria also describe drugs that affect elderly people who are prone to fall. These drugs are benzodiazepines, neuroleptic drugs, and vasodilator drugs with persistent postural hypotension.

Opioid usage is one of the most concerned points in the general population as well as in the elderly. STOPP criteria give the suggestion not to use long-term powerful opiates, e.g., morphine or fentanyl as first-line therapy for mild-to-moderate pain, and regular opiates for >2 weeks in those with chronic constipation without a concurrent laxative.

STOPP criteria also suggest to avoid using drugs in the same class (duplicate drug classes).

There is some intersection between BEERS and STOPP criteria. Anyway, the physician should use both tools as a guide to correlate with the patient's clinical condition and judge for the risk–benefit of the patients.

START criteria are criteria about medications that should be considered in patients aged 65 years old or more with a specific condition and no contraindication. Example of the medications which can be started in the ED are listed in **Box 2**.

POLYPHARMACY

There are various definitions of polypharmacy, both from using unnecessary medication or from using too many medications. In general, polypharmacy is defined as using 5 or more medications and hyperpolypharmacy is using 10 or more medications.

TABLE 2: Medications should be avoided in older adults with certain medical conditions.

Disease or syndrome	*Drug(s)*	*Recommendation*
Heart failure	Avoid in heart failure with reduced ejection fraction: Nondihydropyridine CCBs (diltiazem, verapamil)	As noted, avoid or use with caution
	Use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure: NSAIDs and COX-2 inhibitors	
Syncope	• AChEIs • Nonselective peripheral alpha-1 blockers (i.e., doxazosin, prazosin) • Tertiary TCAs • Antipsychotics: ○ Chlorpromazine ○ Olanzapine	Avoid
Delirium	• Anticholinergics • Antipsychotics • Benzodiazepines • Corticosteroids (oral and parenteral) H2-receptor antagonists: ○ Cimetidine ○ Ranitidine • Meperidine	Avoid
Dementia or cognitive impairment	• Anticholinergics • Benzodiazepines • Antipsychotics	Avoid
History of falls or fractures	• Antiepileptics • Antipsychotics • Antidepressants: ○ TCAs ○ SSRIs ○ SNRIs • Opioids	• Avoid unless safer alternatives are not available; avoid antiepileptics except for seizure and mood disorders • *Opioids:* Avoid except for pain management in severe acute pain
Parkinson disease	• Antiemetics: ○ Metoclopramide ○ Promethazine • All antipsychotics (except quetiapine, clozapine, pimavanserin)	Avoid
History of gastric or duodenal ulcers	• Aspirin > 325 mg/day • Non-COX-2-selective NSAIDs	Avoid unless other alternatives are not effective and the patient can take a gastroprotective agent (i.e., proton-pump inhibitor or misoprostol)
Chronic kidney disease stage 4 or higher (creatinine clearance <30 mL/min)	NSAIDs (non-COX and COX selective, oral and parenteral, nonacetylated salicylates)	Avoid

(AChEIs: acetylcholinesterase inhibitors; CCBs: calcium channel blockers; COX: cyclooxygenase; NSAIDs: nonsteroidal anti-inflammatory drug; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants)

About 30% of adults older than 65 years of age take five or more medications.

Polypharmacy can be caused due to many reasons, ranging from necessary reasons, such as multiple comorbidities of the patients, to unnecessary and preventable reasons, such as prescribing cascade and uncoordinated care. Prescribing cascade happens when the physician misinterprets the adverse effect of one medication as new symptom and adds a new medication to treat the symptom which leads to new more adverse effects. For example, the doctor starts treatment for gout after the patients have hyperuricemia from thiazide diuretics or misinterpret extrapyramidal effects from metoclopramide to Parkinson's disease and start the treatment with levodopa. This can happen due to an incomplete review of the previous drug list (medical discrepancies) or unawareness of the potential adverse effects of prescribed drugs. Medical

TABLE 3: Potentially clinically important drug–drug interactions that should be avoided in older adults.

Object drug and class	*Interacting drug and class*	*Risk rationale*	*Recommendation*
Opioids	Benzodiazepines	Increased risk of overdose	Avoid
Opioids	Gabapentin, pregabalin	Increased risk of severe sedation-related adverse events, including respiratory depression and death	Avoid
Corticosteroids (oral or parenteral)	NSAIDs	Increased risk of peptic ulcer disease or gastrointestinal bleeding	Avoid; if not possible, provide gastrointestinal protection
Lithium	ACEIs or loop diuretics	Increased risk of lithium toxicity	Avoid; monitor lithium concentrations
Phenytoin	Trimethoprim-sulfamethoxazole	Increased risk of phenytoin toxicity	Avoid
Theophylline	Cimetidine or ciprofloxacin	Increased risk of theophylline toxicity	Avoid
Warfarin	Amiodarone, ciprofloxacin, macrolides (excluding azithromycin), trimethoprim-sulfamethoxazole, NSAIDs	Increased risk of bleeding	Avoid when possible; if used together, monitor INR and bleeding closely

(NSAIDs: nonsteroidal anti-inflammatory drug; ACEI: angiotensin-converting-enzyme inhibitors; INR: international normalized ratio)

BOX 1: Potentially inappropriate prescription in older adults.

- *Cardiovascular system:*
  - Digoxin at a long-term dose >125 μg/day with impaired renal function (eGFR < 50 mL/min)
  - Loop diuretic for dependent ankle edema or as first-line monotherapy for hypertension
  - Beta-blocker in combination with verapamil
  - Aspirin with a past history of peptic ulcer disease without histamine H2 receptor antagonist or proton-pump inhibitor
  - Aspirin at dose >150 mg/day
  - Warfarin for first, uncomplicated deep venous thrombosis for >6 months or for first uncomplicated pulmonary embolus for >12 months
- *Central nervous system and psychotropic drugs:*
  - TCA with dementia/glaucoma/cardiac conductive abnormalities/constipation/an opiate or calcium channel blocker/prostatism or prior history of urinary retention
  - Long-term (i.e., >1 month), long-acting benzodiazepines and benzodiazepines with long-acting metabolites
  - Long-term (i.e., >1 month) neuroleptics as long-term hypnotics or in those with parkinsonism
- *Gastrointestinal system:*
  - PPI for peptic ulcer disease at full therapeutic dosage for >8 weeks
  - Anticholinergic antispasmodic drugs with chronic constipation
- *Respiratory system:* Theophylline as monotherapy for COPD
- *Musculoskeletal system:* NSAID with history of a peptic ulcer disease or GI bleeding, unless with concurrent H2 receptor antagonist, PPI or misoprostol/moderate-severe hypertension/heart failure/chronic renal failure/with warfarin/or long-term use (>3 months) for symptom relief of mild osteoarthritis
- *Urogenital system:* Bladder antimuscarinic drugs with dementia/chronic glaucoma/chronic constipation/chronic prostatism
- *Endocrine system:*
  - Glibenclamide or chlorpropamide with type 2 diabetes mellitus
  - Beta-blockers in those with DM and frequent hypoglycemic episodes

(COPD: chronic obstructive pulmonary disease; NSAIDs: nonsteroidal anti-inflammatory drug; PPI: proton-pump inhibitor; TCAs: tricyclic antidepressants)

discrepancies occurred in 71% of patients transferred to a skilled nursing facility. The unawareness of potential adverse effects of prescribing drugs is another cause of prescribing cascade. The doctor should be familiar with the adverse effects of common drug use in the elderly to prevent the prescribing cascade.

UNCORDINATED CARE

With advanced age, people tend to have more comorbidities. People aged 65 years old or more have three or more underlying diseases and one fifth have five or more. With more diseases, patients visit more specialists. Sometimes, patients seek for

BOX 2: Medications that should be considered in older adults with specific conditions.

- *Cardiovascular system:*
  - Warfarin in the presence of chronic AF or aspirin when warfarin is contraindicated
  - Aspirin or clopidogrel with a history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm
  - Antihypertensive therapy where systolic BP consistently >160 mm Hg
  - Statin therapy with a history of coronary, cerebral, or peripheral vascular disease, where functional status remains independent for activities of daily living and life expectancy is > 5 years
  - ACE inhibitor with chronic heart failure
  - ACE inhibitor following acute myocardial infarction
- *Respiratory system:* Regular inhaled beta 2 agonist or anticholinergic for mild-to-moderate asthma or COPD
- *Central nervous system:* Antidepressant with moderate-severe depressive symptoms
- *Gastrointestinal system:* Proton pump inhibitor with severe GORD or peptic stricture requiring dilatation
- *Musculoskeletal system:* Calcium/vitamin D supplement in patients with osteoporosis (fragility fracture, dorsal kyphosis)

(ACE: angiotensin converting enzyme; AF: atrial fibrillation; GORD: gastroesophageal reflux disease)

a second opinion (doctor shopping) or get over-the-counter drugs when they are not satisfied with the treatment or when a new/uncontrolled symptom emerges. All of these reasons can lead to getting the same group of drugs or even the same drug if the medical personnel fail to explore a thorough list of the patient's current medication. This issue can occur with the patient who has been transferred to a different level of care or a different healthcare facility.

ADVERSE DRUG EVENT

Adverse drug event or adverse drug reaction is an unintentional unwanted effect from drug use. More than one -third of community-dwelling older adults experienced ADR. In the decade from 2004 to 2014, the incidence of ADR increased from 20,000 to 450,000 ED visits per year. 28% of hospital admissions of older people in the United States are a result of drug-related problems, up to 70% of which are attributed to adverse reactions to drugs. These can be varied from mild to lethal. There are multiple risk factors of ADR in the elderly, for example, age more than 85 years old, frailty, low body weight or body mass index, six or more chronic health conditions, memory problems, estimated creatinine clearance (CrCl) <50 mL/min, nine or more medications (including prescribed and over-the-counter drugs), 12 or more doses of medication, prior ADR, multiple prescribers, multiple pharmacies, no regular review of patient's medication list, poor communication among providers, and prescription of a complex medical regimen. Common drugs associated with ADE in the older adult are anticoagulants, antipsychotics, nonsteroidal anti-inflammatory drugs, cardiovascular medications, diuretics, anticonvulsants, benzodiazepines, and hypoglycemic medications. From 2013 to 2014, an estimated 34.5% of ED visits related to ADEs occurred among older adults, with anticoagulants, antibiotics, and diabetic agents being responsible for an estimated 46.9% of these visits.

PRINCIPLES OF GERIATRIC DRUG USE

As described above, there are many problems due to medication usage in the elderly and most of them are preventable. These principles will help the physician to decrease adverse events from drug use and also save the cost of unnecessary medication usage and complications of treatment.

- *Start the medication only when having proper indication*: The physician should consider before starting any new medication and make sure that there is a proper indication to start a new drug. Always check for the current medication(s) to avoid "prescribing cascade." Consider if there are other nonpharmacologic treatments for that condition which can delay or lower the dose of medication and decide how long to use the medication; also consider if the medication will be used only for relief of an acute symptom or will be used for treating the chronic disease.
  On the other hand, the physician should not withhold starting medication when there is a proper indication and should not be under treatment because of the fear of adverse effects. Elderly patients tend to get undertreatment as compared with an adult and it can lead to adverse events too. For example, undertreatment of pain can affect activities of daily living, functional impairment, falls, depression, decreased appetite, impaired sleep, and social isolation. Delay in starting preventive medication leads to disease progression or adverse events may occur. Therefore, the physician should use the best evidence from history taking, physical examination, investigation results, combination with life-expectancy, and goal of the life of patient and caregiver.
- *Explore for contraindication*: Before starting any new medication, the doctor should check for all possible contraindications, look for drug–drug or drug–disease interaction, and advise patients and/or caregivers about relative contraindications compared to risk–benefit together. Not only before starting new drugs, but the physician should also consider discontinuing medication if there is any change in the patient's conditions, e.g., change in renal function or worsening of comorbidity.
- *Discontinue unnecessary therapy*: Elderly patients are prone to have more comorbidities; due to this condition, attending more than one specialist is not uncommon in the elderly. Sometimes, the physician feels uncomfortable to discontinue the drugs prescribed by other doctors, especially from another specialist. The necessity of the current drugs should be understood and the physician should consider to stop these when there is no further indication to use them in the patients which include the data of age group, comorbidity, life expectancy, goal of the life of the patients, possible adverse effect outweighing the benefit of the drug, the patient developing adverse effect sign or symptom that may be related to the drug, or if there is another drug that may be superior to the current one. Moreover, the physician should check if the dose

can be reduced, for example, when the drug reaches the ceiling effect or when the renal function is deteriorated. With thorough consideration, more than half of the drug can be discontinued without significant adverse outcomes or death. Over-the-counter drugs are easy for patients to access drugs. Some patients use over-the-counter drugs concurrent with prescribing drugs without knowing that they are the same drugs because of the different trade names. Sometimes, the patient seeks further medication because the prescribing drug has delayed onset to effect the symptom he/she wants to relieve. Patient education about medication onset and schedule for follow-up after prescribing can decrease risk from inappropriate over-the-counter drugs.

Discontinuation of unnecessary drugs can be done in hospitalization, care transition (hospital to home, home to the nursing facility, referral to another level of care), or follow-up period. The primary doctor who has a long relationship with patients and caregivers has a higher chance to talk and explore the patients' drugs. In the setting of the ED, the physician does not usually have enough time to approach all the medications of the patients. Help from multidisciplinary, for example, registered nurse or pharmacist, proves to be helpful in such a case.

- *Herbal remedies and dietary*: Herbal remedies and dietary supplements are not uncommon in older adults. One study found that almost three fourths of patients aged 75 years old and older use at least one of the prescribed drugs and one dietary supplement. Most of the times physician rarely asks the patient about these supplements, some of these supplements can cause durg interactions as well. An example of common drug interaction with a dietary supplement is taking warfarin with ginkgo biloba which can increase the risk of bleeding while taking warfarin with St John's wort can decrease the efficacy of anticoagulation. St John's wort can also increase the risk of serotonin syndrome if the patient takes it with serotonin-reuptake inhibitors. The physician should ask the patients about the current use of herbal remedies or dietary supplement or use brown-bag methods by asking them to bring all of their current medications including over-the-counter drugs and herbal agents to healthcare visits to check for unnecessary and potentially harmful drugs.
- *Start low and go slow*: Due to changes in the patient's physiology, geriatric patients are sensitive to the bioavailability of drug and adverse effects. The physician should consider starting a new drug with a lower dose compared to younger adults and use a shorter follow-up period to adjust the dose. Anyway, the initial dose should reach the therapeutic goal of the symptom or disease that requires treatment.
- *Patient education*: This can help in drug adherence, decrease adverse effects from seeking further over-the-counter drug, and increase the efficacy of the drug. Patient education should include discussion of dosing, scheduling, expected results of the medication, risks, interactions, and an assessment of patient understanding of proper use of the medications.
- *Follow-up*: The physician should schedule a follow-up for the patient to assess the efficacy of the drug, adverse effect of the drug, adherence of the drug, and time point to discontinue the medication.

SUMMARY

Medication usage in the patients is complicated due to changes in physiology with advanced age. The physician should be familiar with the changing processes and concerns about proper prescription and follow-up to decrease the risk of adverse events and to increase the efficacy of the treatment.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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182 CHAPTER

Pain Management in a Geriatric Patient

Elif Dilek Cakal, Mohammad Anzal Rehman, Arif Alper Cevik

INTRODUCTION

The world's population is aging. The global life expectancy at birth has reached 72.3 years. The total number of people aged 65 years or above was 703 million in 2019 and is projected to double to 1.5 billion in 2050. The portion of older adults in the global population will increase from 9 to 16% in the same time frame. Furthermore, people over 80 years of age will proceed from 20–28% of the geriatric population. These estimations suggest that older patients will become an increasing part of medical practice in the upcoming decades.

Emergency departments (EDs) play a significant role in providing health care to older adults. 12–21% of all ED visits are geriatric patients. 32–51% of these ED visits result in hospital admission. In 2017, 22.1% of people aged 65 years or older and 27.6% of people aged 75 years or older had at least one visit to an ED in the United States of America (USA). In 2003, per 100 population, people aged 75 years or older visited EDs approximately 64 times in the USA and 73 times in Ontario, Canada. The widespread use of EDs among older adults warrants that emergency physicians must be prepared to manage geriatric care.

Overall, pain is shown to be the most frequent geriatric chief complaint on presentation to the ED in various series. In one study, while abdominal pain, chest pain, and headache were the most frequent disease-related types of pain, headache, hip pain, and back pain were more prominent in older adults who presented with an injury. In addition to acute complaints, older patients with persistent pain often seek relief in the ED. The considerable need for pain control in daily practice makes it an essential skill of geriatric care in the ED.

UNDERTREATMENT OF PAIN

Studies show that pain is undertreated in all age groups in the ED, but older adults face a higher risk of oligoanalgesia. Compared to younger adults, older adults tend to report less severe pain, get discharged with more severe pain, and have a lower pain reduction in the ED. Also, older adults are less likely to receive analgesics in the ED and at discharge. Overcrowding seems to further increase time to pain assessment and treatment, the portion of patients who received no analgesia, treatment with inappropriate analgesics, and inadequate documentation. Despite pain being among the top chief complaints in older adults, the quality of pain management in the ED remains problematic.

Untreated and undertreated pain in older adults is a multifaceted problem and has an impact on patients, caregivers, the healthcare system system, and the society as a whole. Older adults with chronic pain suffer from adverse functional, physiological, and psychological consequences. Persistent pain in an older adult is associated with increased frailty, social isolation, dependency, neuropsychiatric disorders, sleep disturbances, and decreased functional capacity and quality-of-life. In addition to patients, caregivers of geriatric patients with chronic pain are also susceptible to physical morbidity and physiological distress. Inadequate pain management decreases patient satisfaction in the ED and increases return visits and health care costs. Therefore, managing pain adequately is essential in this age group.

UNDERSTANDING PAIN IN ELDERLY

Pain is a common but sophisticated complaint. It has been traditionally defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Pain may be defined as acute or chronic based on its duration. Acute pain is transient, reversible, and considered useful for survival as it is generally provoked by a threat to the organism, such as a disease or injury. In contrast, chronic or persistent pain is deemed to be a multidimensional syndrome and refers to pain that lasts longer than three months. However, more importantly, chronic pain outlasts the normal healing process, even if it was initially associated with a lesion.

The pain process starts with mechanical, chemical, and thermal irritations to nociceptive fibers; emotional, social, and cultural experiences affect how this sensory is processed in the brain and result in an individual emotional and behavioral response. The fact that pain is inherently subjective and multifactorial poses challenges with the assessment of pain. Physicians have to assess what the patient is experiencing by observing his/her verbal or nonverbal expressions or via self-report or non-self-report measures. Especially in older adults with limited communication, the need for caregiver's interpretation adds to this complexity.

DIFFERENCES OF PAIN MANAGEMENT IN THE ELDERLY

The perception and expression of pain are greatly altered in older adults due to physiological, mental, and social differences. An altered pain process in the peripheral and central nervous systems with normal aging makes pain severity and localization less accurate. In practice, it frequently translates to a lower intensity and atypical abdominal and chest pain of potentially life-threatening origins. In addition to physiological changes, cultural background and personal misconceptions and fears related to pain alter how the pain is perceived and communicated. A common misconception among older adults is that pain is an integral part of aging or chronic diseases. Some may see pain medication as the last resort and avoid asking for treatment for fear of adverse effects or addiction. Training physicians about geriatric pain, institutional strategies, and creating an accessible healthcare system will help to overcome these challenges.

Pharmacologic treatment of pain is also altered due to physiological changes with normal aging. As a general rule, older adults are more sensitive to both the therapeutic and the toxic effects of drugs. The aging-related physiologic changes and their impact on pharmacokinetics are summarized in **Table 1**.

Also, comorbidities increase with age and affect pain management on many levels. Many comorbidities such as hepatic, renal, neurodegenerative, and cardiovascular diseases warrant a careful choice of drugs, dosing, and route of administration. Diseases that alter mental capacity and disabilities, including visual, hearing, and speech impairments, further complicate the assessment of pain and compliance to therapy. Lastly, aging and comorbidities are associated with polypharmacy, which increases the likelihood of adverse reactions and must be taken into consideration when prescribing drug therapies to older adults with comorbidities.

PAIN ASSESSMENT

Elderly patients presenting with pain to the ED are at an increased risk of receiving suboptimal pain management. The disparities in management for these patients stem largely from the unique difficulties in the assessment of pain in this population. In order to ensure the best pain control and patient-oriented outcomes, the provider responsible for older adults in the EDs should attempt to overcome the following barriers during pain assessment:

- *Misconceptions*: Elderly patients, and indeed even some of their healthcare providers, tend to adhere to the traditional belief that pain is a normal consequence of aging. However, despite the increased prevalence of chronic pain in older adults, recent evidence revealed the belief of pain being secondary to advanced age as unfounded. Therefore, all levels of pain should be addressed appropriately and patients counseled regarding the importance of recognizing pain regardless of age.
- *Communication:* The ideal approach to pain assessment involves obtaining the patient's self-report of pain. The patient's self-described account has been found in several studies to be more accurate compared to standard healthcare provider pain assessments. Older patients, however, frequently deny or underreport their pain. Often, their unwillingness to express pain is a consequence of cultural beliefs, with stoicism implicated in many behavioral studies.
- *Cognitive status:* Many elderly individuals have an associated cognitive and/or functional impairment that may impede their ability to adequately express pain. Pain

TABLE 1: Aging-related physiologic changes and their impact on pharmacokinetics.

	Major changes with normal aging	*Pharmacokinetics*	*Clinical impact*

Absorption	• *Transdermal:*
	  ○ Atrophy of the dermis and epidermis
	  ○ Reduced tissue perfusion
	• *Sublingual*: Decreased saliva production
	• *Oral*: Contradictory evidence, including changes in gastric pH and gastric emptying time
		• Significant individual variability in transdermal, sublingual, and oral routes
		• No difference with normal aging in intramuscular and intravenous routes
			Alterations in absorption unlikely to have a significant clinical impact

Distribution	• Increased body fat • Decreased muscle mass • Decreased total body water • Decreased plasma proteins	• Larger lipophilic drug volume of distribution • Smaller hydrophilic drug volume of distribution • Increased free fraction of protein-bound drug	• Increased elimination half-life • Increased serum concentrations • Increased activity
Metabolism	• Decreased liver mass • Decreased liver blood flow • Decreased first-pass effect	• Decreased inactivation of active metabolites • Decreased activation of prodrugs	Increased activity (except for prodrugs)
Excretion	• Decreased renal blood flow • Decreased kidney mass • Decreased glomerular filtration rate	Decreased elimination of drugs	Increased elimination half-life

assessment in these individuals should be guided by a more comprehensive approach, including an evaluation for changes in behavior, movement, facial expression, activity, and mental status.

Pain assessment can be further supplemented by utilizing pain assessment tools and accounts from family or caregivers where available.

PAIN ASSESSMENT TOOLS

Various tools have been formulated to aid the clinician in the assessment of pain in older adults. No single pain assessment tool has been found to be unanimously superior for measurement of pain in older patients. Therefore, the best approach to pain assessment will depend on feasibility, patient capacity, provider's preference, and ability to extrapolate data from multiple sources. **Table 2** outlines a few commonly utilized pain scales that could potentially be applied in the acute care setting.

MANAGEMENT

Goals of Acute Pain Management

In order to ensure the best patient-oriented outcomes for pain in the elderly, care must be taken to promptly and adequately assess and address their pain status. However, identification of pain is often confounded by the fact that older patients have varying degrees of chronic, nonspecific pain that limit their daily functioning. Therefore, management of acute pain in the geriatric population frequently involves utilizing a multifaceted approach, focusing on factors beyond the reduction of pain,

TABLE 2: Common pain assessment tools.

Name	*Description*	*Notes*
Intact cognition		
Faces pain scale (FPS)	Self-report of pain based on selection of visual graphics of facial expression	Can be useful even with mild-to-moderate cognitive impairment
Verbal descriptor scale	Series of phrases describing pain at varying intensities	Can be combined with a pain thermometer (Iowa pain thermometer) or a 10-cm visual analog scale (combination is termed graphics rating scale). Useful even with mild-to-moderate cognitive impairment
Numerical rating scale	Commonly used to assess pain on a 10-point numerical scale	Easy to use, minimizes translational errors
Impaired cognition		
The pain scale	Measures pain in nonverbal patients with dementia using rating of six questions—vocalization, facial expression, physical, physiologic, body language, and behavioral changes	Can be completed in approximately 1 minute
Checklist of nonverbal pain indicators (CNPI)	Score of six nonverbal manifestations of pain—vocalizations, grimaces, bracing, rubbing, restlessness, and verbal complaints—at rest and with movement	More reliable observations during movement than at rest
Pain assessment checklist for seniors with limited ability to communicate (PACSLAC-II)	Revised score for patients with dementia—assesses 31 behavioral traits related to pain (reduced from 60 items in original PACSLAC score). Items factored in activity, movement, facial expressions, social, physiologic, vocal, sleeping, and eating habits	Seemingly preferred by nurses despite a large quantity of variables assessed
Pain assessment in advanced dementia (PAINAD) scale	Measures pain on a 10-point scale for nonverbal patients with dementia using five observations in over 5 minutes—breathing, negative vocalization, facial expression, body language, and consolability	Requires at least 5 min to complete
Critical-care pain observation tool (CPOP)	Assesses for pain in nonverbal intubated or sedated patients by observing four items—facial expression, body movement, muscle tension, and either ventilation compliance (intubated patients) or vocalization (extubated)	Observations can be completed within 1 minute. Shows reliability for pain measurement in critically ill patients with varying levels of consciousness
Algoplus	Score of 0–5 based on the presence (yes/no) of five observations—facial expressions, look, complaints, body position, and atypical behaviors	Designed specifically to evaluate acute pain in elderly with inability to communicate verbally. Can be completed in less than 1 minute. Validated as reliable in five different languages and countries

such as patient history, baseline function, underlying disease and comorbidities, risk of adverse outcomes, side-effect profiles of medication, and, finally, patient preference.

Consequently, pain management strategies that ultimately lead to the best patient satisfaction integrate a shared decision-making approach to analgesia.

Approach to Analgesia

A variety of pharmacologic and nonpharmacologic options are available for pain control in geriatric patients. Pharmacologic therapy, however, remains the mainstay in acute care settings, with nonpharmacologic alternatives usually serving as adjuncts rather than substitutes to medication. Ultimately, the choice of therapy weighs the benefit of pain reduction against the potential side effects, interactions, and adverse outcomes related to the intervention.

Factors such as physiology, drug metabolism, and genotype contribute to the considerable variability in response to medication in older adults. Therefore, it is often recommended to commence drug therapy at lower dosages, especially when using opioids, implementing a *start low, go slow* strategy, with additional medication added sequentially rather than simultaneously. While this approach can mitigate dose-related toxicity, it is important to note that *staying low* and delaying analgesic escalation when needed, may contribute to undertreatment in some patient groups.

PHARMACOLOGIC OPTIONS

Acetaminophen

The American Geriatrics Society recommends acetaminophen as a first-line agent for the treatment of low-to-moderate pain in the elderly, especially when secondary to osteoarthritis. The mechanism of action for acetaminophen is complex and often debated, with central and peripheral inhibition of cyclooxygenase (COX), agonism at transient receptor potential channels, and actions on serotonergic, l-arginine/nitrous oxide, and cannabinoid pathways all being implicated for its analgesic effect.

When given at therapeutic doses that do not exceed the maximum recommended daily dosage of 4 g, the incidence of hepatotoxicity, nephrotoxicity, and gastrointestinal toxicity with acetaminophen use is relatively low. Among other pharmacologic agents, it perhaps has one of the best safety profiles, making it an ideal medication for acute pain of lower intensity. Of particular interest is acetaminophen's apparent synergistic effects when used in combination with other analgesics, thus improving pain management whilst lowering the dosage for each individual drug component. Intravenous formulations of acetaminophen are readily available for use in emergency settings and are similarly efficacious when compared to oral administration.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effects through the inhibition of COX enzymes, thereby preventing the conversion of arachidonic acid to thromboxanes, prostaglandins, and prostacyclins. The World Health Organization analgesic ladder traditionally classified NSAIDs as a "*step-up*" from acetaminophen for pain management. Despite their potential for superior analgesic efficacy, several professional societies caution against their use in the elderly due to an increased risk of gastrointestinal, renal, and cardiovascular side effects. This is further evidenced by the inclusion of NSAIDs in the American Geriatric Society's Beers criteria list of potentially inappropriate medication use for older adults.

When administered, care must be taken to use the lowest doses possible and avoid patients with contraindications to NSAID therapy, such as those with impaired renal function and gastric or cardiovascular disease. Adverse effects can further be ameliorated by co-administration of proton-pump inhibitors on discharge to prevent acid-related gastropathies. Examples of NSAIDs commonly used in the ED include ibuprofen, naproxen, and ketorolac.

Opioids

Opioid drugs act on mu, delta, and kappa opioid receptors to decrease the release of excitatory neurotransmitters and increase neuronal resistance to excitability, thereby reducing pain sensation. They are usually reserved for the treatment of moderate-to-severe pain and include medications such as morphine, hydromorphone, buprenorphine, and fentanyl.

Unlike acetaminophen and NSAIDs, opioids are not limited by a maximal dose beyond which no further pain reduction benefit can be produced (termed the analgesic ceiling). Dosing of opioids should therefore weigh the benefits of pain reduction against the risks of therapy-induced side effects, such as constipation, nausea, somnolence, and respiratory depression. In older patients, an increased fat to muscle mass ratio as well as decreased hepatic and renal clearance means that opioids should be initiated at lower dosages, approximately 25–50% of those used with younger adults.

Tramadol is a weak opioid analgesic that is occasionally used for acute pain relief, since its reduced action on mu receptors lends it the apparent advantage of decreased opioid-related side effects. However, tramadol's safety profile is compromised by its unique ability to lower the seizure threshold, cause metabolic derangements, and potentially cause serotonin syndrome due to its inhibition of serotonin and norepinephrine reuptake.

Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has shown promise as an emerging therapy for pain relief. Motov et al. conducted a randomized controlled trial that revealed the analgesic effects of intravenous subdissociative ketamine to be comparable to morphine for acute pain in the geriatric ED population. Given its potential to reduce coanalgesic administration, coupled with a relatively low risk of side effects, ketamine is rapidly gaining popularity as a useful alternative to pain management in the acute care setting.

NONPHARMACOLOGIC OPTIONS

Regional Nerve Blocks

Regional nerve blocks are an effective method of targeted pain management in patients with extremity fractures. Perhaps the most well studied of these is the femoral nerve block, often

utilized to relieve pain secondary to hip fractures. Regional anesthesia, with or without the guidance of ultrasound, provides rapid analgesia that is selective to the site of pain, without the risk of adverse events normally associated with systemic pharmacologic drug profiles.

Other Nonpharmacologic Therapies

Very few, if any, nonpharmacologic therapies have been studied or are feasible to use in the ED for pain relief. However, preliminary knowledge of the advantages of incorporating these techniques upon discharge can lead to earlier initiation of effective multimodal pain management for the patient. Examples of nonpharmacologic pain management strategies include acupuncture, aromatherapy, transcutaneous electrical nerve stimulation, and cognitive, behavioral, and physical therapies. The use of these interventions has been shown to reduce pain signaling, implying that they may have a role in promoting overall patient comfort and satisfaction, especially in chronic pain.

REASSESSMENT

After initiation of pain management, it is crucial to reassess, at regular intervals, the adequacy of the administered treatment. Ideally, patient response to analgesia should be evaluated for change as early as 15 minutes after administration. Often, however, reassessment of pain status in older adults is performed more than 60 minutes after drug initiation, resulting in suboptimal pain management and aggravated patient discomfort. The Society for Academic Emergency Medicine Geriatric Task Force, in collaboration with members from the American College of Emergency Physicians (ACEP), devised the following quality indicators for geriatric emergency pain management:

- For every elderly patient presenting to the ED, a formal assessment for acute pain should be documented within 1 hour of arrival.
- For patients who remain in the ED for more than 6 hours, a second pain assessment should be done within 6 hours of arrival.
- If analgesic treatment was given in the ED, a reassement should be documented prior to discharge.
- If an older adult presenting to the ED has moderate-to-severe pain intensity, analgesic treatment should be started.
- For patients transferred from nursing homes to the ED, a medication list should be attached to the transfer papers.
- If specific tests have been requested by a nursing home provider from the ED, the physician should document the performance of those tests.

SUMMARY

Aging is an increasing phenomenon all over the world, and it alters how the body processes and the individual perceives pain. In addition to the natural aging process, the increased prevalence of comorbidities and disabilities complicates the detection and communication of pain in older adults. In the ED, undertreatment of pain is a serious barrier and should be resolved through increased training and awareness. Adjusting pain assessment and treatment according to age-related alterations enables an effective and safe practice of pain management.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Geriatric Gynecology

Laxman Bhusal, Rabin Bom

INTRODUCTION

Patients at the extremes of age can present unique and challenging gynecologic-pathologic conditions. Care should be taken by the emergency physician to adapt to challenges in examining unestrogenized genitalia and consider age-specific pathologic conditions. Decreased estrogen production probably weakens the structures supporting the vagina, permits genital atrophy, and possibly contributes to osteoporosis, arteriosclerosis, and other illnesses. Atrophic vaginitis is a common complaint among postmenopausal women. Common symptoms include pruritus, dryness, dyspareunia, burning, and bleeding. Although postmenopausal bleeding is most commonly due to atrophic vaginitis, it should be considered a sign of gynecologic malignancy until proven otherwise. It is the most common cause of postmenopausal bleeding. Examination will reveal thin, pale, and friable mucosa. Conservative treatments, such as sitz baths, and careful hygiene constitute the first line of therapy. Topical estrogen therapy can reduce severity of symptoms and is available in a variety of preparations.

OSTEOPOROSIS

Women should be screened for osteoporosis with bone densitometry beginning at the age of 65 years. Low bone mineral density (BMD) is not required to diagnose osteoporosis in postmenopausal women who sustain a low trauma fracture or have significant kyphosis with multiple risk factors. Screening for vitamin D deficiency in community-dwelling women aged 65 years is becoming a standard of care. For a serum 25-hydroxy vitamin D level of 20 ng/mL, typical repletion regimens use 50,000 IU of cholecalciferol (vitamin D3) once weekly for 6–12 weeks followed by ongoing monitoring.

VULVOVAGINITIS

Both aging and long-term estrogen deficiency increase vulvar susceptibility to trauma and decrease vulvar immune function. The most common symptomatic vulvar and vaginal conditions in the elderly are typical postmenopausal ones, such as atrophy, lichen sclerosis, and candidiasis. Consanguineous vaginal discharge usually can be attributed to a secondary infection that may accompany atrophic changes. Other than topical estrogen, treatment is usually moderate-to-high potency topical glucocorticoids. Chronic vaginal discharge that has not responded to the usual creams and antibiotics may indicate inflammatory vaginitis. The incidence of vulvar cancer rises exponentially after the age of 65 years. Indications for biopsy are the same as in younger women: asymmetry, border irregularity, color variation, rapid change, bleeding, nonhealing ulceration, and lack of a firm diagnosis.

UROGYNECOLOGIC ISSUES

Urinary tract infection (UTI): UTI is the most frequent bacterial infection in the elderly. Management is complicated by diagnostic uncertainty, polypharmacy concerns, more resistant organisms, and host factors that reduce treatment efficacy. For recurrent UTIs, postvoid residual urine volume (PVR) measurement, topical estrogen, and urine cultures and sensitivities prior to initiating treatment are indicated. In frail elderly, the "symptom" might be lethargy, irritability, vague discomfort, or a fall, making this determination difficult.

Urinary incontinence: Evaluation of urinary incontinence includes medication review, examination for neurologic conditions, determination of mobility and dexterity issues, and assessment of medical conditions, such as peripheral edema, diabetes, and hypercalciuria. Fecal impaction should be ruled out, and fecal incontinence (FI) should be queried. Bladder relaxants are effective in older women, but anticholinergic medications may impair cognition and function.

BREAST CANCER

As breast cancer primarily affects women in the post-menopausal years, the number of cases of breast cancer in women in this age group is also increasing. The most common type of cancer is infiltrating ductal cancer; this applies to all ages. The patient should be taught to examine her breasts monthly and report any change to her physician. Hormonal therapy has been proven to be of benefit in appropriate patients with breast cancer; this has also been demonstrated in the elderly female population.

VAGINAL BLEEDING IN THE POSTMENOPAUSAL PATIENT

Vaginal bleeding in postmenopausal women is an important presentation in emergency departments. It is most commonly defined as vaginal bleeding after a period of no menses for at least 1 year. Although atrophic vaginitis may be the most common cause of postmenopausal vaginal bleeding, vaginal bleeding is a common symptom of gynecologic malignancies, such as endometrial, cervical, and, rarely, ovarian cancers. Endometrial cancer is the common gynecologic malignancy causing vaginal bleeding in the postmenopausal women. Emergency physicians should assess for symptoms, family history, and personal risk factors for various gynecologic malignancies. Common risk factors include older age, obesity, early menarche, late menopause, nulliparity, infertility, polycystic ovarian syndrome, diabetes, and estrogen therapy without progesterone and tamoxifen use. Pelvic examination should be performed, including speculum examination with examination of the vaginal walls and cervix. Bimanual examination may reveal fixed masses, nodularity in the cul-de-sac, and palpable ovaries. Therapy for most women with endometrial cancer includes hysterectomy with bilateral salpingo-oophorectomy.

OVARIAN CANCER

The risk factors for ovarian cancer include family history, hereditary breast and ovarian cancer syndrome (*BRCA* gene mutation), early menarche, late menopause, older age at childbirth, and low parity. The presentation can include vaginal bleeding, but, more commonly, a woman presents with nonspecific symptoms, such as abdominal and pelvic pain, bloating, fullness, dysuria, and early satiety. Most ovarian cancers are epithelial cell in origin and affect older women. These are mostly diagnosed in late stage, and proper treatment is difficult.

CERVICAL CANCER

Cervical cancer is the common gynecologic cancer in postmenopausal women. The risk factors include human papillomavirus exposure, early coitarche, sexually transmitted diseases, and multiple sexual partners. The presentation can include postcoital bleeding and vaginal discharge or spotting, and the diagnosis can be made via colposcopy and cervical biopsy. The most common type is squamous cell carcinoma (80%), followed by adenocarcinoma (15%). Treatment is according to the staging of the disease.

BENIGN CAUSES OF VAGINAL BLEEDING

The statement about all postmenopausal vaginal bleeding being cancer until proved otherwise is because of a high index of suspicion for cancer in postmenopausal women. However, most instances of postmenopausal bleeding have benign causes, such as atrophic endometriosis, cervicitis, cervical polyps, endometrial polyps, and hormone replacement therapy (HRT).

Transvaginal ultrasound is the imaging modality of choice for pelvic structures. Endometrial thickness is best measured in the long-axis transvaginal view of the uterus. In postmenopausal patients with atrophic endometrium, it appears as a thin pencil line. Endometrial thickness of 4 mm or less measured anterior to posterior in this view is considered normal and highly predictive that no endometrial cancer is present. Ovarian evaluation by transvaginal ultrasound supplemented by transabdominal ultrasound for extending masses is the imaging modality of choice for a suspected ovarian mass. Worrisome features on ultrasound include complex masses with cystic and solid components, septated cysts, thick cyst walls, and free fluid in the pelvis. Endometrial sampling by a patient's primary care provider or a gynecologist is indicated in postmenopausal women with vaginal bleeding and an endometrial thickness greater than 4 mm on ultrasound.

MENOPAUSAL SYMPTOMS AND HORMONE REPLACEMENT THERAPY

Menopause is defined as the cessation of menstrual periods for 1 year and occurs at the average age of 51 years. Preceding menopause is often a perimenopausal transition marked by hormonal fluctuations and irregular menses. Menopause is a normal physiological process, not a pathological process, clinically characterized as hot flashes, vaginal dryness, poor sleep, and painful intercourse, which are irritating to many women. The discomfort from hot flashes, characterized by intense flushing and sweating lasting for several minutes and potentially occurring multiple times a day, affects about 75% of women. The mechanism behind menopausal symptoms, such as hot flashes, is not known. It is suggested that estrogen withdrawal stimulates the release of norepinephrine and serotonin, which can alter the body's thermoregulatory mechanism in the hypothalamus, predisposing a woman to more intense fluctuations of body temperature. The roles of HRT, including compounded bioidentical hormones, and alternative nonhormonal and herbal remedies for the treatment of menopausal symptoms are described in the literature.

Hormone Replacement Therapy

Role of progesterone: The guidelines recommend that all women with a uterus who are taking systemic estrogen therapy should take progesterone therapy as well to decrease the risk of endometrial cancer. This includes oral and transdermal estrogen use but not local intermittent vaginal estrogen therapy. Women without a uterus do not require progesterone therapy. Although not recommended as primary therapy, progesterone therapy alone has shown benefit for relief of menopausal symptoms in several studies. Both oral megestrol acetate and oral and intramuscular medroxyprogesterone acetate have been beneficial in the reduction of hot flashes compared with placebo. The side effects of progesterone therapy alone include vaginal bleeding, headache, breast tenderness, nausea, and venous thromboembolism (VTE).

Available formulations for HRT: Current estrogen and estrogen–progestogen therapy (EPT) options include oral pills; transdermal patches, gels, and creams; vaginal creams, rings, and tablets; and intrauterine delivery systems. Systemic HRT should involve reassessment yearly

for possible tapering/discontinuation of medication as menopausal symptoms abate.

Special considerations: *Premature menopause*—This is diagnosed when it occurs at or before the age of 40 years. Risks of HRT are less in these young women who are ≤50 years of age. Guidelines support HRT in these premature menopause women until at least the average age of menopause. The current standard of care is to avoid HRT in breast cancer survivor patients.

Bioidentical hormones: These are plant-derived hormones that are created by a compounding pharmacy under a physician's direction. They come in various forms, including oral and injectable agents, are not regulated by the US Food and Drug Administration, and have not been subjected to rigorous testing. In general, compounded bioidentical hormones are not recommended for the treatment of menopausal symptoms.

Nonhormonal therapies: These therapies used for menopausal symptoms include antidepressants and gabapentin, herbal remedies, and lifestyle modifications. A potential mechanism of action for selective serotonin reuptake inhibitors and norepinephrine serotonin reuptake inhibitors in the treatment of hot flashes is an alteration in the set point of the hypothalamic thermoregulatory zone. None of these medications, however, carries an indication for the treatment of menopausal symptoms. In general, their benefits (lessening hot flashes by approximately 1 per day) are more modest than those of HRT (lessening hot flashes by 2 or 3 a day). Typical side effects to these medications include drowsiness, nausea, and headache. In addition, there is some concern that certain antidepressants (paroxetine and fluoxetine) can decrease the active metabolite of tamoxifen and endoxifen, which is used in the treatment and prevention of breast cancer. Thus, in patients receiving tamoxifen, menopausal therapy with venlafaxine or citalopram is preferred. Gabapentin carries an indication for the treatment of seizures and neuropathic pain. Evidence supports its use for the treatment of hot flashes at a dose of 900 mg daily, with typical side effects of dizziness, dry mouth, and fatigue. A few studies also show benefit with the use of pregabalin.

Herbal remedies: Phytoestrogens are plant-derived molecules with estrogenic activity and include products, such as isoflavones, lignin, and coumestans. Phytoestrogens are botanic supplements and thus do not undergo the same standardization and testing as do classic pharmaceuticals. Commonly tried remedies for menopausal symptoms are soy. It is an isoflavone with estrogen and antiestrogen properties, found in high concentrations in Asian diets. Some evidence exists for the reduction of hot flashes with soy supplementation, but reports are conflicting. Soy is not recommended for women with a contraindication to estrogen.

Bioidentical hormones and herbal remedies may carry the same risks as traditional HRT (e.g., increased risk of deep vein thrombosis), so emergency physicians should inquire about their use. Rarely should emergency physicians start a patient on HRT or other medication for menopausal symptoms. Instead, they can assure patients that various hormonal and nonhormonal therapies are available for symptom relief and prompt patients to follow up with a primary care provider or gynecologist.

PELVIC ORGAN PROLAPSE

Pelvic organ prolapse (POP) is defined as the abnormal descent of pelvic structures due to weakening of the pelvic floor. It is classified on the basis of anatomic locations as anterior (bladder or urethral involvement), posterior (rectal involvement) and apical (uterine, cervix involvement). Prolapse occurs because of weakening of the pelvic floor musculature, which can happen in response to the following:

- *Vaginal childbirth*: Increasing parity increases risk (cesarean section is associated with POP as well).
- *Increases in intra-abdominal pressure*: Obesity, straining with chronic constipation, chronic cough
- Aging/menopause
- Genetic predisposition
- Connective tissue abnormalities

Symptoms of POP include a sensation of vaginal pressure or a bulge in the vagina, difficulty voiding or defecating, splinting (digital reduction of prolapse to facilitate voiding or defecation), or recurrent UTIs. Although POP is typically a benign condition, advanced-stage prolapse can cause significant complications, including hydronephrosis and obstructive uropathy, bowel obstruction, or strangulation of prolapsed organs. The first, and cheapest, nonsurgical treatment option is pelvic floor muscle strengthening with Kegel exercises. The other most commonly known option for nonsurgical treatment of POP is the pessary. Surgery remains an option for women in whom nonsurgical treatment was not successful. When anterior or posterior vaginal prolapse is the primary problem, colporrhaphy is used. Most cases of POP can be safely reduced in the ED and referred to outpatient gynecology. Advanced prolapse with evidence of obstruction of either the urinary system or bowel or evidence of pelvic organ ischemia should prompt urgent gynecologic evaluation.

SUMMARY

Vaginal bleeding in postmenopausal women is the most common presenting symptom of endometrial cancer. Thus, although vaginal bleeding is often benign, it always merits diagnostic evaluation. Emergency physicians should stabilize patients and perform a complete blood cell count, pregnancy test, speculum examination to evaluate for cervicitis and urogenital lesions, and bimanual examination. Transvaginal ultrasound or endometrial biopsy is necessary for further evaluation. Ultrasound and CA 125 level are performed if adnexal mass is suspected in postmenopausal patients. Menopause is a physiological process characterized by the cessation of ovarian function and menstrual periods treated with HRT, POP associated with difficulty with urinary, gastrointestinal, and sexual function. Treatment options include Kegel exercises, pessaries, and surgery.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Emerging and Re-emerging Infections

Dharmesh Lal

INTRODUCTION

Emerging infectious diseases (EIDs) are either new to the human population or may experience sudden epidemic growth, and majority of them are zoonotic in nature. An emerging pathogen may be defined as a newly discovered pathogen that has recently appeared within the population. Their definition is on the basis of the appearance of pathogen within population the first time, rapid spread on the basis of increasing incidence, and/or spreading to new geographical areas. EIDs result in increased mortality and morbidity having damaging effects upon livelihood, social fabric, and economic status besides disrupting the existing health delivery system. Infectious diseases causing an increase in incidence and tending to spread geographically fast and wide within decades can be defined as emerging infections. EIDs are on rapid rise in recent years overwhelming the human population globally upsetting the milieu of societies.

IMPORTANT TERMS

Cross-infection: It means infection of one person with pathogenic organisms from another and vice versa. Cross-infection can occur anywhere (e.g., in military barracks, schools, and workplaces).

Epidemic: [From the Greek *epi* (upon), *demos* (people)] The occurrence in a community or region of cases of an illness, specific health-related behavior, or other health-related events clearly in excess of normal expectancy.

Epidemiology: The study of the occurrence and distribution of health-related states or events in specified populations, including the study of the determinants influencing such states, and the application of this knowledge to control relevant health problems and for health planning and management.

Incidence: The number of instances of illness commencing, or of persons falling ill, during a given period in a specific population, more generally, the number of new health-related events in a defined population within a specified period of time. It may be measured as a frequency count, a rate, or a proportion. It is a reflection of control of a health problem.

Endemic: It refers to the constant presence and/or usual prevalence of a disease or infectious agent in a population within a geographic area.

Pandemic: It refers to an epidemic that has spread over several countries or continents, usually affecting a large number of people.

Zoonosis is an infectious disease that has jumped from a nonhuman animal to humans. Zoonotic pathogens may be bacterial, viral or parasitic or may involve unconventional agents and can spread to humans through direct contact or through food, water, or the environment.

Re-emerging infectious disease are defined as "diseases that appear with significant increase in incidence after they have been on a significant decline." Re-emerging viruses, on the other hand, may be defined as viruses that continuously reappear, thus causing many epidemics/outbreaks. Causes for the same are breakage of the ecosystem and weakening of the health systems which can be because of breakdown in public health measures for diseases that were under control or due to appearance of new strains of organisms." Viruses such as enteroviruses (EV), dengue virus (DENV), influenza viruses (e.g., H1N1, H5N1, and H7N9) *Orthomyxoviridae, Paramyxoviridae, Picornaviridae, Coronaviridae, Adenoviridae, Herpesviridae* influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, human coronavirus, to name a few, are considered re-emerging viruses due to their constant reappearance in the population and cause additional large mortality and morbidity. Some of these viruses have also caused huge respiratory damaging infections throughout the world in recent times. Other examples of such diseases are drug-resistant forms of tuberculosis, bacterial pneumonia, and malaria. Drug-resistant strains of the bacteria causing gonorrhea and syphilis are also becoming more widespread, raising concerns of untreatable infections.

Most of the countries despite rising EIDs are still having lower provisions for undertaking research activities. Respiratory infections with epidemic and pandemic potential that cause a global burden have plagued people since the beginning of human history.

ENABLING FACTORS

Any disease to cause epidemic and thereby spread in the community require the presence of three "elements" and their synergistic effects upon each other, called *epidemiological triad*, as shown in **Figure 1**. Each element has inherent characters known as enabling factors, and as is evident from the **Figure 1** most of the factors are human made and resulting from brazen eco-insensitive development causing newer pathogens to emerge or resurgence of earlier controlled pathogens. With changing demographical and environmental dynamics, the EIDs have emerged as posing increasing challenges to the humanity in last few decades. Demographic forces amplify the risks associated with EIDs. The global population is expected to grow to 8 billion within 8 years, with nearly 60% living in relatively crowded urban areas. By 2050, half the world's population will live in tropical environments, which bear a much larger burden of disease. Rapid aging of the global population will further increase susceptibility, as both abilities to fight off infection and efficacy of immunization wane with age. Additionally, air travel increases annually, with >100,000 flights per day as of 2014. These factors favor the emergence, evolution, and spread of new pathogens.

DISEASES PROFILE

For better management and control of these diseases, it is important to understand the causative agent, reservoir, risk factors, and mode of transmission as shown in **Table 1**. Identification, monitoring, and treatment of diseases are the primary objectives of all public health programs. As an example in case of coronavirus disease-2019 (COVID-19) pandemic, the virus is coronavirus, named as COVID-19, having possible reservoirs in bats, and risk factors include people who are elderly and having comorbid conditions while the transmission of the virus is through aerosols and airborne in nature. On the basis of these information, the nonpharmaceutical interventions (NPIs) are the mainstay of the prevention before roll-out of the effective medicines and pharma agents.

Majority of the EIDs are caused by viruses, mutations, and reassortments which are the factors that increase the pathogenicity of these viruses. The future will see more of pandemics due to mutations of viruses and reassortment [in which the host is infected with two different strains of viruses (animal and human viruses) resulting in newer virus with mixed genetic materials], examples of which are bird and swine influenza viruses. Adverse impacts of EIDs include: overwhelming of health systems severely affecting the normal health delivery services such as immunization, delaying, and/or missing even minimum mandatory clinical care like for cancer and tuberculosis (TB) patients, thus causing avoidable deaths and morbidity and mandate provisioning of additional scarce resources for survivors of these EIDs.

Although the majority of recent EIDs have been viral, bacterial infections are also a threat, with the devastating cholera epidemic in Haiti, the foodborne *Escherichia coli* O104:H4 outbreak in Germany in 2011, and the invasive nontyphoidal *Salmonella* in Africa representing prominent examples. Today, the major risk from bacteria comes from antibiotic-resistant strains, such as multiple drug-resistant *Staphylococcus aureus* (MRSA). Whether viral or bacterial, EIDs share common attributes of unpredictability, high morbidity, the potential for explosive growth of cases, and substantial social impacts. TB has been making resurgence due to resistance to various antitubercular drugs while malaria has been reported from many parts of world due to drug resistance and mosquitos showing resistant to various pesticides. Factors having bearing on spread of EIDs are microbiological features and genetic makeup of a pathogen and social determinants of health.

Throughout the years, many viruses have emerged and re-emerged. Viral adaptation mechanisms such as mutation

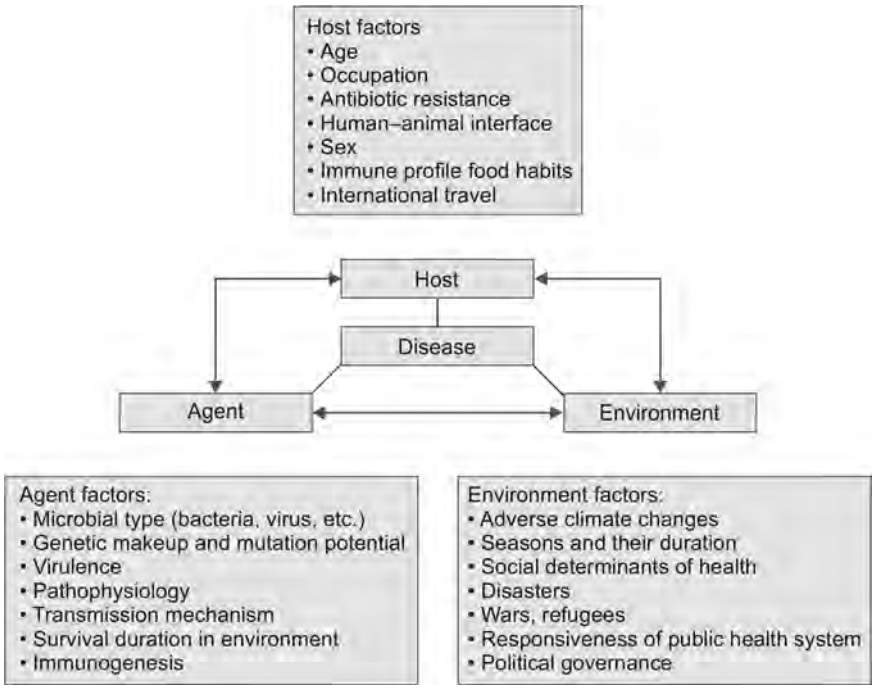

FIG. 1: Epidemiological triad-enabling factors and their interaction.

TABLE 1: Disease profile of various emerging/re-emerging diseases.

Disease	*Geographical distribution*	*Agent*	*Reservoir*	*Risk factors*	*Mode of transmission*	*Clinical features*
Avian influenza	Bangladesh, China, Egypt, India, Indonesia, Vietnam, and Cambodia	Avian influenza virus subtype A H5N1, H5N6, H6N1, H7N7, H7N9, H9N2, H10N8	Wild birds, waterfowl, and poultry	Direct or indirect exposure to infected—live or dead—poultry, and environments contaminated by the virus, are the biggest risk factors	Infection of humans from poultry but rare Human-to-human infection is even more rare, but through airborne	Flu-like symptoms, watery diarrhea, severe pneumonia, and multiorgan failure
Chikungunya	Nearly 40 countries in Asia, Africa, Europe, and the Americas	Togaviridae family of arboviruses, i.e., it is primarily spread by mosquitoes	Humans are the main reservoir in Asia, although monkeys are an important reservoir in Africa	Proximity of mosquito breeding sites to human habitation	Bite of female-infected mosquitoes, which bite throughout daylight hours	Sudden onset of fever, severe headache, chills, nausea, vomiting, and severe joint pains that may persist for weeks or months In some cases, joint pain may persist for several months or even years
Crimean-Congo hemorrhagic fever	More than 30 countries in the African, South-East Asia, European and Eastern Mediterranean regions of WHO	Nairovirus, of the *Bunyaviridae* family. All 32 members of the *Nairovirus* genus are transmitted by ticks, but only three viruses are known to cause disease in humans	Ostriches are carriers and become infected with CCHF from the bite of infected ticks	Majority of cases occur in people working in the livestock industry, since they come in close contact with infected animals. Healthcare workers are especially at risk of acquiring infection while providing intensive care	Direct contact with the blood or tissues of livestock, such as sheep, goats, or cattle but also from tick bites. Human-to-human transmission may occur by exposure to blood and excreta from the affected people, for example healthcare workers	Sudden onset of high fever and chills, headache, dizziness, and muscle pain. Abdominal pain, nausea, vomiting, and diarrhea. Bleeding from the nose, gums, kidneys, and gastric mucosa
Dengue	Worldwide, usually in tropical and subtropical regions	The four distinct but closely related serotypes of dengue virus (DEN-1, DEN-2, DEN-3, and DEN-4) Members of *Flaviviridae* family	Viruses are maintained in a human–mosquito cycle in tropical urban areas	Humans living in tropical and subtropical urban locations in dengue-endemic areas, particularly during the rainy season	Bite of infective female *Aedes* mosquitoes, which, in turn, have acquired the virus while feeding on the blood of an infected person	Flu-like illness with muscle and joint pains; few develop severe dengue or dengue shock syndrome. May include hemorrhagic rash (bleeding into the skin)
Ebola virus disease	Primarily in remote villages in Central and West Africa, near tropical rainforests	Ebolavirus belongs to the *Filoviridae* family (filovirus). Ebolavirus comprises five distinct species: 1. *Bundibugyo ebolavirus (BDBV)* 2. *Zaire ebolavirus (EBOV)* 3. *Sudan ebolavirus (SUDV)* 4. *Reston ebolavirus (RESTV)* 5. *Taï Forest ebolavirus (TAFV)*	Fruit bats of the *Pteropodidae* family are considered to be the natural host. Although nonhuman primates have been a source of infection for humans, they are not thought to be the reservoir but rather an accidental host like human beings	Human contact with infected fruit, bats, or monkeys/apes and the consumption of their raw meat. Human-to-human transmission is through direct or close contact with infected patients, and particularly through contact with blood and body fluids of an infected patient	Close contact with the blood, secretions, organs, or other bodily fluids of infected animals. In Africa, infection has been documented through the handling of infected chimpanzees, gorillas, fruit bats, monkeys, forest antelope, and porcupines found ill or dead or in the rainforest	Sudden onset of fever, intense weakness, muscle pain, headache, and sore throat. This is followed by vomiting, diarrhea, rash, impaired kidney, and liver function, and in some cases both internal and external bleeding

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Disease	Geographical distribution	Agent	Reservoir	Risk factors	Mode of transmission	Clinical features
Hantavirus	North and South America, Europe, and the Asia-Pacific region, including India, Indonesia, Myanmar, Sri Lanka and Thailand	Part of the *Bunyaviridae* family	Wild rodents. Each strain of hantavirus possibly has its own rodent reservoir	Certain occupational groups—such as farmers, sweepers, and laborers who are likely to have high exposure to infected dust and those living in rural areas are at higher risk of infection	Inhalation of the virus in aerosols from urine or feces of infected rodents. Human-to-human transmission is uncommon but possible	Renal syndrome. Two types: HFRS affects the kidney, more common in Asia, while HPS affects the lungs, more commonly seen in the Americas. HFRS: Sudden onset of high fever, chills, and pain in the back, muscles, and abdomen. Profuse bleeding may occur, and kidney function can also be impaired. Tiny red spots and rashes appear on the face and elsewhere. Bleeding may also be seen from the nose and in the urine. HPS: An initial period of general fever, ache, and cough is followed by the sudden onset of acute respiratory distress
Hand, foot, and mouth disease	Worldwide, and increasing in the Asia-Pacific region	*Enterovirus* genus of the *Picornaviridae* family	Humans are the sole reservoir	• Poor hygiene and direct contact with infected patients • Children under the age of 10 years, and especially those under the age of 5 years, are at the greatest risk	Highly contagious and gatherings in places like kindergartens and schools facilitate disease transmission. The virus is transmitted through direct contact with nose and throat discharges, saliva, fluid from blisters, or the stool of infected persons	Usually mild and self-limiting. Typical symptoms are fluid-filled blisters on the hands, feet, and inside of the mouth and/or dehydration due to fever and poor fluid intake. Occasionally, meningoencephalitis in some children, pneumonia, and myocarditis
Japanese encephalitis	Mainly in the Asia-Pacific region	Member of the *Flavivirus* genus in the family *Flaviviridae*	• The virus circulates in ardeid birds (herons and egrets). Pigs are amplifying hosts in that the virus reproduces and infects mosquitoes that bite them but does not cause disease • Humans become infected as accidental hosts when those mosquitoes bite humans	Children in endemic areas are at risk when involved in outdoor activities during and immediately after the monsoon season, when mosquito numbers are at their highest. Travelers and expatriates who stay for prolonged periods in rural areas with active JE virus transmission are likely to have a similar risk to the susceptible resident	Outbreaks usually occur during the rainy season in paddy-growing territories Occasionally, outbreaks have been reported in periurban or slum areas where scavenging pigs are present and waterlogged conditions exist	Rapid onset of high fever, stiff neck, coma, tremors, and convulsions (especially in infants)

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Disease	*Geographical distribution*	*Agent*	*Reservoir*	*Risk factors*	*Mode of transmission*	*Clinical features*
Nipah virus	Bangladesh, India, Malaysia, and Singapore	Member of Paramyxoviridae family	Fruit bats of the genus *Pteropus* (flying foxes) are the main reservoir. NiV is known to infect pigs, dogs, cats, horses, and humans when they consume contaminated food or drink that has been infected by bat secretion (saliva and urine)	• In Bangladesh, the cultural practice of drinking raw date palm sap is a major risk factor for human infection. Human-to-human transmission of NiV reported in recent outbreaks demonstrates the risk for healthcare workers of acquiring the virus from infected patients • Close contact with infected pigs who act as an intermediate and possibly amplifying host after contact with infected bats	NiV is transmitted to humans either from animals (contact with urine, saliva, or contaminated materials) or from other humans	Ranges from asymptomatic infection to fatal encephalitis. Some people can also experience atypical pneumonia and acute respiratory distress
Novel human coronavirus	Outbreaks were reported in China, Hong Kong SAR, Singapore, and Vietnam, and spread to many countries in 2002–2003, notably to Canada	SARS coronavirus (SARS-CoV)	The reservoir was initially thought to be the civet cat but is now believed to be the bat, with the civet cat acting as an intermediate host	Source of infection remains undetermined, although there is circumstantial evidence of animal-to-human transmission. Elderly and those with chronic, immunosuppressive diseases are particularly vulnerable	Close person-to-person contact, e.g., by inhaling droplets and can be transmitted during air travel	Sudden onset of flu-like symptoms. Severe cases progress to a respiratory disease and pneumonia
Rabies	Worldwide (except Antarctica), but >95% of human deaths occur in Asia and Africa	*Lyssavirus* is a genus of the family Rhabdoviridae	Warm-blooded mammals and bats—urban rabies primarily by dogs, and sylvatic rabies by wild animals	Rabid dog bite. Human deaths following exposure to mongoose, jackals, foxes, wolves, and other wild carnivore host species are very rare	Infected through the skin following a bite or scratch by an infected animal. infectious material—usually saliva—comes into direct contact with human mucosa or fresh skin wounds. May be contracted via transplantation of an infected organ such as a cornea	Initial pain or a tingling sensation at the site of the bite; hydrophobia, restlessness, excess salivation, convulsions, and finally death

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Disease	Geographical distribution	Agent	Reservoir	Risk factors	Mode of transmission	Clinical features
Rift valley fever	Africa and occasionally reported in Middle East countries	*Phlebovirus*, a member of the Bunyaviridae family	Infected livestock (sheep, cattle, and goats) infect a variety of mosquito vectors. Virus often enters the bloodstream during early clinical illness in humans	Mainly affects persons in certain occupational groups—such as veterinarians, animal handlers, and slaughterhouse workers. Travelers visiting RVF-endemic locations during periods when sporadic cases or epidemics are occurring	Bite of infected mosquitoes or other insects. Contact with tissues and body fluids of infected animals and/or inhalation of aerosols produced during the slaughter of infected animals	Most human cases are relatively mild. Some patients develop severe flu-like symptoms. However, a small percentage of people develop a much more severe form of the disease that manifests as one or more of three distinct syndromes: ocular, meningoencephalitis, and hemorrhagic
Anthrax	Worldwide	*Bacillus anthracis*	Domestic and wild animals such as cattle, buffalo, sheep, goats, pigs, and horses	Infection in humans is rare. Skin contact with, or inhalation of, aerosolized spores and consumption of undercooked or raw meat or dairy products from infected animals	Cutaneous route; through consumption of undercooked or raw meat or dairy products from infected animals and by inhaling a large number of anthrax spores suspended in the air (the pulmonary form of anthrax, which is the rarest and most severe)	Red marks on the exposed area of skin, gastrointestinal form: pulmonary form
Botulism	Worldwide	*Clostridium botulinum*. Seven types: A, B, E and, rarely, F cause human botulism	Spores found in soil, aquatic sediment, the intestinal content of herbivores and fish. Botulism is caused by a toxin produced by this sporulated form. Type E toxin is associated with fish and marine mammals. Infant botulism is associated with the use of contaminated honey in milk formula	Foodborne botulism can occur in all age groups	Ingestion of preformed toxins; *ρ* wound botulism	Nausea, vomiting, sometimes constipation, followed by toxic effects on the central nervous system (drooping eyelids, blurred or double vision, dizziness, difficulty in swallowing, blurred speech, muscle weakness, and respiratory paralysis)

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Disease	*Geographical distribution*	*Agent*	*Reservoir*	*Risk factors*	*Mode of transmission*	*Clinical features*
Brucellosis	Countries in Asia including China, India, Indonesia and Thailand, and also in South America, the Mediterranean and the Middle East	Various types of the *Brucella* species of bacteria exist (*B. abortus, B. melitensis, B. suis,* and *B. canis*). *B. melitensis* is the most virulent and causes the most severe and acute cases of brucellosis. *B. abortus* is associated with mild to moderate sporadic disease that rarely causes complications	Major reservoirs are cattle and buffalo (*B. abortus*), sheep and goats (*B. melitensis*), swine (*B. suis*), and dogs (*B. canis*). Infection persists throughout the lifetime of the animal	Person-to-person transmission is rare. People in close contact or working with animals are at a greater risk of developing the disease. However, the majority of cases are caused by consuming raw, unpasteurized milk or cheese from infected goats or sheep	• Direct contact with infected tissues or fluids • Ingestion of raw milk or dairy products such as soft cheese. Contamination of a fresh wound with infected matter from animals such as blood, urine, aborted fetuses, and placenta • Accidental needle-stick puncture with *Brucella* • Contact with urine or tissues from infected animals, usually rodents • Contact with surface water, soil, or plants contaminated with the leptospirosis bacteria from the urine of infected animals • Via skin abrasions or exposed mucous membranes, the most common entry point for infection • Human-to-human transmission is rare	• Gradual onset of persistent fever, chills, sweating, headache, muscle pain, backache, joint pain, fatigue, weakness, and weight loss • Chronic debilitating illness. Complications may affect any of the organ systems
Leptospirosis	Worldwide, but is the most common in tropical and subtropical areas with high rainfall	The bacteria *Leptospira interrogans*, of which there are 12 species and over 250 serological variants (serovars)	About 160 mammalian species serve as reservoirs. Rodents are a primary source of infection for humans	• Agricultural and farm workers (rice-paddy and sugarcane workers, for example), as well as those who work outdoors or with animals, are particularly at risk. Recreational hazard for those who swim or wade in contaminated water • At risk include pet shop workers, veterinarians, sewer workers, abattoir workers, meat handlers, and the military • Survivors of natural disasters (e.g., flooding) are also at high risk	• Contact with urine or tissues from infected animals, usually rodents • Via skin abrasions or exposed mucous membranes, the most common entry point for infection • Human-to-human transmission is rare	• Ranges from flu-like symptoms to complications involving pneumonia and multiple organ dysfunction syndromes • Headache, muscle pain, and conjunctival suffusion can develop with progression to severe jaundice, anuria, kidney failure, and even death

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Disease	Geographical distribution	Agent	Reservoir	Risk factors	Mode of transmission	Clinical features
Listeriosis	Worldwide	The bacterium *Listeria* monocytogenes	*Listeria monocyto*genes mainly occurs in soil, forage, water, mud, livestock food, and silage. Animal reservoirs include infected domestic and wild mammals, fowl, and humans Animals can carry the bacterium without appearing ill and can contaminate foods of animal origin such as meat and dairy products	• Multiply in refrigerated foods that are contaminated • Although rare, listeriosis primarily affects older adults, pregnant women, newborns, and adults with weakened immune systems • Intensifies existing debilitating illnesses or conditions such as organ transplantation, diabetes, cirrhosis, renal disease, heart disease, HIV infection, and in persons with malignancies or on corticosteroids. Pregnant women are about 20 times more likely to get listeriosis than other healthy adults	• Consumption of foods contaminated with *Listeria monocytogenes* • Organism can be transmitted from mother to fetus in utero, or during passage through the infected birth canal	• Septicemia and meningitis • Pregnant women may experience a mild, flu-like illness followed by fetal loss or meningitis in their newborn. Acute gastroenteritis with high fever
Melioidosis	South-East Asia, China, and parts of Australia	*Burkholderia pseudomallei*	• No animal reservoir • Widespread in soil and muddy water in endemic areas • Common in moist clay soils	• Most people become infected directly from the environment, e.g., soil • Predisposed conditions—comorbidities/Steroids therapy • Agricultural, laboratory and healthcare workers are particularly vulnerable to occupational exposure	Human-to-human transmission is rare Direct contact with contaminated soil and surface water Infected animals can shed the organism on seeping wounds and, depending on the site of the infection, from other abscesses, nasal secretions, milk, feces, and urine	• Salivary glands—abscess among children • Acute localized infection sometimes occurs at the site of inoculation • Swelling of regional lymph nodes • Lung disease is the most common form • Septicemia • Abscesses and suppurative lesions in a variety of organs

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Disease	*Geographical distribution*	*Agent*	*Reservoir*	*Risk factors*	*Mode of transmission*	*Clinical features*
Plague	Endemic in many countries in Africa, the Americas and Asia. Contact of infected wild rodents with domestic rats may initiate an urban cycle of spread	*Yesinia pestis*	• Rodents are the natural and maintenance hosts Domestic rodents are prone to both the infection and the disease, hence the phenomenon known as "rat fall" • Marmot is a primary carrier in many Asian countries • Dogs may become infected without showing any sign of illness and act as sentinel animals	Humans are at risk when they come into contact with rats in the same habitat. Pneumonic form transmits more efficiently through the inhalation of aerosols. Rodents and insects act as potential reservoirs and carriers of *Y. pestis*	• Indirect or direct transmission • Bite from an infected flea (bubonic plague): bubonic and septicemic • Direct transmission from a plague-infected rodent or animal while handling infected animals or carcasses • Human-to-human spread (pneumonic plague) • Direct contact with droplets contaminated with sputum • Contact with an animal with pneumonic plague, which occurs when *Y. pestis* infects the lungs or when the infected animal coughs near another animal • If a cat develops pneumonic plague, it becomes a source of infection for people through aerosol transmission	Usually start with flu-like symptoms Bubonic (through flea bites): fever, swollen lymph nodes (buboes) and signs of meningitis. Septicemic: Pneumonic (most virulent and least common form): fever, respiratory tract disease, and bright red sputum
Salmonellosis	Worldwide	*Salmonella species* (*S. typhimurium, S. enteritidis*, and >2,500 known types or serotypes)	Poultry (main reservoir), domestic and wild animals	Children are the most vulnerable. infants, the elderly, and persons with compromised immune systems	Consumption of raw or improperly cooked food of animal origin, although many other foods, including green vegetables contaminated from manure, have been implicated in its transmission	Diarrhea, vomiting, and low-grade fever Reactive arthritis

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Disease	Geographical distribution	Agent	Reservoir	Risk factors	Mode of transmission	Clinical features
Scrub typhus	Endemic to a part of the world known as the "tsutsugamushi triangle", extending from northern Japan and the far-eastern Russian Federation to northern Australia and Pakistan. This includes Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka and Thailand	*Orientia tsutsugamushi*, which has five major serotypes.	Chigger mites act as the primary reservoirs for *O. tsutsugamushi*	Essentially, an occupational disease among rural residents in the Asia-Pacific region. An increase in the prevalence of scrub typhus has been reported from some Asian countries, which coincides with urbanization of rural areas	Transmitted to humans and rodents by some species of chigger mites (*Leptotrombidium deliense* and others)	• The chigger bite is painless and may be noticed as a transient localized itch, often found on the groin, armpits, genitalia, or neck • A scab is often seen at the site of the bite • Sudden shaking chills, fever, severe headache, infection of the mucus of the conjunctiva, and swelling of the lymph nodes are also seen • A spotted rash on the trunk may be present. Complications may include pneumonia and myocarditis
Tularemia	Endemic in many parts of the world including North America, Eastern Europe, China, Japan, and Scandinavia. It has been reported from Thailand	• *Francisella tularensis*. Currently, there are four recognized subspecies *F. tularensis (F. tularensis, F. holarctica, F. mediasiatica*, and *F. novicida*) • Clinicians should be aware of tularemia associated with handling of sick pet animals	Rabbits, hares, and rodents are natural reservoirs and often die in large numbers during outbreaks	An underlying disease that suppresses immunity is an important factor for contracting tularemia. Hunters, pet owners, and farmers are high-risk groups for exposure to infection	Contact with infected animals or bitten by ticks, deerfly. or other insects that feed on infected animals. Inhalation of dried animal matter, skinning or dressing killed animals, or drinking water contaminated by animal carcasses. No direct human-to-human transmission	• Sudden onset of high fever, headache, muscle and joint pains and swollen, and painful lymph nodes • Slow healing sores and lesions develop at the entry site of bacteria. Pneumonia is common after inhalation

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Disease	Geographical distribution	Agent	Reservoir	Risk factors	Mode of transmission	Clinical features
Teniasis/ cysticercosis	• *Taenia solium (T. solium)* and *Taenia saginata (T. saginata)* are distributed worldwide • *T. saginata*—found in countries where cattle and buffaloes are raised for human consumption • *T. solium* where pigs are raised for human consumption • *T. solium* has been reported from India, Indonesia, Nepal, and other countries of the Asia-Pacific region	*T. solium* (pork tapeworm) and *T. saginata* (beef tapeworm). *T. solium* is responsible for human cysticercosis	Cattle and buffaloes for beef tapeworm and pigs for pork tapeworm	• Related to pig husbandry practice, and in countries where open defecation is common and scavenging pigs are found in the community • Lack of meat inspection, and consumption of raw or undercooked meat	Ingestion of raw beef/pork containing the cysticercus. Humans are the final host for both *T. saginata* and *T. solium*, but humans can also be the intermediate host for *T. solium*. However, carriers of *T. solium* carry a substantial risk of acquiring cysticercosis by feco-oral autoinfection and members of their households are also at increased risk	Intermittent fecal shedding of proglottids (segments), gastrointestinal discomfort, nausea, diarrhea, loss of appetite, and loss of weight. Seizures, headaches, learning difficulties, and convulsions are symptoms of neurocysticercosis. Cysticercosis of other tissues is almost always asymptomatic
Toxoplasmosis	Worldwide	*Toxoplasma gondii*	Cats and other felines. Intermediate hosts include most species of birds and mammals	• Very common • Infection is often highest in areas that have hot, humid climates, and low altitudes. • IUGR	Ingestion of undercooked, contaminated meat • Drinking water or milk contaminated with *Toxoplasma gondii*. • Mother-to-child (congenital) transmission (congenital) transmission or mother-to-fetus through the placenta. Animal-to-human (zoonotic) transmission • Accidentally swallowing the parasite through contact with cat feces that contain toxoplasma, such as while cleaning cat litter	• Mild flu-like symptoms • Enlarged lymph nodes in the head and neck • Pneumonia • Central nervous system disturbances • Complications of eyesight • Other systemic diseases
Trichinellosis	Worldwide, most frequently in regions with temperate climates, including mountainous regions in South-East Asia	*Trichinella spiralis*: *Trichinella larvae* are encysted in muscle tissue of meat from domestic or wild animals	Wild boar, domestic pigs, bears, rodents, and horses	Consuming raw or undercooked meat infected with the *Trichinella* parasite, particularly from wild game (e.g., boar) or pork	Consumption of raw or undercooked meat	Diarrhea, abdominal pain, nausea, vomiting. Eyelid or facial edema (fluid retention), conjunctivitis, fever-associated chills, muscle pain, and itchy skin. Occasional heart failure, pneumonia, or encephalitis

(CCHF: Crimean-Congo hemorrhagic fever; HFRS: hemorrhagic fever with renal syndrome, HPS: hantavirus pulmonary syndrome; NiV: Nipah virus; IUGR: intrauterine growth restriction)

[e.g., ribonucleic acid (RNA) viruses], reassortment (e.g., influenza virus), and recombination (e.g., enteroviruses) aid in the evolution of the virus, allowing it to cause new outbreaks, and potential pandemics, with each re-emergence. Emerging viruses such as severe acute respiratory syndrome-associated coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola virus, Zika virus (ZIKV), chikungunya virus (CHIKV), Nipah virus (NiV), and the most recent SARS-CoV-2 have also resulted in large epidemics and pandemics.

Costs associated with these EIDs are huge and unpredictable. The COVID-19 pandemic will likely end up costing between $8.1 and $15.8 trillion globally.

CONTROL MEASURES

Applications of "public health" measures mainly using the applied epidemiology are important to contain the spreading epidemics by understanding the causative and enabling factors for its spread and also the pathophysiology of disease for effective diagnosis and treatment as now being seen in COVID-19 pathogen. All the causative factors need to be studied in a disaggregated manner for understanding the major enabling causative factors of the disease. Predictability is an important factor for controlling these diseases, and many countries are still facing challenges on these accounts. Real-time data collection and capacity to respond accordingly play a major role in gravity of spread of the disease and its consequences.

In order to combat both emerging and re-emerging viruses, effective drugs and vaccines are needed to treat and prevent the viral infections. However, in order to do so, certain biosafety-level facilities are required for the handling of viruses that are considered to be highly pathogenic agents, such as biosafety level 3 (BSL-3) facilities for SARS-CoV-2, MERS-CoV, CHIKV, and avian influenza, and BSL-4 for Ebola, Marburg virus (MARV), Lassa virus (LASV), and NiV. This poses a major limitation in the development of vaccines and drugs against the viruses.

There is a need to identify first the causative pathogen, its microbiological features including genetic makeup, and its source of origin as mostly these are zoonotic in nature. Combined efforts of veterinarians and medical scientists need to work together for identifying the causative pathogen and its epidemiological features. Increasing human–animal interactions due to deforestation and adverse climatic changes are also leading to a newer infectious disease among human race. Lack of public health infrastructure and/or application of its scientific principles lead to EIDs as seen even during ongoing COVID-19 pandemic. Strengthening the public health systems with increasing focus on the surveillance system can help in checking the emergence and spread of these diseases and many governments around the world have been spending resources for these and many are committing after COVID-19 experience. Despite each EID having some unique features, they have certain basic commonalities which have been accepted in the form of International Health Regulations (IHRs, 2015). IHRs provide an overarching legal framework that defines countries' rights and obligations in handling public health events and emergencies that have the potential to cross borders. The IHRs are an instrument of international law that is legally binding on 196 countries, including the 194 WHO Member States. They create rights and obligations for countries, including the requirement to report public health events. The regulations also outline the criteria to determine whether or not a particular event constitutes a "public health emergency of international concern." At the same time, the IHRs require countries to designate a National IHR Focal Point for communications with WHO to establish and maintain core capacities for surveillance and response, including designated points of entry. Additional provisions address the areas of international travel and transport such as the health documents required for international traffic. Finally, the IHRs introduce important safeguards to protect the rights of travelers and other persons in relation to the treatment of personal data, informed consent, and nondiscrimination in the application of health measures under the regulations. Taking cues from IHRs, many countries have strengthened their response and surveillance systems but there remain gaps largely in poor countries to formulate the national action IHR plan and implement the strategies and policies due to political and economic differential priorities. Unpredictabilities of EIDs and their huge adverse impacts upon livelihood, community, and health system, there is requirement of more resources,development of ecofriendly policies and universal global response. Equally, the important element is the level of responsiveness of the public health system and its applications on the basis of strict scientific rationale.

ELEMENTS OF AN EPIDEMIC MANAGEMENT SYSTEM

Emerging infectious diseases are the major threat to the community. A robust mechanism to manage the epidemic is necessary in any healthcare system management (**Fig. 2**). Components of the epidemic management system include good laboratory network, capacity of the healthcare system to respond quickly, well-equipped tertiary care center and availability of medication, infodemic management, national surveillance system, and strong referral system.

National Surveillance System interconnected with other countries: The surveillance system is an important component of the public health system where real-time data management aids in capturing the possibilities of outbreak and epidemic of diseases. For this, the country needs to have its IHR national plan in place and it entails the data sharing and management practices to control the epidemics among countries.

Strong referral system: Ideally, an effective referral system is to have seamless and coordinated functional complementary relationships among all tiers of the health delivery system as depicted in **Figure 3** so as to able to deliver the timely and best possible care at all levels. This becomes all the more important during an epidemic where patients requiring tertiary care including intensive care unit (ICU) services, as seen during the ensuing COVID-19 epidemic, can be shifted to higher medical centers as part of the referral system.

Wide network of laboratory systems easily available up to the community level: Laboratory-based testing such as RT-PCR and antigen diagnostic tests form the mainstays of managing an epidemic and its spread and finally its control as even for COVID-19 pandemic. WHO advocates "Test, Test and Test strategy." Laboratory services need to have in-built quality

control measures along with integration across different tiers of the health systems and other related branches such as virology, microbiology, and even with the veterinary department. Uniformity in laboratory services across the country in an integrated fashion plays an important role in surveillance and epidemiological management of the epidemics. A network of laboratory systems right from the community level till the national level is crucial in effective management of an epidemic and needs to be included in the country's health delivery strategy and budgeting.

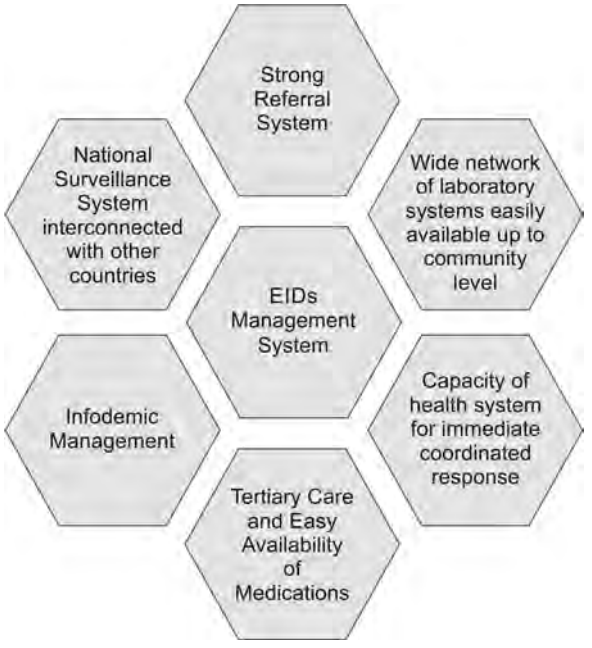

Strong Referral System
National Surveillance System interconnected with other countries
Wide network of laboratory systems easily available up to community level
EIDs Management System
Infodemic Management
Capacity of health system for immediate coordinated response
Tertiary Care and Easy Availability of Medications

FIG. 2: Elements of a robust emerging infectious disease (EID) management system.

Infodemic management system: Right information at right time in right format are the three important elements of a commutation strategy generating appropriate health-seeking behavior, particularly during the ensuing epidemic. This was also experienced during polio management and is currently being experienced during the COVID-19 pandemic in many countries. Complete elimination is not possible but infodemic can be controlled to a large extent so as not to affect the containment strategy of an epidemic. For this, ensure that people have access to factual information in a timely manner that is easily understood and from a credible source and in an easy-to-understand language. The information to be shared should be based on existing scientific evidences in a transparent manner using mix of communication strategies and with the principle of reinforcing and continuous learning.

Tertiary care and easy availability of medication: High standard of equitable tertiary care plays a significant role in reducing the adverse outcomes among patients infected by the pathogen causing the epidemics and also in transmission among the community. Hospitals should have a readily available plan and capacity to be rolled out during overflow of the patients due to ensuing epidemic including documented exclusive epidemic response plan detailing the restructuring of logistics, infrastructure, functions, and manpower.

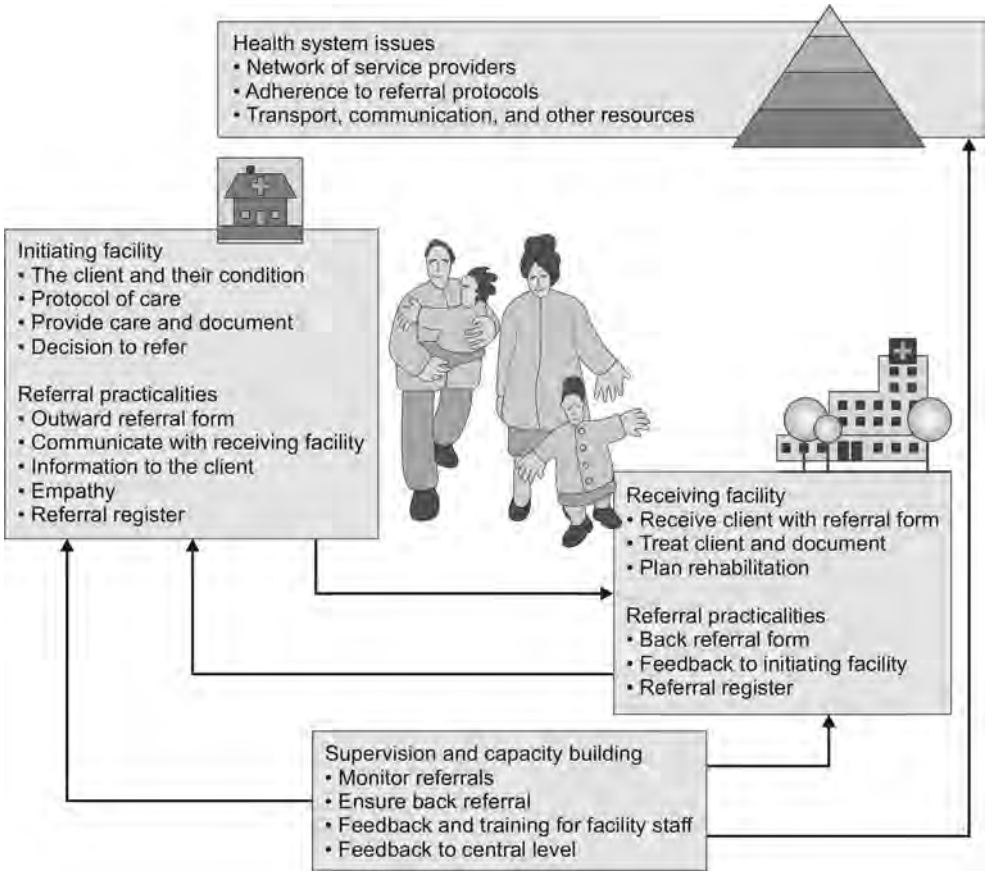

Health system issues
• Network of service providers
• Adherence to referral protocols
• Transport, communication, and other resources
Initiating facility
• The client and their condition
• Protocol of care
• Provide care and document
• Decision to refer
Referral practicalities
• Outward referral form
• Communicate with receiving facility
• Information to the client
• Empathy
• Referral register
Receiving facility
• Receive client with referral form
• Treat client and document
• Plan rehabilitation
Referral practicalities
• Back referral form
• Feedback to initiating facility
• Referral register
Supervision and capacity building
• Monitor referrals
• Ensure back referral
• Feedback and training for facility staff
• Feedback to central level

FIG. 3: Referral system.

Easy and freely availability of medication as part of clinical management as standardized by the nodal governmental agency, of the patients arising from an epidemic, helps in reducing the adverse effects among the diseased, as experienced in COVID-19 pandemic using dexamethasone and oxygen therapy. Continuity of the pharmacy along with nonepidemic services also needs to be continued like elective and emergency care. Delivery of medication at the community level also plays an important role during an epidemic situation as part of containment strategy and reducing the morbidity and mortality. Inventory management protocols in conformity with the national epidemic response plan are to be developed and followed for ensuring sufficient and timely supplies of the necessary items including medication.

Capacity of the health system for an immediate coordinated response: Health system preparedness during an epidemic situation needs to be of such a level so as to be able to cope with a sudden surge of patients during an epidemic besides maintaining the routing healthcare services. All the components of the health system, private and public, besides those provided by nongovernmental organizations (NGOs), trusts, etc., must be able to adapt to the national epidemic plan in a unison coordinated manner for testing, referral, hospital care, and community-based services. Using IT platforms, all these components may be networked and deliver the services in a swiftly, coordinated and synergistic manner. During an epidemic situation, the legal and statutory provisions as applicable in a country's context may also be used as contained in the national epidemic response plan.

VACCINE DEVELOPMENT

A vaccine is a kind of drug used largely for prevention of diseases by producing immunity through stimulating T cells and B lymphocytes for varied duration and is the most cost-effective way to control the spread of diseases. Vaccines are designed to elicit antibody responses greater and more effective than the natural infections (by antigens) but without any disease's signs and symptoms. Effective antibodies are to be of the neutralizing type able to effectively negate the infectivity of the pathogen's ability to infect host cells. Neutralizing antibodies vaccines include those for influenza and smallpox. Some of the vaccines like those for tuberculosis and HIV require cell-mediated immunity (CMI). Effectivity and duration of protection for any vaccine depends on genetic characteristics, of the pathogen, quality of the immunogenicity produced, and mechanism of action. Mutations may make the vaccine redundant as it changes the antigenic composition of the pathogen. Vaccines have been produced and are in use for many diseases saving billions of lives globally. The latest to join the group is the COVID-19 vaccine (refer to COVID vaccine) produced using a different platform technology. However, for many infections, the vaccines are yet to be found.

Stages of Vaccine Development

Vaccine development follows the stringent robust scientific protocols before being introduced for mass usage by the community (**Flowchart 1**). Many international agencies and countries have their own regulatory authorities to approve the introduction of a particular vaccine for their nationals. Development of vaccines including after introduction for human use, need more stringent protocol for their usage particularly for infants elderly, pregnant women and even for healthy people. The COVID-19 vaccine is going to be given to almost everyone globally.

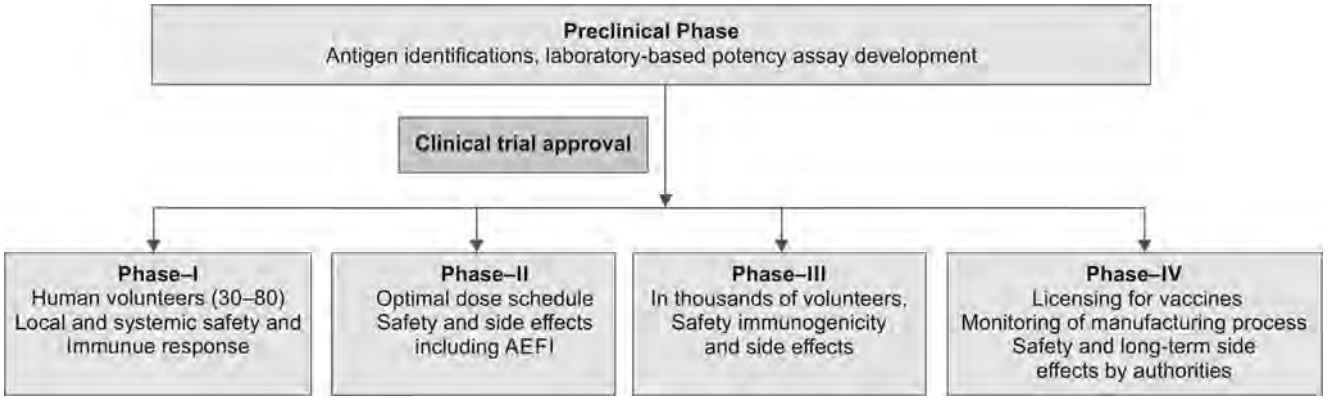
Preclinical Phase

During this phase, the substance is identified to act as an antigen to elicit an immune response in the body similar to the pathogen against whom the vaccine is to be developed. A number of such candidates are tried and the chosen one has the best immunogenic response and level of protection.

Phase I: During this phase, the vaccine is first time tested on human volunteers, usually 30–80, to assess its safety and level of immune response.

Phase II: Hundreds to few thousands volunteers are part of this phase. Phase II studies aim to determine the most effective dose and expand the safety experience with the vaccine. Side effects such as pain/swelling at the injection site, myalgia, headache, and possible adverse effects following immunization (AEFI) are seen.

Phase III: In this stage of the clinical trial, thousands of volunteers receive the vaccine to study its effectiveness. A comparison study is done where an equal number of participants gets the vaccine under study and other group receive the placebo. These groups are followed for months, as



(AEFI: adverse effects following immunization)

FIOWCHART 1: Stages of vaccine development.

in COVID-19 vaccine, to years to see the development of any side effects and level of immune response. Reporting of any serious AEFIs leads to pause the continuation of the trial till all the data are reviewed in depth to decide the continuation of the trial or otherwise. Recently, there were some reports of serious AEFIs during this phase from the AstraZeneca vaccine trial and it was paused before restarting again after a thorough review by regulatory authorities.

Most of the countries as an exception have given Emergency Use Authorization (EMU) after reviewing the data from Phase III trial where the occurrence of side effects, both local and systemic, are studied including efficacy and upon fulfilling the set norms the vaccine is permitted for mass human use, though the usual practice is after Phase IV as described below.

Phase IV: After licensing of the vaccine for production and usage, the regulatory authorities continue to monitor the manufacturing processes so as to monitor the safety and long-term side effects, also known as "postmarketing surveillance." During this phase the manufacturing practices, AEFIs, and duration of immunity are monitored for safety and effectiveness.

SUMMARY

The COVID-19 pandemic has made us realize the huge inadequacies in responding to the EIDs. EIDs have been posing a huge socioeconomic and health burden across countries as the world is now increasingly being connected and therefore there is a strong need for greater responsiveness of the health systems. Real-time surveillance backed by laboratory facilities is the most important aspect to prevent occurrence of these EIDs and for controlling during their occurrence. Implementation of IHRs as now being further strengthened by the WHO in the wake of the COVID-19 pandemic by each country including a global co-ordinated response system will help in containment at the country level and largely at the global level.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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185 CHAPTER

Immunization and Postexposure Prophylaxis for Infections

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INTRODUCTION

Immunization is the process of stimulating the body's own immune system to produce specific proteins called antibodies against specifically selected bacteria or viruses in order to prevent illness. To achieve this process, substances called vaccines are used; hence, the process is referred to as either immunization or vaccination. Where does the patient live, what vaccines did he/she receive during childhood, where is he/she planning to travel, how long will the trip last, and what are the activities planned to be carried out— are the factors that will determine which vaccines are recommended for an adult. Usually, vaccines provide lifelong protection from the disease; in some situations, specially if given during childhood, some vaccines need a second dose, which is referred to as a booster dose. Associated medical conditions also determine indications of vaccination in adult and travelers.

There are different types of vaccines, active, passive, and toxoids. Regardless of the type, the process is similar. Unlike immunity gained naturally by getting the disease and falling ill, this process is based on weakening the substances used, to a point where they are sufficient to stimulate the immune system to create antibodies against the bacteria or virus without yet actually causing the disease. Active vaccination refers to using the specific bacteria or virus that causes the disease in order to stimulate the immune system to generate its own antibodies.

Another form of active immunization is toxoids, which are used for diseases where the bacteria itself does not cause the disease but a specific toxin that it releases does, e.g., diphtheria and tetanus. Similarly, a weakened form of this toxin is used to stimulate the immune system to generate its own antibodies. On the other hand, passive vaccination or immunization refers to giving the patient preformed antibodies from donors that have generated these antibodies against specific organisms. Unlike active immunization, passive immunization is a weaker process, which is not recommended for healthy adults but may be required in certain situations, such as in immune-compromised individuals.

As a general rule, vaccines are mostly considered safe. They have a long history of preventing death and saving lives all over the world, with a good safety profile. In very rare instances like with any other medical substance, they can cause an allergic reaction or some form of encephalopathy or encephalitis leading to seizures. The more common effects are mild and include local redness, soreness, or a low-grade fever. The next section will summarize the most common vaccines recommended. For each vaccine, we will review the etiology/causes, clinical presentation, investigations (suspected lab abnormalities), and vaccine/treatment and we will end with special considerations (immune-compromised, pregnancy/breastfeeding, healthcare professionals, and travelers).

INFLUENZA

Viral infections are highly contagious and are commonly referred to as the flu. Common presenting features are fever lasting 2–5 days, headache, myalgia, runny nose, and sore throat. *Investigations*: Clinical diagnosis and testing are sometimes done for documentation in a new outbreak or in patients at risk of complications. The vaccine is available in three different forms: Intramuscular (IM), intradermal (ID), or nasal spray. The ID vaccine and nasal spray uses a smaller dose. For elderly or patients with risk of severe infection, the IM higher dose is recommended or the vaccine with an adjuvant which increase the effectiveness of the vaccine. Mostly symptomatic, antiviral medications are used either for treatment or for prevention of illness. For treatment, they decrease the duration of illness by approximately 1 day. They are not recommended if symptoms >48 hours. They are usually used for elderly patients or patients with chronic medical illnesses who are at risk of developing severe complications. For prevention, they are used for the same group of patients mentioned above after exposure who did not take the vaccine.

Special considerations:

- Immune-compromised—recommended
- Pregnant/breast feeding—inactive form recommended (preferably before pregnancy if possible)
- Healthcare professionals—recommended
- Travelers—depending on the season of travel (spreads in the winter)

Haemophilus influenza type-B—*Haemophilus influenza* serotype b (Hib) bacteria. *H. influenza* is the leading cause of bacterial meningitis. Due to its vascular invasion tendency, it has the ability to cause other disease, such as epiglottitis, pneumonia, empyema, pericarditis, bacteremia, and septic

arthritis. Clinical presentation will depend on the area involved. It mainly requires a clinical diagnosis, and treatment is started empirically. For invasive disease, microbiological testing with cultures is required from sterile sites for confirmation. Active vaccination with two to three primary doses and a booster dose as part of childhood vaccination has a protection efficacy against ~95% of the disease. Beta-lactam agents (e.g., amoxicillin or a second- or third-generation cephalosporin) are the preferred antimicrobial agents. Alternative agents include fluoroquinolones, macrolides, tetracyclines, and aminoglycosides.

Special considerations:
- Immune-compromised—recommended (specifically post splenectomy)
- Pregnancy/breast feeding—no specific recommendation as long as it was taken as part of childhood vaccine, no specific contraindication; if needed, preferably during third trimester
- Healthcare professionals—no specific recommendation as long as it was taken as part of childhood vaccine.
- Travelers—no specific recommendation as long as it was taken as part of childhood vaccine

PERTUSSIS

Bordetella pertussis bacteria cause protracted illness, presenting with paroxysmal coughing, affecting daily function. It leads to serious complications, including failure to thrive, apnea, pneumonia, respiratory failure, seizures, and death threat in younger patients. Pertussis is mainly a disease of clinical diagnosis, although cultures or molecular testing can be used for suspicious cases. Due to the duration, treatment is started on clinical suspicion, to prevent spread of the disease. Pregnant women who have been previously immunized with a full three-dose series of tetanus and diphtheria (Td) vaccine should receive a single dose of tetanus, diphtheria, pertussis (Tdap) vaccine, ideally during the early part of the 27–36-week gestational age range. For suspected cases of pertussis and cough ≤3 weeks, antibiotics are recommended. Macrolides are the antibiotics of choice. Azithromycin or clarithromycin have a better compliance profile and are better tolerated than erythromycin. For patients who have macrolide intolerance, trimethoprim-sulfamethoxazole is an acceptable alternative. If cough is persistent for 3–6 weeks, antibiotic may not affect the cough duration or severity but are used to reduce the likelihood of transmission to others. Therefore, for pregnant women, healthcare workers, and individuals working with infants, antibiotics are recommended for persistent cough up to 6 weeks.

Special considerations:
- Immune-compromised—no specific recommendations
- Pregnancy/breast feeding—recommended booster for 27–36 weeks if previously immunized. If not, a full three dose series is required
- Healthcare professionals—no specific recommendations
- Travelers—no specific recommendations

DIPHTHERIA

Gram-positive bacillus *Corynebacterium diphtheriae* may lead to a respiratory disease, a cutaneous disease, or an asymptomatic carrier state. Classical throat examination demonstrates an adherent gray pseudomembrane that bleeds with scraping. Definitive diagnosis requires culture of *C. diphtheria* with specimens collected from respiratory tract secretions or cutaneous lesions and a positive toxin assay. Routine laboratory results are usually nonspecific and may include a moderately elevated white blood cell count and proteinuria. Depending on the location and severity of infection, a combination of antitoxin and antibiotics is required. In general, erythromycin or procaine penicillin G are the antibiotics used. Antibiotics are used to decrease the growth preventing further toxin production, slows local spread, and reduce transmission.

Special considerations:
- Immune-compromised—no recommendations
- Pregnancy/breast feeding—recommended
- Healthcare professionals—no recommendations
- Travelers—no recommendations

TETANUS

Toxin-producing anaerobe *Clostridium tetani causes tetanus.* Tetanus can present in one of four clinical patterns: generalized, local, cephalic, and neonatal. The most common and severe clinical form of tetanus is generalized tetanus. Generalized tetanus characteristically has tonic contraction of their skeletal muscles and intermittent intense muscular spasms. Since patients with tetanus have no impairment of consciousness or awareness, both the tonic contractions and the spasms are intensely painful. Clinical diagnosis is based on typical presentation. Since tetanus is one of the few bacterial diseases that does not confer immunity following recovery from acute illness, all patients with tetanus should receive active immunization with a total of three doses of tetanus and diphtheria toxoid spaced at least 2 weeks apart, commencing immediately upon diagnosis. Tetanus toxoid should be administered at a different site than tetanus immunoglobulin. Treatment is usually in the intensive care unit, symptomatic management with airway observation, and management as needed.

Special considerations:
- Immune-compromised—no specific recommendations
- Pregnancy/breast feeding—recommended
- Healthcare professionals—no specific recommendations
- Travelers—no specific recommendations

PNEUMOCOCCUS

Pneumococcus is as gram positive diplococci, e.g., *Streptococcus* may give rise to noninvasive infections: Ear sinus infections and pneumonia; and invasive infections: Bacteremia and meningitis. *Diagnosis is by* isolation of the organism from blood or other normally sterile body sites, such as cerebrospinal fluid (CSF), more than 25 white blood cells and fewer than 10 epithelial cells per high-power field, and a predominance of gram-positive diplococci on Gram stain. There is also the urinary antigen test based on an immunochromatographic membrane technique to detect the C-polysaccharide antigen of *Streptococcus pneumoniae*. Vaccination is recommended for: Infants and children below 2 years and adults 65 years and older and special groups:

Special groups: Children, elderly people with chronic illness, with cochlear implants, or CSF leaks, or who smoke cigarettes.

Antibiotics in penicillin and erythromycin are used for the noninvasive group. Wide-spectrum antibiotics are used for the invasive group. Once the sensitivity of the bacteria is known, a more targeted antibiotic may be selected. Two types of vaccines are available: (1) Pneumococcal conjugate *vaccine (PCV13)* and (2) *pneumococcal polysaccharide vaccine (PPSV23)*.

Special considerations:
- Immune-compromised—recommended
- Pregnancy/breast feeding—not recommended
- Healthcare professionals—no specific recommendation
- Travelers—no specific recommendation

MENINGOCOCCUS

Neisseria meningitidis bacteria cause meningococcal meningitis which present as: fever, headache, stiff neck, nausea, vomiting, photophobia), altered mental status (confusion), lethargy, and poor feeding and irritability in newborn. *Meningococcemia*: Sepsis and rash; fever; fatigue; vomiting; cold hands and feet; cold chills; severe aches or pain in the muscles, joints, chest, or abdomen; rapid breathing, and diarrhea. Isolation and identification of *N. meningitidis* are done with a Gram stain of the CSF sediment or by detection of specific antigens in the CSF by a latex agglutination test or using rapid diagnostic tests (RDTs). Positive results for any of these tests can rapidly provide evidence of infection, even if cultures fail to grow. Meningococcal conjugate vaccines and serogroup B meningococcal vaccines are recommended. Prompt treatment with antibiotic upon clinical suspicion, cardiopulmonary support, and wound care is recommended as needed.
- 11–12 years old—should be vaccinated
- 16 years old—may give a booster dose
- 16–23 years old—to be vaccinated with a serogroup B meningococcal vaccine if—they have complemented component deficiency, functional or anatomic asplenia; they are living with an HIV patient; they are a first-year college student living in a residence hall; or they are a military recruit.

Special considerations:
- Immune-compromised—recommended
- Pregnancy/breast feeding—If high risk, no contraindication to administration
- Healthcare professionals—they are a microbiologist who is routinely exposed to *N. meningitidis*
- Travelers—recommended for those traveling or residing in countries in which the disease is common

HERPES ZOSTER (VARICELLA)

Varicella zoster virus (VZV) *causes* fever, malaise, and painful rash with dermatomal distribution.

It can be identified by polymerase *chain reaction (PCR)*: Live vaccine recombinant zoster vaccine is recommended for people aged 50 years and older. Antiviral medications, acyclovir, valacyclovir, and famciclovir, are recommended to shorten duration and analgesia.

Special considerations:
- No specific recommendation
- Pregnancy/breast feeding—not recommended, post-exposure prophylaxis with varicella zoster immunoglobulin can be given in nonimmune pregnant women
- Healthcare professionals—no specific recommendations
- Travelers—no specific recommendations

HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) is a sexually transmitted disease. It causes common warts. Persistent infection can lead to: Cervical, vaginal, and vulvar cancers in women; penile cancers in men; and oropharyngeal and anal cancers in both men and women. Pap test is recommended for precancer changes and HPV DNA test for HPV. *Vaccine*: 9-valent HPV is given to all adolescents of 11–12 years through to 15 years of age in a two-dose regimen, second 6–12 month from the first dose. It contains inactivated human papillomavirus.

Special considerations:
- Immunocompromised—a three-dose regimen is recommended (0, 1–2, 6 months)
- Pregnancy/breast feeding—not recommended, limited safety profile
- Healthcare professionals—no specific recommendations
- Travelers—no specific recommendations

TUBERCULOSIS

A bacterium called *Mycobacterium tuberculosis* causes fever, chills, night sweats, weight loss, cough, gastrointestinal (GI) symptoms, and bone pain, depending on the affected area. Tuberculosis (TB) skin test (Mantoux) tells if a person is infected or not. TB blood test [interferon-gamma release assays (IGRAs) or T spot] signifies if a person has latent TB infection (LTBI) and acid–fast bacilli (AFB) on a sputum smear along with chest X-ray diagnosis of TB disease. Bacillus Calmette–Guérin (BCG) vaccine is given to infants in countries where TB is common.

The four-drug regimen for LTBI uses isoniazid (INH), rifapentine (RPT), or rifampin (RIF). It should be modified if the patient is drug resistant. For TB disease: INH, RIF, ethambutol (EMB), and pyrazinamide (PZA) are given.

Special considerations:
- Immune-compromised—contraindicated
- Pregnancy/breast feeding—not recommended
- Healthcare professionals—recommended for high percentage or continuous transmission or exposure with isoniazid- and rifampin-resistant TB
- Travelers—no specific recommendations

MEASLES/MUMPS/RUBELLA

Measles: RNA virus from genus *Morbillivirus*. *Mumps*: RNA mumps virus. *Rubella*: RNA virus classified as Rubi virus. Measles presents as fever, cough, maculopapular skin rash, and conjunctivitis with serious illnesses, such as pneumonia and encephalitis. Mumps presents as fever, headache, muscle aches, tiredness, loss of appetite, tender swollen salivary glands, deafness, and in severe cases encephalitis. Rubella presents as fever, sore throat, conjunctivitis, arthritis in women, and miscarriages and birth defects in pregnant

women. Measles can be identified by detection of measles-specific IgM antibody and measles RNA by real-time PCR (RT-PCR) through nasopharyngeal swaps.

- *Vaccine*—live, attenuated vaccine recommended
- *Second doses*—first at 12–15 months of age and second at 4–6 years of age
- Two doses, 28 days apart for teenagers without evidence of immunity
- One dose at least for adults without evidence of immunity

Special considerations:

- Immune-compromised—not recommended.
- Pregnancy/breastfeeding—not recommended, IV immunoglobulin for postexposure within 6 days (measles)
- Healthcare professionals—if no evidence of immunity
- Travelers—unvaccinated adults and infants from 6 through 11 months

CHICKENPOX

Varicella zoster virus infection manifests as a nonspecific viral illness followed by a vesicular rash. The patient's condition can progress to more serious pneumonia and encephalitis. It can be detected by direct virology or PCR detection from body fluids and vesicles scraping. It is a live attenuated virus vaccine. Routine vaccination is recommended for all patients. For patients aged above 60 years of age, note the previous history of chickenpox and chronic medical condition. Antiviral reduces the duration and severity of illness if the patient receives it within 24–48 hours after new vesicle formation. It can be managed by supportive treatment and management of complications.

Special considerations:

- Immune-compromised—varicella vaccine is recommended for patients with mild-to-moderate immune suppression. It is recommended for patients at least 14 days before receiving immunosuppressive therapy.
- Pregnancy/breastfeeding—varicella vaccine is not recommended to be administered during pregnancy. Pregnant women suspected to be at risk of varicella zoster infection are given two vaccines postpartum: One immediately in the postpartum period and the second vaccine at 4–8 weeks postpartum.
- Healthcare professionals—no specific recommendations
- Travelers—no specific recommendations

HEPATITIS A

Hepatitis A virus (HAV) presents as fever, abdominal pain, loss of appetite, vomiting, and jaundice.

Detection of antihepatitis A virus (anti-HAV) IgM antibodies and the determination of total anti-HAV by enzyme immunoassay for diagnosis: inactivated (killed) vaccine, routinely given to children 12 through 23 months of age.

Special considerations:

- Immune-compromised—no specific recommendation
- Pregnancy/breast feeding—no specific recommendation
- Healthcare professionals—no specific recommendation
- Travelers—recommended for high-risk areas

HEPATITIS B

The clinical features of hepatitis B virus (HBV) are fever, liver cirrhosis, liver cancer, liver failure, and death. *Children and adults*: Three-dose vaccine series administered IM, the second and third administered 1 and 6 months after the first months (**Table 1**).

Special considerations:

- Immune-compromised—recommended if not vaccinated
- Pregnancy/breast feeding—not contraindicated if high risk of exposure
- Travelers—no specific recommendations if previously vaccinated

A seroprotective (adequate) level of anti-HBs after completion of a vaccination series is defined as anti-HBs ≥10 mIU/mL; a response <10 mIU/mL is inadequate and is not a reliable indicator of protection.

YELLOW FEVER

The causative agent is a single-stranded RNA virus and a member of the Flavivirus family. Yellow fever is a mosquito-borne viral hemorrhagic fever which presents as a mild, nonspecific febrile illness to severe life-threatening hemorrhage with multiorgan failure. Nucleic acid amplification test is done to detect yellow fever virus (YFV) in various body fluids (urine, serum, and CSF). YFV-specific IgM or fourfold raise in IgG levels is found. A single live attenuated virus vaccine is recommended for a person more than 9 months of age traveling to or living in areas with a high risk of virus transmission. *Treatment*: Mainly supportive treatment and management of complications. Antivirals and steroids are of no proven benefit in treating yellow fever.

Special considerations:

- Immune-compromised—patients require revaccination every 10 years before traveling to endemic areas with YFV.
- Pregnancy/breastfeeding—patients require revaccination regardless of the trimester before traveling to endemic areas with YFV.
- Healthcare professionals—workers dealing with live YFV require revaccination every 10 years.
- Travelers—travelers who have had their vaccination more than 10 years ago and are traveling to high-risk areas and intend to stay for prolonged periods require revaccination.

POLIO

Poliovirus is a member of the enterovirus family that colonizes the gastrointestinal tract. Transmission is mainly through the fecal-oral route. *Mucocutaneous and respiratory manifestations*: Nonspecific febrile illness followed by maculopapular rash on palms and soles and upper and lower respiratory tract infections. *Neurologic and systemic manifestations*: Present as aseptic meningitis, acute flaccid paralysis, and encephalitis. Nucleic acid amplification test (NAAT) is done to detect poliovirus through various body fluids (urine, serum, and CSF). Poliovirus-specific IgM antibodies in the CSF or serum are found. *Inactivated polio vaccine (IPV)*: Incorporated into routine vaccination schedule given at age of: 2 months,

TABLE 1: Postexposure prophylaxis for hepatitis B.

Vaccination and antibody response status of exposed person	*Status of source*		
	Source HBsAg-positive	*Source HBsAg-negative*	*Source not tested or status unknown*
Unvaccinated	HBIG × 1; initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated			
Known responder	No treatment	No treatment	No treatment
Known nonresponder			
After 3 doses	HBIG × 1 and initiate revaccination	No treatment	If known high-risk source, treat as if source were HBsAg-positive
After 6 doses	HBIG × 2 (separated by 1 month)	No treatment	If known high-risk source, treat as if source were HBsAg-positive
Antibody response unknown	Test exposed person for anti-HBs: • If adequate-no treatment • If inadequate - HBIG × 1 and vaccine booster	No treatment	Test exposed person for anti-HBs: • If adequate-no treatment • If inadequate-initiate revaccination

(HBIG: hepatitis B immune globulin; HBsAG: hepatitis B surface antigen)

4 months, 6–8 months, and 4–6 years. *Oral polio vaccine (OPV)*: Live attenuated, oral drops which are given during polio eradication campaigns. Antivirals and immunoglobulins are of no proven benefit in treating poliovirus infection.

Special considerations:
- *Immune-compromised*—IPV is recommended for patients traveling to high-risk areas.
- Pregnancy/breast feeding—IPV is not contraindicated in breastfeeding mothers. It is recommended for patients traveling to high-risk areas.
- Healthcare professionals—IPV is indicated in personnel in close contact with patients who traveled to an area with a high risk of polio.
- Travelers—IPV is indicated for travelers to high-risk areas.

TYPHOID

Salmonella typhi and paratyphi A, B, and C cause typhoid through the fecal-oral route transmission. Typhoid and paratyphoid fever have an incubation period from 6 to 30 days. The onset of symptoms is insidious with gradually increasing fever, fatigue, and abdominal pain. Complications causing death include gastrointestinal hemorrhage and perforation. Bone marrow blood culture is done for detecting . species. Vaccine: *Indications*
- Travelers to areas endemic with *Salmonella typhi*
- Person with close contact with a documented *Salmonella typhi* carrier
- Microbiologists and laboratory workers working with cultures of *Salmonella typhi*

Management includes mainly supportive treatment and management of complications in addition to early antibiotic treatment. Quinolones and third-generation cephalosporins are associated with higher cure rates.

Special considerations:
- Life attenuated vaccine is contraindicated in immunocompromised, and the oral vaccine is of limited efficacy.
- Pregnancy/breastfeeding—oral live attenuated virus is contraindicated while there is no evidence that a parenteral form is contraindicated.
- Healthcare professionals—no specific recommendations
- Travelers—travelers to endemic areas require immunization to be completed at least 2 weeks prior to exposure.

JAPANESE ENCEPHALITIS

Japanese encephalitis virus (JEV) is a mosquito-borne Flavivirus. This virus is found in Asia and parts of the western Pacific at agricultural areas where rice farming is prominent. The incubation period of Japanese encephalitis (JE) ranges from 5 to 15 days. The prodromal phase of JE starts as a nonspecific febrile illness (fever, nausea, vomiting, headache, and malaise). This phase is followed by the encephalitis phase. Encephalitis presents with altered mental status, focal neurological deficit, and abnormal movements. Status epilepticus and motor neuron weakness are poor prognostic signs. JEV-specific IgM antibodies are found in the CSF or serum. NAAT to detect viremia is insensitive to diagnose JE. Virus-specific IgM antibodies can be detected from CSF or serum. Preventive measures to prevent JE include mosquito control, animal immunization, and human immunization.

Vaccine: Recommended for residents of endemic areas, laboratory workers exposed to live infectious JEV, and travelers who plan to stay more than 1 month in endemic areas during JE outbreaks. Management includes mainly supportive treatment and management of complications. Antivirals and steroids are of no proven benefit in treating JE.

Special considerations:
- No specific recommendations for vaccination in immunocompromised patients
- Pregnancy/breast feeding—JE vaccine is recommended for pregnant women traveling to endemic areas and planning to stay for a long period.
- JE vaccine is not contraindicated in breast-feeding women.

- Healthcare professionals—JE is recommended for laboratory workers dealing with live infectious JEV.
- Travelers—JE is recommended for travelers intending to stay for >1 month in an endemic area with JE.

RABIES

Rabies is caused by an RNA virus of the *Rhabdoviridae* family. Transmission occurs via saliva of an infected host to an uninfected victim through bites. Rabies infection in human presents in five phases.

The incubation period ranges between 1 month and 2 months but can be as early as 7 days postexposure and up to >6 years postexposure. *Prodromal phase*: Nonspecific symptoms includes nausea, vomiting, fever, and paresthesia at the bite site. *Acute neurological phase—encephalitic (furious) rabies*: Hyperactive symptoms aggravated by thirst, fear, light, or noise. During this phase characteristic phobic spasms occur, mainly aerophobia and hydrophobia .

Paralytic (dumb) rabies: It is ascending paralysis that is difficult to diagnose since it resembles other neurological diagnoses that present with progressive paralysis. *Coma*: Common precipitants include spasm of respiratory muscles, nodal dysrhythmia, and cardiogenic shock. Recovery is mainly noted in patients who received immediate postexposure prophylaxis (PEP). Direct fluorescent antibody (DFA) is carried out on two samples from brain tissue. *Human*: Antirabies virus antibody detection in serum, CSF, and saliva. Reverse transcriptase followed by RT-PCR in saliva or nuchal biopsy is carried out for detecting rabies virus RNA. DFA testing is carried out for detecting rabies virus.

Inactive vaccine can be given as preexposure prophylaxis or as PEP. Rabies immunoglobulin is administered post exposure in high-risk groups.

Preexposure prophylaxis is indicated for: Personnel at risk of exposure to live rabies virus (laboratory staff, veterinarians, animal handlers, and wildlife officers), children living or visiting rabies-endemic areas, and travelers visiting rabid-endemic areas. *Dose regimen*: Rabies vaccine is administered IM on days 0, 7 and 21 or 28.

Postexposure prophylaxis steps: *Wound treatment*: Immediate wound washing and flushing in addition to disinfection with detergent. Avoid suturing the sound. Rabies vaccine and immunoglobulins (RIG) are administered according to the category of exposure (**Table 2**).

Rabies vaccine is administered IM on days 0, 3, 7, and 14. Rabies immunoglobulin, 20 IU/kg body weight, is infiltrated around and into the wound. The remaining volume is administered IM at an anatomically distant site from the vaccination area. Wound cleansing and supportive care are recommended. Antirabies vaccine and immunoglobulins are administered for bites from infected animals.

Rabies vaccination is deferred in immune-compromised: Until immune suppression status resolves. If not possible, then a preexposure regimen is administered and antibody response is checked in 2–4 weeks. *PEP measures of immunocompromised are:* Wound cleansing. RIG administration for category II and III exposures. Rabies vaccine regimen is changed from the four-dose regimen to the five-dose regimen (0, 3, 7, 14, and 28).

TABLE 2: Recommendation of postexposure prophylaxis.

Category of exposure	*Description*	*Postexposure prophylaxis*
Category I	• Touching or feeding a potentially rabid animal • Licks on intact skin	• Not clinically relevant exposures • No PEP indicated
Category II	• Licking uncovered skin • Minor scratches or abrasions without bleeding	• Wound disinfection • Antirabies vaccine only
Category III	• Single or multiple transdermal bites • Contamination of exposed skin or mucus membranes with saliva	• Wound disinfection • Antirabies vaccine • Rabies immunoglobulin

(PEP: postexposure prophylaxis)

If possible, withhold other immune-suppressant agents during PEP.

Pregnancy and breast feeding are not contraindications for PEP.

Preexposure prophylaxis is indicated for personnel at risk of exposure to live rabies virus (laboratory staff, veterinarians, animal handlers, and wildlife officers) and for travelers to rabid-endemic areas.

SMALLPOX

Variola virus transmission occurs through person-to-person contact and saliva droplets. Signs and symptoms occur after an incubation period. This is followed by a prodromal phase (2–3 days) which is characterized by high-grade fever (40°C). This is followed by the most contagious stage which starts with red spots in the mouth and tongue followed by vesicular or pustular rash spreading down from face to limbs and trunk that finally scabs off 3 weeks after the appearance of rash. *Electron microscopy*: This is done at the World Health Organization (WHO) smallpox biological safety level 4 laboratory. *Polymerase chain reaction* is done to detect variola virus DNA. Vaccinia vaccine is not recommended for the general population. Its use is indicated for: Laboratory personnel in direct contact with cultures or animals contaminated with orthopoxviruses causing infection in humans (variola, monkeypox, and cowpox). The mainstay of treatment is supportive in addition to antivirals (tecovirimat, brincidofovir, or cidofovir) in outbreak cases. Vaccinia vaccine is an absolute contraindication in immune-compromised, pregnancy, and breast feeding unless there is a smallpox outbreak. Vaccination in travelers and healthcare professionals is contraindicated unless the patient is in close contact with orthopoxvirus–infected humans, tissue, or animals.

ANTHRAX

Anthrax is a zoonotic disease caused by gram-positive, spore-forming bacteria *Bacillus anthracis*. Although *B. anthracis* spores are used as a biological weapon, outbreaks of the infection are not uncommon. Humans exposed to *B. anthracis* spores by direct contact or through inhalation

TABLE 3: Recommended Adult Immunization Schedule.

Recommended vaccination / Age group	Influenza inactivated/ Influenza recombinant or Influenza live attenuated		Tetanus Diphtheria Pertussis (Tdap, Td)	Measles Mumps Rubella	Varicella	Zoster recombinant or Zoster live		Pneumococcal	Meningococcal	Haemophilus influenzae Type B	Hepatitis A	Hepatitis B	Human papillomavirus
18–25	One dose annually	One dose annually	One dose Tdap then Td/Tdap booster dose every 10 years	One/two dose as indicated	Two doses (if born post-1980)	Not Applicable	Not Applicable	One/Two doses in additional risk factors	One/Two doses depending on vaccine and if additional risk factors and clinical decision making	One or three doses depending on indications and if additional risk factors are present	Two/three doses depending on vaccines with additional high-risk patient	Two/three doses depending on vaccines with additional high-risk patient	Two/three doses depending on age at initial vaccination or condition
26–50	One dose annually	One dose annually	One dose Tdap then Td/Tdap booster dose every 10 years	One/two dose as indicated	Two doses (if born post-1980)	Not Applicable	Not Applicable	One/Two doses in additional risk factors	One/Two doses depending on vaccine and if additional risk factors	One or three doses depending on indications and if additional risk factors are present	Two/three doses depending on vaccines with additional high-risk patient	Two/three doses depending on vaccines with additional high-risk patient	Two/three doses depending on age at initial vaccination or condition
51–65	One dose annually	Not Applicable	One dose Tdap then Td/Tdap booster dose every 10 years	Not Applicable	Two doses recommended if added risk factors or another indication	Two doses	Not Applicable	One/Two doses in additional risk factors	One/Two doses depending on vaccine and if additional risk factors	One or three dose depending on indications and if additional risk factors are present	Two/three doses depending on vaccines with additional high-risk patient	Two/three doses depending on vaccines with additional high-risk patient	Not Applicable
>65 years	One dose annually	Not Applicable	One dose Tdap then Td/Tdap booster dose every 10 years	Not Applicable		Two doses	One dose	One/Two doses in additional risk factors	One/Two doses depending on vaccine and if additional risk factors	One or three dose depending on indications and if additional risk factors are present	Two/three doses depending on vaccines with additional high-risk patient	Two/three doses depending on vaccines with additional high-risk patient	Not Applicable
Additional risk factors: Diabetes; End-stage renal disease or on hemodialysis; Chronic liver disease; Heart or lung disease; Chronic alcoholism; Asplenia; Complement deficiency; Pregnancy; Healthcare worker													

(Td: tetanus and diphtheria; Tdap: tetanus, diphtheria, pertussis)

develop anthrax that presents in one of the following forms: symptoms related to anthrax exposure are nonspecific and resemble other viral infections. Patients can exhibit itchy blisters that progress to painless ulcers with black center (eschar). Other nonspecific features include dyspnea, chest tightness, nausea, vomiting, fever, and abdominal pain. Diagnosis of *B. anthracis* depends on the history of exposure to an infected animal and the presence of prodromal symptoms in addition to demonstrating gram-positive bacilli in tissue cultures or blood stream. Tissue cultures might be negative in patients who receive antibiotics prior to sample retrieval. Vaccination against *B. anthracis* is not routinely recommended for the general population. *B. anthracis* vaccines are given as pre-event or postevent vaccination. *Pre-event vaccination*: *B. anthracis* vaccination is only recommended for high-risk population at an increased risk of occupational exposure.

The recommended dose is five IM doses administered at days 0, week 4, and months 6, 12, and 18. The population at high risk of exposure includes: Laboratory workers who are at a high risk of repeated exposure to virulent *B. anthracis*, military personnel who are at a risk of exposure to aerosolized *B. anthracis*, environmental investigators who repeatedly enter contaminated areas with *B. anthracis* spores, and emergency response personnel who are at a risk of encountering aerosolized *B. anthracis*. *Postexposure prophylaxis*: The Center for Disease Control and Prevention recommends PEP with 60 days of appropriate antibiotics in addition to three subcutaneous doses of the *B. anthracis* vaccine. PEP is recommended for unvaccinated personnel after exposure to *B. anthracis*. The mainstay of treatment is supportive care in addition to early antibiotic initiation. Ciprofloxacin and doxycycline are preferred antibiotic choices for anthrax PEP.

Special considerations:

- Not recommended in immune-compromised
- Pre-event vaccination is not recommended in pregnant and breast-feeding women who have low-risk exposures. PEP is recommended following exposure to *B. anthracis* and breast feeding is not a contraindication for vaccine administration.
- Pre-event vaccination is generally not recommended in children.
- Postexposure prophylaxis is recommended following exposure to *B. anthracis*.
- Healthcare professionals—pre-event vaccination is generally not recommended. PEP is recommended following exposure to *B. anthracis*.
- Travelers—pre-event vaccination is generally not recommended. PEP is recommended following exposure to *B. anthracis*.

SUMMARY

The main objective of the immunization is the stimulation of the body's own immune system to produce specific proteins called antibodies against specifically selected bacteria or viruses in order to prevent illness. Vaccines are used for this purpose; the process is referred as either immunization or vaccination. Various factors determine the vaccination, e.g., epidemiology, childhood vaccination, travel plan, travel duration. Usually vaccines provide lifelong protection against the disease; in some situations, specially if given during childhood, some vaccines need a second dose, which is referred to as a booster dose. Associated medical conditions also determine indications of vaccination in adult and travelers (**Table 3**).

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Tropical Infections in Travelers

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INTRODUCTION

The world has become a small place. Globalization has promoted traveling, and connectivity has improved, and thus people are traveling far more than before. In 2019, almost 27 million people traveled out of India and in December 2019, around 1.2 million tourists arrived in the country.

India, being a tropical country, is endemic to many of the tropical diseases that can present as pyrexia of unknown origin. Since most of them present as fever, diagnosing an infection can be a challenge and requires a thorough history and clinical examination to rapidly narrow down the differential diagnoses.

ETIOLOGY/CAUSES

Fever is the most common symptom encountered in tropical infections. In the present pandemic situation, it has become a norm for the emergency physician to consider every fever in a person with travel history as COVID-19 infection unless other causes are diagnosed. Common causes of fever in a returning traveler are dengue, malaria, enteric fever, leptospirosis, scrub typhus, and chikungunya. It is equally important for the clinician to consider other causes of fever, such as autoimmune diseases, drugs, and malignancy, while evaluating the patient. A history of travel to different areas in the tropics may provide a clue to the emergency physician in diagnosing the clinical condition of the patient (**Table 1**).

EVALUATION: HISTORY AND PHYSICAL EXAMINATION

A detailed history and a good clinical examination will direct initial tests and management and inform any infection control measures that need to be taken. A good and meticulous history taking will help in narrowing down the differential diagnosis. A good history includes assessing the onset of travel and its relation to the onset of illness, if the travel was to a rural or urban area, the type of accommodation, food and water, activities such as freshwater swimming and caving, contact with any sick patient, animals, or new sexual partners. It is also important to record exposure to any insect bites and examine for the same. Incubation periods for common infectious agents are given in **Table 2**. Mostly travelers present with infections have incubation periods of <21 days and several travelers can clinically manifest after return for >30 days (e.g., malaria, tuberculosis, hepatitis, filariasis). The most common infection presenting >30 days after exposure is *P. vivax* malaria (25% of patients with this infection present after 30 days). While evaluating a traveler with a febrile illness, the emergency physician should inquire about the following topics:

- Details about travel dates/season
- Countries and destinations visited (rural/urban locations)
- Exposure to bites/vectors/animals

TABLE 1: Infections according to geographic distribution.

Geographic area visited	*Common diagnosis to be considered*	*Differential diagnosis*
Caribbean	Chikungunya, dengue, malaria (Hispaniola), Zika	Acute histoplasmosis, leptospirosis
Central America	Chikungunya, dengue, malaria (primarily *Plasmodium vivax*), Zika, enteric fever	Leptospirosis, histoplasmosis, coccidioidomycosis, leishmaniasis
South America	Chikungunya, dengue, malaria (primarily *P. vivax*), Zika	Bartonellosis, leptospirosis, enteric fever, histoplasmosis
South Central Asia	Dengue, enteric fever, malaria (primarily nonfalciparum)	Chikungunya, scrub typhus
Southeast Asia including India	Dengue, malaria (primarily nonfalciparum)	Chikungunya, leptospirosis
Sub-Saharan Africa	Malaria (primarily *P. falciparum*), tickborne rickettsiae (main cause of fever in southern Africa), acute schistosomiasis (Katayama fever), dengue	African trypanosomiasis, chikungunya, enteric fever, meningococcal meningitis

- Types of food and water consumed
- History of vaccination and chemoprophylaxis
- Unprotected intercourse and partners
- Timing and sequence of illness/symptoms

Examination should comprise an assessment of how unwell the patient is along with a meticulous examination to look for any localizing features which may point to a diagnosis, such as jaundice, rash, skin lesions, lymphadenopathy, retinal or conjunctival changes, hepatosplenomegaly, or neurological findings. The examination should include looking for genital lesions and a thorough examination for eschars (pointing to rickettsial infections) as these are often found in "hard-to-assess" places such as the natal cleft and under the breasts. Patients with respiratory distress, hypotension or shock, hemorrhage, confusion, meningism, or other neurological findings should be urgently investigated. Even if an initial physical examination is unremarkable, it should be repeated if the diagnosis is unclear, as new findings may appear in due course of hospitalization that will help in the diagnostic process (such as skin lesions or a tender liver).

Fever associated with any of the following syndromes (**Table 3**) deserves special importance, because it may indicate a disease of public health importance, where immediate infection control and containment actions may be warranted (**Table 4**).

- Skin rash with or without conjunctivitis (seen in measles, meningococcemia, hemorrhagic fevers such as Ebola, dengue, and hemorrhagic fever)
- Rapid respiratory rate [seen in COVID-19 pneumonia, avian influenza, Middle East respiratory syndrome (MERS)]
- Persistent cough (seen in COVID-19, pulmonary tuberculosis, pertussis)
- Decreased consciousness (seen in meningococcal meningitis, rabies)
- Bruising or unusual bleeding without injury (seen in hemorrhagic fevers)

TABLE 2: Incubation periods for common and severe infections acquired during travel.

Short <10 days	Typhoid, dengue, rickettsial, meningitis, encephalitis, chikungunya, *Shigella Salmonella*, VHF, influenza, *Legionella* mononucleosis
Medium 11–21 days	Malaria, typhoid, leptospirosis, brucellosis, hepatitis A, schistosomiasis, amebic liver, abscess Q fever, African trypanosomiasis, rickettsial, VHF, HIV, seroconversion
Long >30 days	Tuberculosis, reactivation, malaria, leishmaniasis, filariasis, schistosomiasis, rabies, African trypanosomiasis, enteric protozoal, enteric helminthic

(HIV: human immunodeficiency virus; VHF: viral hemorrhagic fever)

TABLE 3: Fever-associated syndrome.

Common clinical findings	*Infections to consider after tropical travel*
Fever and rash	Dengue, chikungunya, Zika, measles, spotted fever or typhus group rickettsioses, enteric fever (skin lesions may be sparse or absent), meningococcemia, acute HIV infection, varicella
Fever and abdominal pain	Enteric fever, amebic or pyogenic liver abscess
Fever and normal or low white blood cell count	Dengue, malaria, rickettsial infection, enteric fever, chikungunya, Zika, acute HIV
Fever and hemorrhage	Viral hemorrhagic fevers (e.g., dengue, yellow fever, Ebola, Lassa fever), meningococcemia, leptospirosis, spotted fever group rickettsial infections
Fever and arthralgia or myalgia (sometimes persistent)	Chikungunya, dengue, Zika, Ross River virus, muscular sarcocystosis, trichinellosis
Fever and eosinophilia	Acute schistosomiasis, drug hypersensitivity reaction, fascioliasis, sarcocystosis, trichinellosis, angiostrongyliasis, and other parasitic infections (rare)
Fever and respiratory symptoms/pulmonary infiltrates	Influenza and other common bacterial and viral pathogens, COVID-19 legionellosis, tuberculosis, acute schistosomiasis, Q fever, leptospirosis, Middle East respiratory syndrome, acute histoplasmosis or coccidioidomycosis, psittacosis, melioidosis, pneumonic plague
Fever and altered mental status/central nervous system involvement	Cerebral malaria, arboviral encephalitis (e.g., Japanese encephalitis, West Nile virus), meningococcal meningitis, rabies, African trypanosomiasis, scrub typhus, angiostrongyliasis, tickborne encephalitis, rabies
Fever and jaundice	Acute viral hepatitis (A, B, C, E), yellow fever and other viral hemorrhagic fevers, severe malaria, leptospirosis
Mononucleosis syndrome	Epstein–Barr virus infection, cytomegalovirus infection, toxoplasmosis, acute HIV infection
Fever persisting >2 weeks	Malaria, enteric fever, Epstein–Barr virus infection, cytomegalovirus infection, toxoplasmosis, acute HIV infection, acute schistosomiasis, brucellosis, tuberculosis, Q fever, visceral leishmaniasis (rare)
Fever with onset >6 weeks after travel	*Plasmodium vivax* or *ovale* malaria, acute hepatitis (B, C, or E), tuberculosis, amebic liver abscess, melioidosis, African trypanosomiasis

TABLE 4: Red flags requiring further infection prevention measures in travelers.	
Risk of viral hemorrhagic fever	Fever in the past 24 h and travel to viral hemorrhagic fever–endemic country in the past 21 days plus any of the following: • Travel to area with known current viral hemorrhagic fever outbreak • Living in basic rural conditions in Lassa-endemic area • Visited caves or mines or had contact with or eaten primates, antelopes, or bats in area with Ebola or Marburg outbreak • Had tick bite or contact with animal slaughter in an area with Crimean–Congo hemorrhagic fever • Contact with known or strongly suspected case of viral hemorrhagic fever in the past 21 days
Risk of Middle East respiratory syndrome coronavirus	Severe respiratory infection requiring hospitalization and fever and clinical or radiological evidence of pneumonia plus any of the following: • Travel to area with known Middle East respiratory syndrome coronavirus outbreak in the past 14 days • Contact with confirmed case of Middle East respiratory syndrome coronavirus in the past 14 days • Contact with camels or consumption of camel products in area with Middle East respiratory syndrome coronavirus in the past 14 days
Risk of avian influenza	Fever and clinical or radiological evidence of pneumonia or other severe illness suggestive of infectious process plus one of the following: • Travel to China in the past 10 days, or • Contact with a known case of avian influenza in the past 10 days

- Persistent voluminous diarrhea (seen in cholera)
- Jaundice (seen in hepatitis A, leptospirosis)

CLINICAL PRESENTAION

Pyrexia of unknown origin: It is defined as fever >38.3°C (101°F) on several occasions in a patient with more than three outpatient visits or 3 days' admission in a hospital. Most of these happen within 2 weeks of travel and the most common cause is malaria, especially in travelers retuning from Sub-Saharan Africa. Other causes include dengue (particularly travelers returning from Southeast Asia), typhoid or paratyphoid fever, and rickettsia. Other infections, such as HIV, mononucleosis, leptospirosis, schistosomiasis, amebic liver abscess, brucellosis, and toxoplasmosis, should be considered and advice from infectious diseases units is advised unless the cause is quickly apparent.

Fever and respiratory symptoms: Upper respiratory infections are mostly viral. *Streptococcus* and *Haemophilus* are also usual causes. Differentials for a lower respiratory tract infection must include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*, and respiratory syncytial virus. Less prevalent pathogens such as *Staphylococcus aureus*, avian influenza viruses, and Middle East respiratory syndrome coronavirus must be considered in patients who travel to high-risk regions. Pulmonary edema is a rare complication of severe malaria. Hence, in patients who are suspected with malaria, fluid resuscitation should be exercised with caution.

Fever and central nervous system (CNS) symptoms: Specific neurological diagnoses in a traveler are rare. Fever and headache are common symptoms and seen in systemic infections such as malaria, dengue and chikungunya infection, and rickettsial diseases. Malaria and meningitis are the most common treatable causes of fever and CNS symptoms and must always be excluded first. Cerebral malaria is caused by *Plasmodium falciparum* and can present with confusion, headache, seizures, or decreased consciousness. Any patient with neurological symptoms and a history of travel to a malaria-endemic region should be considered to have cerebral malaria and investigated. Other causes of fever and encephalopathy include bacterial infections (typhoid, Lyme disease, leptospirosis) and HIV seroconversion.

Fever and eosinophilia: Acute allergic reaction, malignancy, or parasitic infection are the common causes of *peripheral* eosinophilia. In the context of a returning traveler, fever and eosinophilia give rise to a high index of suspicion for helminthic infections. Mild elevation of peripheral eosinophil count (351–1,500 cells/mL) can be considered as nonspecific; moderate (1,500–5,000 cells/mL) to severe (>5,000 cells/mL) elevations in traveling individual are highly suggestive of invasive helminthic infection. In febrile travelers with eosinophilia, the following differential diagnoses should be considered: Schistosomiasis (Katayama fever), hyperinfestation of strongyloidiasis, lymphatic filariasis, invasive hookworm disease, and migratory ascaris lumbricoides. Stool analysis should be done as initial workup for ova and parasites, serology for strongyloidiasis, and depending on the clinical picture and the area of travel, examination of blood smears and skin snips to detect microfilariae.

Fever and skin manifestations: Skin manifestations in travelers include rashes, ulcers, bites, and stings. The differential diagnosis is wide (**Table 5**). For maculopapular rashes, these include dengue, rickettsial disease, and mononucleosis-type syndromes include acute HIV infection; purpuric rashes may be seen in dengue hemorrhagic shock, meningococcal infection, sepsis with disseminated intravascular coagulation, and viral hemorrhagic fevers; and urticarial rashes can be seen in acute schistosomiasis. Eschars are commonly caused by rickettsial disease such as African tick bite fever or anthrax or can be mistaken for a chancre.

TROPICAL INFECTIONS PRESENTING AS UNDIFFERENTIATED FEVER

After international travel, fever can be present without localizing symptoms in approximately 3% of patients. Because

TABLE 5: Differentiating cause of fever on the basis of rash type.

Rash	*Infections*
Purpuric	Dengue, hemorrhagic syndrome, meningococcal infection, viral hemorrhagic fever, rickettsial infection, severe leptospirosis
Maculopapular	Arboviral infection, rickettsial infection, VHF, HIV, seroconversion, typhoid, dengue, fever leptospirosis, brucellosis
Vesicular	Herpes simplex virus varicella
Ulcerative	Chancre: Trypanosomiasis, Eschar: Anthrax, African tick typhus, Ulcer: Leishmaniasis, syphilis, tropical ulcer

(HIV: human immunodeficiency virus; VHF: viral hemorrhagic fever)

of chief complaint, a person usually seeks medical care after travel. Generally, a nonspecific viral illness is considered the common cause of fever in patients presenting after travel, the same as in persons who have not left their home country; however, additional diseases including malaria, dengue, typhoid, and hepatitis must be considered. Following malaria, the most common imported communicable diseases causing undifferentiated fever are dengue, enteric fever, and rickettsial disease. Certain travel destinations are associated with a higher risk of acquiring specific diseases. Thus, the date of return to the home country and the date of the onset of symptoms should be included in a detailed travel history. The incubation period for the disease is important to know if an illness began after the patient's return and after the termination of exposure to exotic pathogens. The incubation period has an important role to play in the differential list of diseases that would be consistent with the time course.

Malaria

Regardless of travel duration or use of chemoprophylaxis, in patients having fever after returning from malaria-endemic regions, the diagnosis must be excluded. Of the several species, four *Plasmodium* species are of clinical relevance that cause disease in humans: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Of these, *P. falciparum* is responsible for complicated and severe disease while *P. vivax* is responsible for chronic and recrudescent disease. Bite of the female anopheles mosquito and other multiple species as well is responsible for transmission. The life cycle consists of hepatic and hematologic stages; the intraerythrocytic stages are responsible for the clinical spectrum of disease. Most clinical symptoms of malaria develop between 9 and 14 days after exposure (median 12), and the minimum incubation period for *P. falciparum* is 6 days. Significantly, longer incubation periods are observed for *P. vivax* and *P. ovale* ranging from 8 days to several months. Vivax infection presents within 2 months after the exposure in the majority of cases; however, cases of *P. vivax* and *P. ovale* have presented several years after exposure, which is likely to constitute disease recrudescence. No specific signs and symptoms are pathognomonic for malaria. Fever, myalgia, arthralgia, and headache are the common clinical presentations in most of the patients. Abdominal pain, diarrhea, cough, and dyspnea may present in few patients. Rash and lymphadenopathy are rarely present and are clues to an alternative diagnosis. Renal failure, jaundice, and respiratory failure, including acute respiratory distress syndrome, may be the features of severe and complicated cases of *P. falciparum* infection. Children with severe disease typically present with severe anemia, acidosis, and respiratory distress. Severe disease can present with CNS involvement in both adults and children, can lead to neurologic sequelae in survivors, and carries a 15–20% mortality rate. After returning from the tropics, patients who present with fever and neurologic findings should be evaluated for malaria and meningitis and treated promptly. Laboratory diagnosis of malaria is classically made by examination of Giemsa-stained thick peripheral blood films. Thick peripheral blood films have increased sensitivity and advantage of allowing more red blood cells to be examined per high-powered field in comparison with thin films. Similar to other point-of-care tests, malarial rapid diagnostic tests (RDTs) have been introduced into clinical practice for antigen detection. RDTs are fairly simple to use. It is important that when severe *P. falciparum* infection is suspected, diagnosis should never supersede empiric treatment. Two major classes of drugs are available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate and artemether). *See Chapter 190: Malaria for details*.

Dengue

Dengue fever represents an arboviral disease caused by a family of four arboviruses that are endemic in most tropical and subtropical regions. The viruses are transmitted primarily by day-biting mosquito *Aedes aegypti* and has an affinity for water-filled small containers and water pools in urban environments. A high prevalence of dengue fever is seen in Southeast Asia, Oceania, the Caribbean, and Latin America. Approximately one third of the world's population lives in dengue-endemic countries. In febrile travelers returning from Southeast Asia, dengue is currently more than twice as common as malaria. The incubation period of dengue virus is 4–8 days.

The clinical syndrome of classic dengue fever is characterized by a retroorbital pain (typically lasting 5–7 days), myalgia, arthralgia ("break-bone fever"), and petechial appearance rash. The petechiae usually seen on the face, soft palate, extremities, and axilla appear during the early febrile phase. Dengue infection presents as a wide spectrum of diseases ranging from mild febrile illness (dengue fever) to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). A more serious spectrum of DHF/DSS is characterized by coagulopathy and increased vascular permeability. Easy bruising, bleeding at venipuncture sites, and a positive tourniquet test are the hemorrhagic manifestations. Often, as the fever subside in 3–7 days, edema, effusions, and the circulatory collapse develop due to changes in vascular permeability and may lead to DSS. The initial diagnosis of dengue fever in individuals returning from endemic areas is based on fever and constitutional symptoms. Laboratory investigations suggestive of dengue infection include thrombocytopenia, leukopenia, and elevated levels of liver enzymes. DHF is defined as the triad of thrombocytopenia, hypoproteinemia, or evidence of effusions. DSS is characterized by hypotension (systolic blood pressure <90%, a narrow pulse pressure <20 mm Hg). Profound hemodynamic shock occurs in patients with DHF/DSS and Leukopenia (<5,000/mL) along with thrombocytopenia and require admission to a high level of care.

Serologic diagnosis relies on acute and convalescent serum titers, with convalescent samples drawn 3 weeks after infection. Antipyretics, oral fluids, and bed rest are the mainstay of treatment for mild or classic dengue fever. Capillary leakage usually occurs between days 4 and 7 of illness, and more severe disease can develop. Aggressive fluid replacement with normal saline or lactated Ringer solution is appropriate if DHF/DSS is suspected. At present, no effective vaccine exists for the virus. *See Chapter 189: Dengue for further details.*

Enteric Fever (Typhoid and Paratyphoid)

Two serotypes of the gram-negative bacillus *Salmonella enterica*, (1) Serovar Typhi; and (2) Serovar Paratyphi, are the main causative agents for typhoid fever. When these disseminate to cause systemic illness, they are collectively called enteric fever. Infection comes from contaminated food and water where standards of personal and environmental hygiene are low and occur via an oral-fecal route. Typhoid fever has an incubation period of 7–18 days. Affected individuals invariably present with fever. Intestinal mucosa can be invaded by bacteria and then reach to bloodstream through lymphatics, where they replicate and cause systemic illness. Clinical features start as low-grade fever and then become persistent and high grade by the second week. Other common symptoms are headache (typically dull and frontal), abdominal pain, constipation or diarrhea, and cough. During early in the course of the disease, "rose spots" (2–3-mm blanching, pink-red macules) appear for a brief period seen mostly in fair-skinned persons. Theoretically "Faget sign" (relative bradycardia during high fever) has been described in association with typhoid fever but is rarely seen in clinical practice. Complications such as disseminated intravascular coagulation, intestinal perforation, gastrointestinal bleeding, and meningitis/encephalitis occur in 10–15% of patients, most commonly as delayed manifestations. Peyer patches within the intestinal mucosa are the focus for gastrointestinal hemorrhage and perforation. Blood culture is considered as gold standard for diagnosis of enteric fever, although stool cultures, urine cultures, bone marrow biopsy, and serology can play a role. During the first week of illness, blood cultures have their highest yield, but their diagnostic sensitivity is only 40–80%, which underscores the importance of serial cultures. Bone marrow biopsies can have a higher yield though rarely indicated. Serologic testing using the Widal test is not recommended because of its poor sensitivity (47–77%) and specificity (50–92%). Empiric treatment should be started based on clinical diagnosis and in suspected cases because culture results and serology take time to be obtained. Early administration of appropriate antibiotics, supportive care, and correction of fluid losses is the mainstay of treatment. Hospitalization is recommended for diagnostic and therapeutic purpose in patients suspected of having enteric fever (*Salmonella typhi* or *Salmonella paratyphi* bacteremia). Third-generation cephalosporins are considered first-line therapy because fluoroquinolone-resistant strains are all sensitive to ceftriaxone. Gastrointestinal bleeding and perforation should be suspected if a patient with enteric fever clinically presents with abdominal tenderness; a low index of suspicion should be maintained for complications; early imaging and surgical consultation are recommended for peritonitis.

Rickettsial Infection

Rickettsial diseases are classified as zoonotic infections caused by obligate intracellular, gram-negative bacteria. The arthropods vectors are typically ticks, fleas, lice, and mites. The common cause of undifferentiated fever in returned travelers must be excluded. Following a bite from an infected arthropod vector, rickettsial diseases typically have an incubation period of 1–2 weeks. Short (5–7 days) incubation periods in classic rickettsial disease consist of primary lesions (eschars) at the bite site, fever lasting for a few days up to 2 weeks, lymphadenitis, and a maculopapular rash that develops 3–5 days after onset of symptoms. About half of the patients present with the classic triad of eschar, lymphadenitis, and rash. Headache, myalgia, arthralgia, malaise, and diarrhea may also present. An eschar at the site of a tick or louse bite may be seen on physical examination which the patient describes as lasting for 1 or 2 weeks, but its absence does not rule out the disease. The next most common examination finding is lymphadenitis. The clinical presentation of rickettsial disease is similar to that of other diagnoses presenting with undifferentiated fever after travel. Polymerase chain reaction (PCR), culture, and serologic analysis are available for definitive microbiological diagnosis. PCR is sensitive, specific, and rapid. Because diagnosis is difficult to make and is frequently delayed, initiate prompt and appropriate treatment in the absence of confirmatory data on the basis of clinical suspicion and presumptive diagnosis. The mainstay of treatment (preferred regimen) is tetracyclines with doxycycline (100 mg twice daily for 3–14 days, depending on the clinical scenario). Patients should improve within the first 48 hours. Failure to do so should prompt the treating physician to review the original diagnosis.

Leptospirosis

Leptospirosis is acquired by humans after contact with contaminated soil or water and caused by a spirochete. Swimming or boating in contaminated fresh water as well as gardening or farming is associated with infection. Leptospirosis is most commonly seen in travelers returning from tropical and subtropical climate regions. Returning travelers with fever, myalgia, headache, rash, and a history of fresh water exposure should prompt suspicion for leptospirosis. Uveitis, conjunctivitis, hematuria, and aseptic meningitis can also associate with illness. Most commonly, serology testing is used for the diagnosis but this method is usually not rapid. Dark-field microscopy and subsequent culture may also be helpful. Blood and cerebrospinal fluid are ideal within the first 10 days of disease. Urine samples have a better yield after the first week of illness. Leptospirosis is self-limited in most of the cases. Treatment with penicillin or tetracycline is effective and is recommended in all cases. Complications associated with leptospirosis are by renal failure, acute respiratory distress syndrome, or myocarditis. Liver failure, if present, is usually reversible.

HEPATITIS A

Hepatitis A is caused by a virus spread by fecal-oral contact, one of the most common vaccine-preventable, travel-related infections. Traveling to endemic areas, such as Latin America,

Asia, and Africa, is associated with a higher risk of infection. Factors responsible for spread of hepatitis A are poor water quality and poor sanitation. Hepatitis A infections have decreased significantly over the last 20 years as vaccination is most effective when given at least 4 weeks before travel. It may be protective even if given on the day of travel. The incubation period of hepatitis A is 28–30 days. Patients typically may present with complaints of anorexia, nausea, vomiting, or malaise with fever, right upper quadrant pain, and jaundice. Liver function tests reveal elevations of aminotransferases, possibly into the thousands, and identification of anti-hepatitis A virus IgM antibody is diagnostic. Most cases are self-limited and treatment is supportive, but fulminant liver failure is a rare complication.

MENINGOCOCCAL MENINGITIS

Meningococcal disease is potentially a life-threatening illness in cases of meningococcal sepsis even with appropriate antibiotic regimens. Hearing loss, neurologic damage, or loss of an extremity are seen as significant long-term complications of the illness in survivors. Vaccination is available and should be given at least 7–10 days before travel. The incubation period typically ranges between 2 and 10 days. Clinical features start with fever and malaise followed by severe headache, nausea, vomiting, and stiff neck. The most common skin finding in this disease is petechiae or ecchymotic lesions and may occur early in the course before systemic complications develop. High-dose parenteral antibiotics such as ceftriaxone and vancomycin should be started in suspected cases. The steroid is probably not beneficial in meningococcal disease. Once the gram-negative cocci are isolated in cerebrospinal fluid, definitive therapy should be started. Antibiotic prophylaxis with rifampin or ciprofloxacin should be started in close contacts of patients.

TROPICAL DISEASES PRESENTING AS DIARRHEA

Traveler's Diarrhea

Traveler's diarrhea, most frequently associated with enterotoxigenic *Escherichia coli* or *Campylobacter*, is the most common travel-related infection due to increased exposure to local food and water. It is defined as an illness after travel featuring three or more unformed stools in 24 hours and is associated with at least one symptom of enteric disease, such as cramping, abdominal pain, nausea, vomiting, and fever. Traveler's diarrhea needs to be distinguished from dysentery, which is defined as the presence of visible blood in the stool. Dysentery may be caused by *Salmonella*, *Shigella*, and many of the same organisms that cause uncomplicated traveler's diarrhea, such as *Campylobacter*. Patients who present with acute nonbloody diarrhea may be treated empirically with fluids, antibiotics, and antimotility agents. Most cases can be cured by a single dose of ciprofloxacin, 750 mg, or azithromycin, 1 g, by mouth. Additionally, for reducing the duration of symptoms, antimotility agents such as loperamide are safe and effective. Although multiple prophylactic regimens are available for the prevention of traveler's diarrhea, they are not generally recommended for several reasons. Prophylactic therapy of a newer agent, rifaximin, can be recommended especially in immunocompromised patients. For dysentery, a 3-day course of ciprofloxacin or azithromycin is recommended.

Cholera

Cholera is caused by *Vibrio cholerae*, a gram-negative rod, acquired via contaminated water or food and clinically presents with watery diarrhea and acute dehydration. Primary treatment for cholera is oral rehydration and intravenous fluids, and electrolyte replacement should be administered in patients with severe illness. Antibiotics are helpful in shortening the clinical course of the disease and lowers the *V. cholerae* excretion, thus reducing the potential spread of the disease. Antibiotics used in traveler's diarrhea, such as ciprofloxacin, doxycycline, and azithromycin, are also effective against *V. cholerae*. Antimotility medications carry a risk of prolonging the disease and are not recommended and should be avoided.

TROPICAL INFECTIONS WITH A PRIMARILY DERMATOLOGIC PRESENTATION

Cutaneous Larva Migrans

Cutaneous larva migrans infection presents as an epidermal eruption and occurs mostly in Africa, the Caribbean, and Southeast Asia. It is caused by infiltration of hookworm larvae through intact skin, usually in the feet. It also includes a history of exposure of walking barefoot at a beach in most of the cases. The incubation period ranges from minutes to weeks. The cutaneous larva migrans lesions are intensely itchy and erythematous tracts are serpiginous, growing a few centimeters each day.

The foot, buttock, and abdomen or trunk are the most commonly affected anatomic sites. Topical thiabendazole 15% for 1–2 weeks is used for effective treatment of cutaneous larva migrans. Oral thiabendazole is associated with side effects, such as altered mental status, gastrointestinal upset, or rash. A single dose of ivermectin can be used as a more recent treatment approach. Cryotherapy can be tried in pregnant patients but is often ineffective.

Cutaneous Myiasis (Furuncular Myiasis)

Cutaneous myiasis, caused by the human botfly or the tumbu fly, it is the implantation and development of fly larvae in human skin. The larvae are transmitted to humans via a mosquito bite or by eggs hatching on the skin with subsequent penetration. The incubation period varies with the type of fly; the incubation period of botfly is usually 5–12 weeks and that of the tumbu fly is usually 7–10 days. The typical lesions are 1–2 cm furuncle-like with crusting, odoriferous, purulent, or serosanguinous discharge, and larval movement can be seen within central punctum. Patients often have a painful feeling of crawling sensations within the lesion and itching, head, forearms, and legs are often involved. The diagnosis is clinical, and treatment consists of manual removal of the larva; applying occlusive substances on lesion can cause the larva to migrate to the skin surface. To avoid hypersensitivity or foreign body reactions to the larval antigens, it is important not to rupture the larva. Surgical excision is generally not required.

Leishmaniasis

Leishmania is caused by a tiny intracellular protozoan parasite of the genus *Leishmania* transmitted by the bite of the sandfly and symptoms occur 1 week and 3 months after the bite. Visceral and cutaneous are the two major forms identified; visceral leishmaniasis is rare in travelers, but cutaneous cases are occasionally seen. Cutaneous leishmaniasis clinically presents as nonpainful, slowly growing multiple violaceous and granular ulcers (3–12 cm in diameter), typically affecting lower legs and face. Diagnosis is made by skin scraping. Although some lesions may heal spontaneously, treatment consists of prolonged intravenous therapy with sodium stibogluconate, a pentavalent antimony compound.

Lyme Disease

Lyme disease is caused by a bacterial spirochete *Borrelia burgdorferi* and transmitted to humans through a prolonged bite of the Ixodes tick. The initial skin lesion, erythema migrans rash, is present in 60%–80% of patients and generally appears 3–30 days after the bite. This skin lesion starts with an erythematous papule at the site of the bite, which expands over the next days to weeks with central clearing to result in the classic annular lesion. Malaise, myalgia, arthralgia, and generalized lymphadenopathy are the other early manifestations of Lyme disease. The disease progresses to monoarticular or oligoarticular arthritis in 60% of untreated patients. In a small group of patients, neurologic complaints, such as facial nerve palsy, or cardiac complications, most commonly atrioventricular block, are seen. Diagnosis is largely clinical on the basis of characteristic rash, else serology can be used. Early disease can be treated with cefuroxime, doxycycline, or amoxicillin for 21 days. Tick's bite can be prevented by wearing long sleeves and long pants, avoiding walks in heavily forested areas, and wearing insect repellent. A single 200-mg dose of doxycycline is effective at preventing the disease in an area endemic for Lyme disease.

IMPORTANT TROPICAL DISEASES RARELY OCCURRING IN TRAVELERS

Yellow Fever

Yellow fever can occur in unvaccinated travelers and manifests as hemorrhagic fever. Yellow fever is caused by virus which is small (40–60 nm), single-stranded RNA virus of the family *Flaviviridae* and transmitted by *Aedes* species mosquitoes. Jungle areas in South America and Africa are the endemic areas for this disease. Prevention of mosquito bites and immunization against the yellow fever are the most important methods of prevention. The vaccine, a live attenuated vaccine, is usually well tolerated and should be taken 4 weeks before travel. Post vaccination yellow fever like systemic disease within 5 days have been reported, i.e., yellow fever vaccine associated viscerotropic disease, yellow fever vaccine associated neurotropic disease and post vaccination encephalitis. Fever, jaundice, hemorrhage, and renal failure are the common clinical presentations of yellow fever with high viral load within 2–3 days after infection. The clinical course of illness is described in three phases:

1. *First phase is seen for 36–48 hours*: Fever, malaise, myalgia, nausea, vomiting, irritability, and dizziness are the initial symptoms with laboratory features of leukopenia and elevated transaminase levels.
2. *Second phase (latent phase up to 48 h)*: Fever subsides. Improvement of other symptoms is seen and patients recover without development of jaundice.
3. *Third phase*: Recurrence of initial symptoms in 10–15% of patient with the addition of jaundice and bleeding diathesis followed by multiorgan system failure. Diagnosis can be confirmed by enzyme-linked immunosorbent assay (ELISA). Treatment is supportive and for severe cases, intensive care treatment is given.

Avian Flu

Millions of cases of influenza A occur every year mostly with an identified close contact with chickens, waterfowl, or other birds. The patient usually presents with febrile respiratory illness 2–5 days after exposure, often accompanied by leukopenia or lymphopenia. The few initial influenza symptoms may progress to subsequent pneumonia and worsening respiratory distress. Pharyngeal swabs are preferred for detection of H5-specific RNA (diagnostic) because the virus is present in higher concentrations in the throat and lower respiratory tract. Zanamivir and oseltamivir neuraminidase inhibitors should be started in any suspected cases. The mainstay of prevention of annual influenza is the influenza vaccine.

African Sleeping Sickness

African trypanosomiasis (sleeping sickness) is caused by *Trypanosoma* parasites and transmitted by Glossina tsetse flies. If the untreated disease is fatal, death occurs within weeks to years from the time of infection depending on the type of parasite infection. The risk to travelers is low, but there are approximately one or two imported cases each year. Thirty-six countries of sub-Saharan Africa are the endemic areas for this disease. The symptoms of this illness are similar to several other travel-related infections, including malaria and rickettsia infection. The common symptoms of african trypanosomiasis are lethargy, headache, gastrointestinal symptoms, myalgia, and delirium are the other associated symptoms. The parasites can be identified in the blood or other aspirates to confirm the diagnosis. Travelers who present with fever and cutaneous chancres should prompt suspicion of trypanosomiasis. Central nervous system involvement should be ruled out by lumbar puncture, because it dictates the choice of antiparasitic therapy. In patients without central nervous system involvement, treatment with suramin is indicated. A 200-mg test dose should be given before administering the drug by slow infusion due to a risk of anaphylaxis.

PEDIATRIC CONSIDERATIONS

After travel, illnesses in children are grouped into four general categories: (1) Diarrheal syndrome, (2) Dermatologic disorders, (3) Systemic febrile illness, and (4) Respiratory disorders. Children should also receive pretravel advice, like in adults. They may present to a clinician with illness in the early phase and require hospitalization also. A high index of suspicion should be maintained for children, the same as for adults, presenting with undifferentiated fever after travel and all evaluations for fever should be performed considering malaria, dengue, and enteric fever. Pediatric patients with

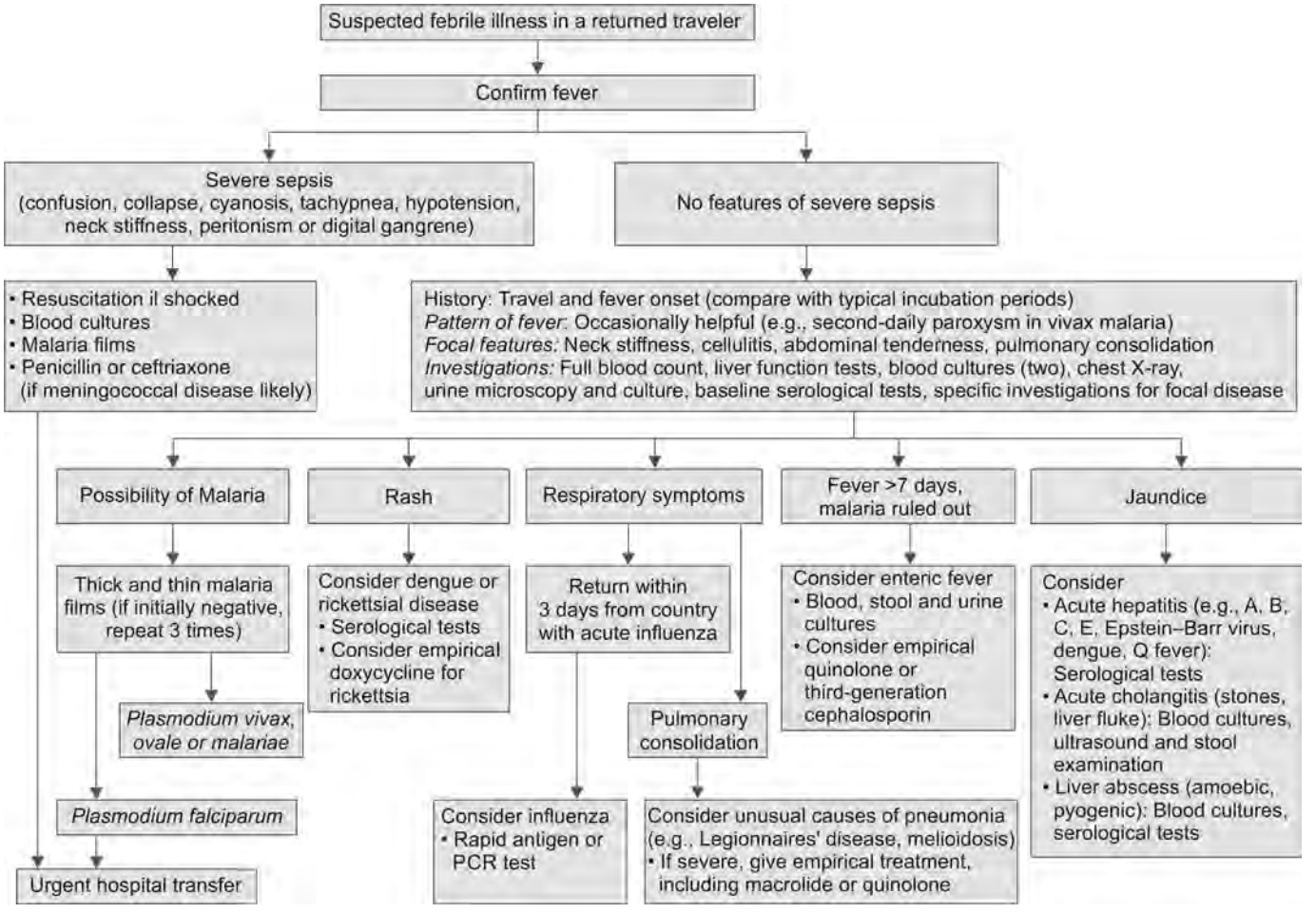
undifferentiated fever after travel should be admitted promptly for management.

PROTECTION OF CONTACTS AND STAFF

Routine infectious precautions and local hospital guidelines should be followed with source isolation and respiratory/droplet confinement and should be implemented for all patients with undifferentiated fever after travel to the tropics until potentially hazardous diseases are excluded. COVID-19, anthrax, diphtheria, encephalitis, enteric fever, hepatitis (acute), novel influenza, measles, meningitis, mumps, pertussis, plague, poliomyelitis, rabies, tuberculosis, travelers with respiratory illness and rash, varicella and herpes zoster, and viral hemorrhagic fever are the infections which require special consideration. Laboratory staff are also at risk so they should therefore be informed if any of the following infections are being considered: Enteric fever, brucellosis, Q-fever, melioidosis, and, in particular, the viral hemorrhagic fevers. Notification of certain infectious diseases is mandatory for local health authorities, and public health surveillance should begin at local, state, and regional levels. Clinicians should be familiar with state and national requirements during working with patients who return ill from travel. Healthcare providers must be aware about reporting and surveillance within the scope of practice, essential for proper surveillance and disease control.

SUMMARY

One of the common problems presenting to the emergency department is infections in travelers. A detailed travel history will provide clues to the clinician regarding the risk of unusual tropical infections and one should enquire about places visited, the activities enjoyed, and the living conditions. Evaluation of tropical infections in travelers is summarized in **Flowchart 1**. *Plasmodium* infection should be ruled out by the use of blood smears in any patient returning from a malaria-endemic region with an undifferentiated fever. The traveler's diarrhea is also most the common condition in returning travelers, which can be effectively managed with antibiotics and antimotility agents. Rare diseases in the returning traveler are avian flu, yellow fever, and African sleeping sickness. Adequate care must be taken for COVID-19 infection. Overseas acquired infection can be prevented by vaccines, food and water precautions, and insect bite avoidance. For travel to certain regions, yellow fever vaccine is required. Avoiding uncooked foods, eating thoroughly washed foods in clean water, and eating only peeled fruit will help in reducing the infection during travel. Most of the cases require empiric treatment based on the clinical presentation because acquisition of confirmatory laboratory data is often delayed.


Suspected febrile illness in a returned traveler
Confirm fever
Severe sepsis
(confusion, collapse, cyanosis, tachypnea, hypotension, neck stiffness, peritonism or digital gangrene)
No features of severe sepsis
• Resuscitation if shocked
• Blood cultures
• Malaria films
• Penicillin or ceftriaxone
(if meningococcal disease likely)
History: Travel and fever onset (compare with typical incubation periods)
Pattern of fever: Occasionally helpful (e.g., second-daily paroxysm in vivax malaria)
Focal features: Neck stiffness, cellulitis, abdominal tenderness, pulmonary consolidation
Investigations: Full blood count, liver function tests, blood cultures (two), chest X-ray, urine microscopy and culture, baseline serological tests, specific investigations for focal disease
Possibility of Malaria
Rash
Respiratory symptoms
Fever >7 days, malaria ruled out
Jaundice
Thick and thin malaria films (if initially negative, repeat 3 times)
Consider dengue or rickettsial disease
• Serological tests
• Consider empirical doxycycline for rickettsia
Return within 3 days from country with acute influenza
Consider enteric fever
• Blood, stool and urine cultures
• Consider empirical quinolone or third-generation cephalosporin
Consider
• Acute hepatitis (e.g., A, B, C, E, Epstein–Barr virus, dengue, Q fever): Serological tests
• Acute cholangitis (stones, liver fluke): Blood cultures, ultrasound and stool examination
• Liver abscess (amoebic, pyogenic): Blood cultures, serological tests
Plasmodium vivax, ovale or malariae
Pulmonary consolidation
Plasmodium falciparum
Consider influenza
• Rapid antigen or PCR test
Consider unusual causes of pneumonia (e.g., Legionnaires' disease, melioidosis)
• If severe, give empirical treatment, including macrolide or quinolone
Urgent hospital transfer

FLOWCHART 1: Summary of evaluation of tropical infections in travelers.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Zoonotic Infections

Olita Shilpakar, Devendra Richhariya

INTRODUCTION

Zoonosis is a term that describes diseases transmitted from vertebrate animals or insects to or from humans. It is caused by bacteria, viruses, fungi, or parasites. One of the most important vectors causing zoonotic infections is ticks. Risk factors include occupational exposure to animals, immunocompromised patients, or recent travel history, mostly during spring or summer (**Table 1**). Zoonotic infections can present with fever, myalgias, headache, and malaise. The common zoonotic infections are listed in **Table 2**.

TICK-BORNE INFECTIONS

Ticks are arthropods distributed worldwide and are hematophagous parasites of humans and animals. They transmit rickettsial, bacterial, spirochetal, viral, and protozoal diseases. During a bite, the saliva of ticks produces inflammatory factors or toxins that can cause local inflammation, edema, hemorrhage, or hyperemia. A common finding that accompanies the bite of blood-sucking ticks is a characteristic rash seen as an erythematous lesion of 1–4 mm in size. The common tick-borne infections are listed in **Table 3**.

TABLE 1: Risk factors for zoonotic infections.

Population at risk	*Examples*
Agricultural workers	Farmers, cattle ranchers
Animal processing workers	Slaughterhouse workers, animal product handlers
Pet owners	Owners of dogs, cats, rodents, birds, fishes
Professional animal handlers	Veterinarians, animal researchers
Immunocompromised patients	HIV, diabetes mellitus, carcinoma, congenital immunodeficiencies

(HIV: human immunodeficiency virus)

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever (RMSF) is an acute, febrile, systemic tick-borne illness. The causative agent is *Rickettsia rickettsii* which is an obligate intracellular pleomorphic organism. *Dermacentor* ticks (*D. variabilis* and *D. andersoni*) and *Rhipicephalus sanguineus* ticks are the vectors while dogs, rodents, horses, cattle, cats, and deer are the animal reservoirs.

Clinical Features

Children are more commonly affected by RMSF than adults. The incubation period ranges from 2 to 14 days. A history of tick bite may not always be reported by the patient and may present with fever, headache, myalgia, malaise, nausea, vomiting, diarrhea, and abdominal pain during the early stage of the disease. As the disease progresses, respiratory failure, renal insufficiency, neurological deficits, meningismus, and myocarditis may be evident. The triad of fever, rash, and tick bite is the classical presentation of RMSF. The rash is seen as an erythematous blanching maculopapular lesion and petechiae over the arms, forearms, feet, and ankles occurring 2–4 days following fever. However, it is not pathognomonic of this disease.

Diagnosis and Treatment

Laboratory studies are nonspecific, but RMSF can be suggested in cases of normal total counts, decreased platelets, elevated liver enzymes, and hyponatremia. The diagnosis can be confirmed by a rise in the antibody titer between acute and convalescent serum, skin biopsy, or a culture. Doxycycline is the treatment of choice in rickettsial diseases for all age groups (**Table 4**).

TICK PARALYSIS

Tick paralysis occurs worldwide and is more common in children than adults. It results from injection of neurotoxic

TABLE 2: Common systemic zoonotic infections.

Agent and reservoir	*Clinical findings*	*Investigations*	*Treatment*
Brucella canis (dogs)	Nonspecific fever	Serology blood culture	Doxycycline plus gentamicin or rifampin
Chlamydophila psittaci (birds)	Fever, flulike illness, pneumonia, endocarditis	Serology sputum culture	• Doxycycline • Alternative: ○ Azithromycin ○ Levofloxacin
Coxiella burnetii (cattle, sheep, goats, cats)	Fever, pneumonia, hepatitis, meningitis, endocarditis	Serology PCR	Doxycycline or fluoroquinolone or macrolide
Ehrlichia species (ticks)	Nonspecific fever, hepatitis, meningitis	Serology, peripheral blood smear, PCR	Doxycycline or Rifampin as alternative
Leptospira species (birds, rodents)	Fever, pneumonia, conjunctivitis, lymphadenopathy	Serology, darkfield microscopic examination of body fluids	• Penicillin G IV. Ceftriaxone IV as alternative • Mild disease: Oral doxycycline or azithromycin
Francisella tularensis (rabbits, cats)	Fever, rash, sepsis, pneumonia	Serology	IV aminoglycosides. Alternative: doxycycline
Rickettsia rickettsii (ticks)	Fever, diarrhea, or typical presentation of Rocky Mountain spotted fever	Clinical diagnosis, skin biopsy, antibody titer	Doxycycline or chloramphenicol
Salmonella enterica (dogs, cats, turtles)	Fever, abdominal pain, meningitis, endocarditis	• Blood culture • Stool culture	• Fluoroquinolones • Third-generation cephalosporins
Yersinia pestis (rodents)	• Bubonic: Fever, buboes • Pneumonic: Cough, dyspnea, shock	• Blood culture • Culture from sites	Doxycycline, fluoroquinolones, streptomycin, or chloramphenicol

(PCR: polymerase chain reaction)

TABLE 3: Tick-borne infections.

Disease and pathogen	*Arthropod vector*	*Animal reservoir*	*Clinical features*
Babesiosis (*Babesia microti*)	Ixodes dammini, Ixodes scapularis	Cattle, horses, dogs, cats, rodents	Fatigue, fever, anorexia, nausea, headache, abdominal pain, emotional lability, rash
Colorado tick fever (*Orbivirus*)	*Dermacentor andersoni* (wood tick)	Deer, porcupine	Fever, myalgias, photophobia, abdominal pain, sore throat, conjunctivitis, lymphadenopathy
Human granulocytic Anaplasmosis (*Anaplasma phagocytophilum*)	*I. scapularis, I. pacificus*	Dogs, deer	Fevers, chills, malaise, nausea, cough, sore throat, pulmonary infiltrates
Lyme disease (*Borrelia burgdorferi*)	*I. dammini*	Deer, sheep, deer mice	Erythema migrans, meningitis, encephalitis, neuropathy, arthralgia
Rocky Mountain spotted fever (*Rickettsia rickettsii*)	• *D. andersoni* • *D. variabilis*	Mammals	Petechiae, pulmonary infiltrates, jaundice, myocarditis, encephalitis, lymphadenopathy
Relapsing fever (*Borrelia* species)	*Ornithodoros* species	Body lice, rodents, humans	Fever, chills, headache, myalgias, arthralgias
Tularemia (*Francisella tularensis*)	• *Dermacentor* species • *Amblyomma* species	Rabbits, deer, dogs	Pneumonia, lymphadenopathy, arthralgias inoculation site ulceration

substances secreted by the salivary glands of ticks during a blood meal. Prolonged attachment of the tick for 2–7 days can result in paralysis of the host. Symptoms begin with weakness in the lower extremities. The paralysis ascends to the trunk, upper extremities, and head within hours and may lead to respiratory failure and death. It is diagnosed by the presence of tick on the body though a cerebrospinal fluid (CSF) analysis is usually normal. Removal of ticks and symptomatic management are the keys to its treatment.

LYME DISEASE

Lyme disease, the most common vector-borne disease in the United States, is a tick-borne illness caused by the spirochete *Borrelia burgdorferi*. The black-legged tick, also known as the *Ixodes* deer tick, is the vector, whereas deer, sheep, and deer mice are the reservoirs of this disease. The longer time taken by the ticks to feeds on the host causes more risk of acquiring the infection.

TABLE 4: Treatment of tick-borne infections.

Tick-borne zoonotic infection	*Specific treatment*
Rocky Mountain spotted fever	• *Adult*: Doxycycline 100 mg PO or IV twice a day for 7 days or for 2 days after temperature normalizes • Consider initial loading dose of 200 mg IV for seriously ill patients • Though contraindicated, it can be used in pregnancy during life-threatening conditions • *Children (<45 kg)*: Doxycycline 2.2 mg/kg twice daily • *Chloramphenicol (alternative)*: 50 mg/kg/day divided into four doses for 7 days
Lyme disease	• *Early stage or mild secondary*: 14–21 days of doxycycline (100 mg PO twice a day), amoxicillin (500 mg PO three times a day in adults, 50 mg/kg/day divided into three times a day in children), or cefuroxime (500 mg PO twice a day in adults, 30 mg/kg/day divided into three times a day in children) • *Severe illness, CNS positive, or high-degree heart block*: Ceftriaxone 2 g IV for 14–30 days • A single 200-mg oral dose of doxycycline given within 72 h of a high-risk deer tick bite is effective in preventing Lyme disease
Tick-borne relapsing fever	Doxycycline (100 m PO/IV twice a day for 7–10 days) Alternative: Erythromycin (500 m PO/IV four times a day for 7–10 days)
Tularemia	• *Adults*: Streptomycin 1 g IM/IV twice a day, or gentamicin 5 mg/kg IV divided every 8 h. Treat for 10 days • *Children*: Streptomycin 15 mg/kg IM twice daily (max 2 g/day) • *Mild disease*: Ciprofloxacin 750 mg PO twice a day, or doxycycline 100 mg PO twice a day. Treat for 21 days • *Prophylaxis for lab exposures*: Doxycycline 100 mg PO twice a day or ciprofloxacin 500 mg PO twice a day. Treat for 14 days
Babesiosis	• Atovaquone (750 mg PO every 12 h) plus azithromycin (500 mg PO on day 1, then 250 mg daily). Treat for 10 days • If relapse occurs, treat for 6 weeks or 2 weeks after negative blood smear • *Severe disease in adults*: Clindamycin (1,200 mg IV twice a day or 600 mg PO three times a day) + quinine (650 mg PO three times a day). Treat for 7–10 days
Ehrlichiosis and anaplasmosis	• Doxycycline 100 mg PO twice a day for 7–14 days • For children weighing <45 kg, the dose is 2.2 mg/kg twice a day

(CNS: central nervous system)

Clinical Features

There are three stages of Lyme disease:

1. The *first stage (early Lyme disease)* usually begins with *erythema migrans*, a slow expanding erythematous plaque with central clearing, also known as the bull's eye or target lesion, which occurs at the site of the tick bite. It is seen in approximately 80% of cases and develops within 2–30 days after the bite. If untreated, erythema migrans resolves spontaneously in 3–4 weeks. Low-grade intermittent fever, chills, fatigue, myalgias, anorexia, nausea, vomiting, arthralgias, and lymphadenopathy are the presenting symptoms.
2. The *second stage (early disseminated disease)* occurs within a few days to months following the initial infection. It is characterized by fever, neuropathies, cardiac abnormalities, arthritis, ocular manifestations, and multiple annular or target skin lesions. *Facial nerve palsy* is the most common neurologic manifestation. Headache, neck stiffness, altered mentation, cerebellar ataxia, encephalitis, radiculopathy, mononeuritis multiplex, and facial palsy can occur in neuroborreliosis. The patient may present with joint abnormalities in the form of asymmetric oligoarticular arthritis of the knees or with cardiac abnormalities, such as varying degrees of atrioventricular block, ST and T wave changes, conduction delay, or congestive heart failure.
3. The *third stage (late disseminated stage)* of illness involves continuous inflammation for more than a year after the initial infection. It is characterized by chronic arthritis, myocarditis, subacute encephalopathy, axonal polyneuropathy, and leukoencephalopathy. Exacerbation and remission of arthritis may extend for several years.

Diagnosis

The presence of erythema migrans is an aid in diagnosing the disease early. Polymerase chain reaction, fluorescence immunoassay, or Western immunoblot testing are done in the later stages of the disease. Treatment of Lyme disease is with doxycycline or amoxicillin or third-generation cephalosporins (**Table 4**).

TICK-BORNE RELAPSING FEVER

Relapsing fever is caused by gram-negative bacteria of the *Borrelia* species and Spirochaetales order. Human *Borrelia* infections are associated with arthropod vectors known as *Ornithodoros* ticks. The principal zoonotic reservoirs are wild rodents, specifically tree squirrels, rats, mice, and chipmunks.

Clinical Features

Fever, chills, myalgia, malaise, arthralgia, abdominal pain, and a rash or a pruritic eschar of 1–3 mm at the site of a tick bite may be the initial presentation of tick-borne relapsing fever (TBRF). The average incubation period is 7 days. Characteristically, the 3-day-long febrile episodes alternate with 7-day-long afebrile periods. This cycle repeats three to five times before resolution. Relapse is caused by the spirochete's ability to undergo antigenic variation within the body of the infected host. Two classical stages of clinical illness are manifested. The first stage is called the *chill phase* with high fevers, mental status changes, tachycardia, and tachypnea lasting approximately 30 minutes, followed by a *flush phase* with a rapid decrease in temperature and sweating. Neurological involvement is less common but may cause nuchal rigidity, peripheral neuropathies, and papillary abnormalities. Laboratory investigations may reveal leukocytosis and thrombocytopenia. The disease is usually self-limited, if untreated.

Diagnosis

Diagnosis is confirmed by darkfield microscopy or Wright- or Giemsa-stained peripheral blood smears. Tetracycline is the drug of choice (**Table 4**). Postexposure doxycycline is considered for prophylaxis of patients with a confirmed tick bite from endemic areas.

TULAREMIA

Tularemia is caused by a gram-negative, nonmotile, intracellular, coccobacillus *Francisella tularensis*. Ticks of the *Dermacentor* species (wood tick, dog tick) and the *Amblyomma* species (lone star tick) are the zoonotic vectors. Animal reservoirs are rabbits, hares, and deer. Tularemia is contracted through bites, inhalation, or through open wounds while in contact with an infected zoonotic host. The incubation period is between 3 and 6 days but may range from 2 hours to 3 weeks. Six important clinical forms occur, namely *ulceroglandular*, *glandular*, *typhoidal*, *pneumonic*, *oculoglandular*, and *oropharyngeal*. The *ulceroglandular form* occurs in 80% of cases and presents with fever, chills, myalgias, and a maculopapular skin lesion. The *glandular form* consists of painful adenopathy. The *typhoidal form* presents with high fever, chills, and abdominal pain and can cause organ failure and death. Pneumonic tularemia is the deadliest form of the disease. Laboratory findings of tularemia are nonspecific. The drug of choice is streptomycin. Alternative treatment includes gentamicin, ciprofloxacin, imipenem, doxycycline, and chloramphenicol (**Table 4**).

BABESIOSIS

Babesiosis is transmitted by ticks which carries *Babesia microti*. *Ixodes* ticks are the principal vectors and the zoonotic reservoirs are domesticated mammals, rodents, and deer. Symptoms occurs 1–4 weeks after exposure with malaise, anorexia, fever, chills, myalgia, headache, and hemolytic anemia. Risk factors involve immunocompromised patients and splenectomy. Laboratory finding are anemia, thrombocytopenia, and liver and renal failure. A Giemsa- or Wright-stained peripheral blood smear may show an erythrocytic ring that is seen in malaria. Treatment involves atovaquone plus azithromycin or clindamycin for 7–10 days (**Table 4**).

TREATMENT OF TICK-BORNE INFECTION

Early removal of ticks can help in prevention of the disease since the time required for the infection is at least 24–48 hours of attachment to the host. An embedded tick can be removed manually by tweezers or forceps gently without puncturing its body which may otherwise lead to the release of pathogens. The skin surface is cleansed and disinfected after removal of the tick.

Measures to help prevent tick exposure include avoiding tick-infested areas, wearing clothes covering the body, using tick repellents or application of topical ointment containing *N,N*-diethyl-m-toluamide to exposed skin, permethrin for clothes, and use of bed nets.

The indications of prophylactic treatment of tick bite include:

- Identification of the tick as *Ixodes scapularis*
- Tick attachment for >36 hours with tick engorgement
- Tick bite in an area with a *Borrelia burgdorferi* carrier rate of >20%

Prophylaxis includes a one-time dose of doxycycline 200 mg for adults or 4 mg/kg in children.

ZOONOTIC MENINGITIS AND ENCEPHALITIS

Zoonotic encephalitis is an arboviral infection transmitted via the hematogenous route by an arthropod or insect vector from an animal host. *Brucella canis*, borreliosis, *Coxiella burnetii, Ehrlichia* species, leptospirosis, Lyme disease, RMSF, and psittacosis are important nonviral zoonotic infections where encephalitis may be evident. The initial clinical features include fever, malaise followed by headache and altered mental status. The CSF analysis shows elevated opening pressure, slightly elevated proteins, normal glucose, and lymphocytic predominance although CT scan of head may not show any significant finding. CSF cultures are usually sterile; however, the organism can be detected by using an enzyme-linked immunosorbent assay of serum. Supportive care is the mainstay of treatment.

Zoonotic meningitis can be caused by brucellosis, listeriosis, plague, salmonellosis, tularemia, leptospirosis, Lyme disease, ehrlichiosis, Q fever, RMSF, or psittacosis. CSF findings are the same as in encephalitis. In case of a suspected case, empirical coverage of antibiotics should be administered immediately to reduce mortality and morbidity.

ZOONOTIC RESPIRATORY INFECTION

Upper respiratory zoonotic infection: Upper respiratory infection of zoonotic origin can present with prolonged exudative recurrent pharyngitis. The patient can present with sore throat, fever, and leukocytosis and is refractory to antistreptococcal therapy. *Bordetella* species, *Yersinia pestis*, *Streptococcus* species, and *Corynebacterium ulcerans* are some of the common causes of exudative pharyngitis. Household pets, such as dogs, cattle, and birds, can be the source of these infections in humans.

Lower respiratory zoonotic infection: Community-acquired pneumonia presenting atypically with cough, fever, chills, myalgias, and rash can be considered as a case of zoonotic pneumonia. Occupational history, history of recent travel, or animal exposure holds importance in the diagnosis. The important zoonotic pneumonias are inhalational anthrax, brucellosis, psittacosis, Q fever, pasteurellosis, and pulmonic plague. The treatment of important lower respiratory zoonotic infections is mentioned in **Table 5**.

ZOONOTIC DERMATOLOGIC INFECTION

Dermatologic zoonotic infections result from inoculation of the skin of hands and forearms with bacteria, viruses, and fungi and may present as a nonspecific generalized maculopapular rash. *Bacillus anthracis* (anthrax), *B. henselae* (cat-scratch disease), *Erysipelothrix rhusiopathiae* (erysipeloid), *Francisella tularensis* (tularemia), and *Listeria monocytogenes* (listeriosis) are some of the important bacterial zoonotic dermatoses. Most of the infections are noticed in animal handlers, livestock workers, veterinarians, and slaughterhouse workers. More than 95% of all anthrax infections are due to cutaneous anthrax, also known as woolsorter's disease. *Blastomyces dermatitidis* (cutaneous blastomycosis) and *Sporothrix schenckii* (sporotrichosis) cause fungal zoonoses. Viral zoonotic dermatoses include *Vaccinia* species (cowpox) and *Paravaccinia* species (pseudocowpox).

TABLE 5: Zoonotic pneumonias.

Disease	*Specific treatment*
Inhalational anthrax (*Bacillus anthracis*)	• *Adult*: Initially, ciprofloxacin 400 mg IV every 12 h + clindamycin 900 mg IV every 8 h + rifampicin 300 mg IV every 12 h + one-time infusion raxibacumab 40 mg/kg diluted over 2.25 h • *Once stable, oral*: Ciprofloxacin, 500 mg PO every 12 h + clindamycin 450 mg PO every 8 h + rifampicin 300 mg PO every 12 h • Continue for 60 days
Brucellosis (*Brucella* species)	• *Mild disease*: Doxycycline 100 mg PO twice daily for 6 weeks + gentamicin, 5 mg/kg daily for 7 days • *Alternative*: Doxycycline 100 mg PO twice a day, + rifampin 600–900 mg PO daily for 6 weeks • *Neurologic involvement*: Doxycycline 100 mg IV/PO twice a day + rifampin 600–900 mg PO daily + ceftriaxone 2 g IV twice a day • Continue treatment until cerebrospinal fluid normalizes
Q fever (*Coxiella burnetii*)	• Doxycycline 100 mg PO twice a day for 2–3 weeks • *Alternative*: 2–3 weeks of a fluoroquinolone or a macrolide
Psittacosis (*Chlamydophila psittaci*)	• Doxycycline 100 mg PO for 5–7 days • *Alternative*: Azithromycin dose pack or levofloxacin 750 mg PO for 5–7 days
Pulmonic plague (*Yersinia pestis*)	• Gentamicin 5 mg/kg IV daily for 10 days • *Alternative*: Streptomycin 15 mg/kg IV/IM twice a day for 10 days • *Postexposure prophylaxis*: Doxycycline 100 mg PO twice a day or ciprofloxacin 500 mg PO twice a day for 7 days

ZOONOTIC INFECTIONS FROM PETS

Majority of zoonotic infections are caused by household pets, such as dogs and cats, and a small number by pet birds, reptiles, rodents, and fishes. Anthrax, brucellosis, campylobacteriosis, cryptosporidiosis, echinococcosis, toxocariasis, and tularemia are some of the important zoonoses with dogs and cats as the definitive host. Similarly, birds and fowls account for zoonoses, such as psittacosis, ornithosis, listeriosis, and salmonellosis.

EMERGING ZOONOTIC VIRUSES OF BAT ORIGIN

Over the last few years, it is evident and recognized that emergence of zoonotic infections is on the rise. The increase is due to both the increase in the rate of zoonotic infections globally and also improved ability to detect and identify agents. New technologies have expanded the sensitivity and scope of our detection and diagnostic capability. However, if there is no significant disease outbreak, a pathogen may remain undetected. Zoonotic agents from their natural reservoir host rarely transmit species to another species, and in most zoonoses human-to-human transmission is rare. However, increased spill over events will increase the chances of the emergence of an adapted virus that will be highly transmissible. The number and diversity of viruses identified in bats is extraordinary and is the subject of many recent reviews. Most significant bat-related zoonotic viruses which have had a major impact on public health in different parts of the world over the past 2 decades are discussed further.

Paramyxoviruses

Hendra virus: The first detection of "Hendra Virus (HeV)" emergence was in 1994. Although the virus appears to have been circulating in Australian flying foxes for a long time. Over the last few years, the incidence of HeV spill over events in Australia has drastically increased, peaking in 2011 with 18 independent outbreaks in horses in Queensland and New South Wales. All human infections can be traced back to close contact with infected horses and there is no evidence of human-to-human infection so far.

Nipah virus: In 1998, another bat-related paramyxovirus emerged in Malaysia, named "Nipah virus", (NiV) this highly infectious virus was first detected in humans and commercially farmed pigs exhibiting respiratory and neurological disease. A slightly different NiV detected in Bangladesh and India in 2001 and causing regular outbreaks of fatal encephalitis in humans, with evidence of direct bat-to-human and human-to-human transmission and mortality of between 70 and 100%.

Coronaviruses

Severe acute respiratory syndrome virus: Severe acute respiratory syndrome (SARS) emerged in late 2002 and represents the best examples of emergence of infectious disease. Palm

civets were found infected with SARS virus but further extensive epidemiological and surveillance studies demonstrated that the true reservoir of the SARS and SARS-like coronaviruses was bats of the genus *Rhinolophus*, civets were probably an amplifying and/or adaptation.

Middle East respiratory syndrome virus: Recently, another coronavirus responsible for an acute respiratory disease has emerged named as "Middle East respiratory syndrome (MERS)". The fatality rate is between 40 and 50%. Genome sequencing has confirmed that this virus is most closely related to coronaviruses in bats in Asia, South Africa, and also in different parts of the world. All these indicating that bats are likely natural hosts of MERS or MERS-like viruses and that the emergence of similar viruses in other parts of the world is a significant possibility. The route of introduction into the human population remains unknown. A serological study detected neutralizing antibodies in camels from the Middle East but exact role of camels (or other animals) in MERS coronavirus (CoV) transmission to humans is yet to be established.

Filoviruses

Ebola and Marburg viruses are among the deadliest viruses known to humankind and Ebola has caused massive die-offs of great apes in Central Africa. The transmission of filoviruses to humans is believed to occur mainly through "bushmeat" activities, i.e., the capture and slaughtering of wild animals, including nonhuman primates. Recent data indicated that bats could be the potential natural hosts of Ebola and Marburg viruses in Africa. Filovirus RNA has been identified in a number of fruit bat species from central African countries. It has also been shown that the incidence of Marburg hemorrhagic fever in mine workers in southern Uganda could be attributed to possible transmission from infected bats (*Rousettus aegyptiacus*) that had colonized the mine. Genetic analysis confirmed that the Marburg virus isolated from the infected mine workers was similar to those circulating in the *R. aegyptiacus* population. This virus posing a significant potential threat to public health as this virus emerged in the pig population in the Philippines. Detection of Ebola–Reston specific antibodies in *R. amplexicudatus* bats suggests that bats may also be the natural host of Ebola–Reston virus.

Other Bat-borne Viruses

These include viruses of known zoonotic transmission, such as the Menangle virus in Australia and the related Tioman and Melaka viruses in Malaysia, and many other related bat reoviruses. Bat viruses related to known human pathogens have also been detected in large numbers, including bat lyssaviruses, parainfluenza viruses, hantaviruses, hepaciviruses, and pegiviruses. The public health threat of these viruses is unknown, but it would be judicious to place these viruses under a close watch for potential spill over.

EMERGING ZOONOTIC VIRUSES FROM OTHER SOURCES

It should be emphasized that, while bat viruses represent one of the most important sources of recent emergence, there are many other important zoonotic viruses with a significant impact on public health that have emerged or re-emerged.

West Nile virus (WNV): It is a member of the family *Flaviviridae* and is endemic in many parts of the world. As an arbovirus, WNV is transmitted by mosquitoes between birds and mammals.

Chikungunya virus (CHIKV): It is a member of the genus *Alphavirus*, family *Togaviridae* and first isolated from a febrile patient in Tanzania in 1952. It is an enzootic virus found in tropical and subtropical regions of Africa, in Indian Ocean Islands and in some parts of Asia. Serological and virus isolation studies confirm that nonhuman primates are the host in CHIKV transmission and *Aedes* mosquitos are the main vectors. There is emerging genetic evidence to suggest that the virus has acquired multiple mechanisms for evolutionary adaptation to the vector. There is a significant impact of climate change on mosquito distribution and evolution, thus CHIKV will be an important zoonotic virus to be monitored for further spread and future outbreaks.

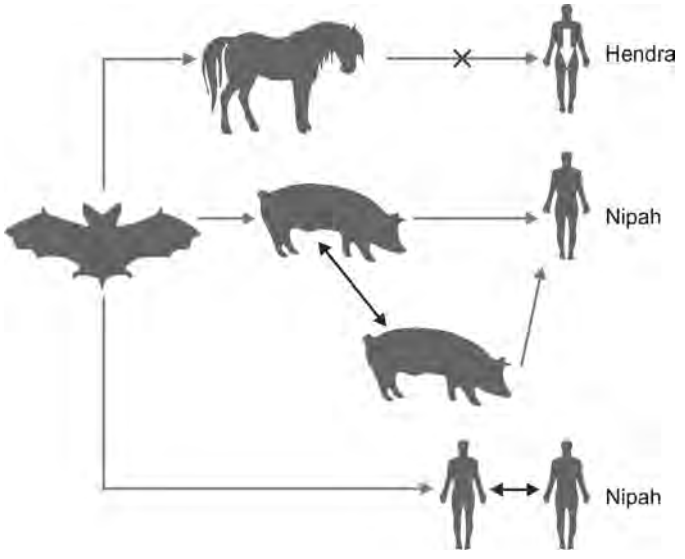
Crimean–Congo hemorrhagic fever virus (CCHFV): It is a member of the genus *Nairovirus*, family *Bunyaviridae*. Ticks of the genus *Hyalomma* are considered to be both the main vector and the natural reservoir. These ticks are present on the ground and can infest a number of small and large mammals so that they can carry the virus without any symptoms, in their blood for further transmission to other animals and/or humans. Although tick bites are the main route of transmission to humans, direct contact with the body fluids, and tissue or blood of infected animals can also lead to human infections. Most infections with CCHFV lead to a mild and nonspecific febrile illness, some patients develop severe hemorrhagic disease, as suggested by its name. The fatality rate of CCHFV infection in humans can vary from 5 to 30% depending on the virus strain, the location, and the public health infrastructure associated with outbreaks. Climate change could be the risk factor that has the greatest potential to cause an expansion in the geographical distribution of CCHFV.

PREVENTION AND CONTROL OF EMERGING ZOONOTIC DISEASES

Emergence of zoonotic disease is multifactorial process. The environmental factors which significantly affect the pathogens and their reservoir hosts are constantly changing with significant pace. Climate and habitat changes have a significant effect on vector distribution. The environmental changes are due to the modernization of farming practices, habitat destruction, human encroachment, and climate change. It is very important to understand the impacts of these changes on the interactions between pathogens and their hosts and between the host and other species because these interactions are responsible for disease emergence. Understanding the environmental changes and their impacts allow us to develop mitigation strategies and effective and timely response. It is believed that the initial transmission of the SARS coronavirus from a currently unidentified bat species to the amplifying hosts, including the civet cat, occurred due to drastic changes in farming and trading activities. The geographical distribution

of zoonotic pathogens such as WNV, CHIKV, and dengue virus are also changing and expanding due to newly established habitats. It is important to recognize various influencing factors and their roles in the emergence of different viruses and make the strategy to control them.

One Health approach: The "One Health Initiative" defines "One Health" as "the collaborative efforts of multiple disciplines working locally, nationally and globally to attain optimal health for people, animals, plants, and our environment". Emerging interspecies and transboundary zoonoses infections require improved understanding between various groups to develop control strategies, implementation of surveillance and response activities between the animal–human. Consider the interactions of humans and animals with ecosystems and the environment as important control strategies (**Fig. 1**).



(×: vaccine to prevent transmission to human; ↓: postexposure human antibodies to reduce viral replication)

FIG. 1: One Health strategies: Human-Animal-Environment ecosystem.

SUMMARY

Zoonotic diseases are infectious diseases that are naturally transmitted from vertebrate animals to humans and vice versa. They are caused by all types of pathogenic agents including bacteria, parasites, fungi, viruses, and prions. Since last few decades, their impact on public health has increased although they have been recognized for many centuries. Currently, world is experiencing huge socioeconomic impact of zoonotic pathogens transmitted from animals to humans worldwide. As the emergence of SARS-CoV-2 from an unknown reservoir leading to the pandemic require effective communication between all levels of response, understanding the origins and evolution of the pathogen to develop policies that can mitigate its spread. It is being increasingly recognized that a "One Health approach" at the Human-Animal-ecosystem interface is needed for effective investigation, prevention, and control of any emerging zoonotic disease.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Tetanus

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INTRODUCTION

The tetanus is characterized by muscular rigidity and spasms caused by tetanus toxin (tetanospasmin), which is produced by *Clostridium tetani*, an anaerobic bacillus, whose spores survive in soil and cause infection by contaminating wounds. The estimated global incidence of tetanus is approximately 1 million cases annually. Mortality rates due to tetanus vary across the world, depending on healthcare access, and in the absence of medical treatment the mortality rate reaches to almost 100%. This chapter discusses the pathophysiology, symptomatology, and medical treatment of *C. tetani* infection and the possibility of using botulinum toxin for tetanus-induced rigidity and spasms.

PATHOPHYSIOLOGY OF TETANUS TOXIN

Tetanus toxins act by a mechanism similar to botulinum toxin. Tetanus toxin is taken up into nerve terminals of lower motor neurons, the nerve cells that activate voluntary muscles. It is a zinc-dependent metalloproteinase that targets a protein [synaptobrevin/vesicle-associated membrane protein (VAMP)] that is necessary for the release of neurotransmitter from nerve endings through fusion of synaptic vesicles with the neuronal plasma membrane. Flaccid paralysis may be the initial symptom of local tetanus infection, caused by interference with vesicular release of acetylcholine at the neuromuscular junction, as occurs with botulinum toxin. Extensive retrograde transport of tetanus toxin occurs in the axons of lower motor neurons, and tetanus toxin reaches the spinal cord or brainstem. Tetanus toxin crosses the synapses and is taken up by nerve endings of inhibitory gamma-aminobutyric acid (GABA)ergic and/or glycinergic neurons that control the activity of the lower motor neurons. Once tetanus toxins inside the inhibitory nerve terminals, they cleave VAMP, thereby inhibiting the release of GABA and glycine, resulting in functional denervation of the lower motor neurons, which leads to rigidity and spasms due to hyperactivity and to increased muscle activity.

SYMPTOMATOLOGY OF TETANUS

Tetanus toxin causes rigidity and spasms due to hyperactivity of voluntary muscles. Rigidity is the tonic, involuntary contraction of muscles while spasms are short-lasting muscle contractions that can be elicited by sensory stimulation or by stretching of the muscles; they are termed "reflex spasms." A highly reduced ability to open the mouth as rigidity of the temporal and masseter muscles leads to trismus (lockjaw). During physical examination, attempts at opening the mouth may induce spasms that cause the complete clenching of the jaws. Tetanus can be classified as *generalized tetanus*, *neonatal tetanus* (which is a generalized form in children <1 month), *local tetanus*, and *cephalic tetanus* (which tetanus is localized to the head region). Generalized and neonatal tetanus affect the muscles of the whole body and lead to opisthotonos (the backward arching of the column due to rigidity of the extensor muscles of the neck and back) and may cause respiratory failure and death due to rigidity and spasms of the laryngeal and respiratory muscles. Local and cephalic tetanus account for only a minority of cases; however, they can develop into the generalized form. Depending on the type of the tetanus local/cephalic or generalized/neonatal, tetanus typically manifests as trismus/lockjaw, risus sardonicus, dysphagia, neck stiffness, abdominal rigidity, and opisthotonos, i.e., hyperactivity of muscles of the head, neck, and trunk. The limbs tend to be less severely affected, but with full opisthotonos, decorticate posture occurs (flexion of the arms and extension of the legs). In both local/cephalic and generalized tetanus, trismus is frequently the initial symptom but the tetanus may present in any form described above. In addition, general muscle ache, focal flaccid paralysis, and an array of unusual symptoms reflecting unusual patterns of neuronal inactivation, including diplopia, nystagmus, and vertigo, may occur. The tetanus toxin affects not only the motor system but also the autonomic system. Episodes of tachycardia, hypertension, and sweating, sometimes rapidly alternating with bradycardia and hypotension, are common autonomic dysfunction, especially in generalized tetanus. Autonomic symptoms usually occur a week after the occurrence of motor symptoms. Tetanus-mediated respiratory insufficiency is a treatable condition with the availability of modern intensive care; autonomic dysfunction has become a major cause of death in tetanus victims. Sensory nerves may also become invaded by the tetanus toxin, causing altered sensation, such as pain and allodynia.

DIAGNOSIS

Tetanus is largely a clinical diagnosis, and no laboratory test is recommended to diagnose the tetanus. Tetanus mostly occurs in a person with an inadequate or unknown immunization history and tetanus can even occur in a person with protective antitetanus antibodies. Strychnine poisoning may present as generalized tetanus. Other differential diagnoses of tetanus are drug-induced dystonic reaction, hypocalcemia tetany, malignant neuroleptic syndrome, serotonin syndrome, Stiff person syndrome, peritonsillar abscess, peritonitis, bacterial meningitis, rabies, and temporomandibular joint disease.

TREATMENT OF TETANUS

Treatment of tetanus is supportive and consists of identification of wound and debridement and removal of spores, and further toxin production can be prevented. As the disease itself does not provide the immunity so tetanus immunization should be provided. A patient with respiratory compromise should be admitted in the intensive care unit for immediate neuromuscular blockade and intubation support. Treatment is summarized in **Table 1**.

Wound cleaning and antibiotic are the mainstay of the acute treatment of tetanus and are based on the eradication of *C. tetani*, e.g., with *intravenous metronidazole*, 500 mg every 6 hourly, or penicillin, 100,000–200,000 IU/kg/day for 7–10 days. *Tetanus immunoglobulin* is given once intramuscularly to inactivate any free tetanus toxin; doses of 250 IU intramuscularly in an adult and 4 unit/kg in children are given as postexposure prophylaxis, while 3,000–6,000 IU intramuscularly is recommended for treatment of clinical tetanus, though the tetanus immunoglobulin does not reduce the symptoms of tetanus but may reduce the mortality. A part of the tetanus immunoglobulin dose should also be infiltrated in and around the wound. Muscle symptoms may aggravate further, although the clostridia have been eradicated and antitoxin has been given, because the tetanus toxin continues to be transported axonally and trans-synaptically and to cleave VAMP. A meta-analysis indicated that intrathecal administration of antitoxin could inactivate tetanus toxin during its trans-synaptic transport; intrathecal administration is also superior to the intramuscular route with respect to survival. Vaccination should be included in the treatment because immunity may not develop after an episode of tetanus. Give tetanus toxoid (0.5 mL intramuscularly) at the time of presentation, at 6 weeks and 6 months after injury. Muscular rigidity and spasm often interfere with respiration and is a likely cause of death, so treatment of these features is of vital importance. The patient also suffers from severe pain due to rigidity and spasms, which stimulates muscle activity. Muscle relaxation is customarily achieved with benzodiazepines, which augment the effect of GABA on the GABAA receptors of lower motor neurons. *Baclofen* may also be effective which acts on GABAB receptors; when given intrathecally, its sedative effect is avoided. In the setting of an intensive care unit, propofol, another GABAA receptor modulator, may be used as may nondepolarizing muscle relaxants (pancuronium and pipecuronium), which act directly on the muscle motor end plates by competing for the acetylcholine-binding site. *Magnesium*, a calcium antagonist, may be effective in relieving rigidity and spasms and acts by reducing both acetylcholine release and the muscle response to acetylcholine. Magnesium also seems to reduce autonomic dysfunction, which is of importance, because antiadrenergic drugs, especially β-blockers, may produce untoward effects, including cardiac arrest. *Dantrolene* reduces calcium mobilization and muscle contraction by binding to the ryanodine receptor in muscle. To avoid the triggering of spasms by noise or other sensory stimulation, tetanus patients should be in a calm environment. Immunization with formaldehyde-inactivated tetanus toxin (toxoid) is recommended to achieve the prophylaxis against tetanus. For instance, contamination of the umbilical stump of the newborn is a primary cause of neonatal tetanus. These issues are interrelated: A good immunization status in pregnant women leads to reduction in the prevalence of neonatal tetanus, because maternal antitetanus toxin antibodies are transferred across the placenta to the child in utero.

TABLE 1: Summary of tetanus treatment.

Steps	*Interventions*
Wound	Identify wound and wound debridement.
Antibiotic therapy	Metronidazole 500 mg IV 6 hourly, theoretically penicillin can enhance the effect of tetanospasm
Immunization	• Tetanus toxoid (TT) 0.5 mL IM at presentation, then after 6 weeks and then after 6 months • Tetanus immunoglobulin 3,000–6,000 units IM (opposite arm of TT and some amount around the wound site)
Muscle relaxation	Diazepam
Respiratory distress management	Sedation neuromuscular blockade (succinylcholine/vecuronium for intubation) mechanical ventilation
Autonomic dysfunction management	• Magnesium sulfate loading dose 40 mg/kg IV, then continuous infusion 2 g/h or • Labetalol 0.25–1 mg/min IV infusion • Morphine sulfate 0.5–1 mg/kg/h • Clonidine 300 μg every 8 hourly

(IM: intramuscularly; IV: intravenously)

THE ROLE OF BOTULINUM TOXIN IN TETANUS-INDUCED RIGIDITY AND SPASMS

The botulinum toxins are zinc metalloproteinases which enter the nerve terminals of lower motor neurons that attack synaptic vesicle proteins. Botulinum toxin A cleaves synaptosomal-associated protein (SNAP-25); botulinum toxins B, D, F, and G cleave synaptobrevin (which is also attacked by tetanus toxin); and botulinum toxin C cleaves SNAP-25 and syntaxin. The botulinum toxins undergo less axonal and trans-synaptic transport as compared to tetanus toxin. Therefore, the nerve terminals of lower motor neurons are affected by botulinum toxins, inhibiting the release of acetylcholine and activation of voluntary muscles. For this reason, they may have a role in reducing the muscular hyperactivity in tetanus patients. Theoretically, the action of botulinum toxin could be more rapid in tetanus in which the activity of the lower motor neurons is much increased. Dosage varied somewhat but resembled those commonly used to treat dystonia.

ADVANTAGES AND DISADVANTAGES OF BOTULINUM TOXIN TREATMENT IN TETANUS

Early and common symptoms of tetanus, in both generalized and cephalic, are trismus and dysphagia. These features cause major threats for the patient including respiratory failure and autonomic dysfunction described above. A patient of tetanus cannot swallow normally or evacuate the mouth and predisposes to aspiration of normal salivation and pneumonia. Difficulty in eating and problem in maintaining oral hygiene occur due to trismus, which is an important issue, because the condition may last for many weeks, endangering dental health. Trismus can also cause involuntary tongue biting, which may be very painful. Tetanus-induced trismus can be relieved safely by the use of botulinum toxin. The procedure is considered safe, given that the masseter and temporalis muscles are at some distance from the larynx; injection should be administered into the cricopharyngeal muscles to relieve dysphagia.

Botulinum toxin for the treatment of trismus and dysphagia should be considered at an early stage in tetanus, because it reduces the risk of aspiration and pneumonia, allowing dental care and food intake, and may contribute to a more favorable course of the disease. Painful neck rigidity can be relieved by botulinum toxin injections into the trapezius, splenius capitis, levator scapulae, and sternocleidomastoid muscles; vital structures, such as the carotid artery, are present near these muscles, so care must be taken to avoid spread of botulinum toxin to the larynx. No information is available on the use of botulinum toxin in generalized tetanus in which large truncal muscles are affected, such as the abdominal and erector spinae muscles.

Hyperactivity of abdominal muscles in Parkinson's disease and dystonia can be successfully treated by use of botulinum toxin. Back pain syndromes can also be treated with injection of botulinum toxin into several levels of the erector spinae muscles in the L1–L5 area. Botulinum toxin is helpful in reducing the need of muscle relaxants in the treatment of tetanus that affects consciousness and the long-lasting effect of botulinum toxins (>3 months).

Difficulty of treating all affected muscle groups in generalized tetanus with botulinum toxin is one of the disadvantages. Even so, botulinum toxin should be considered in generalized tetanus, in which the rigidity of certain muscle groups may pose a special therapeutic challenge and threat to life. The botulinum toxin has a slow onset of action, and gradual increase in effect over 1–3 weeks necessitates simultaneous treatment with other muscle-relaxing drugs. It is important to monitor patients closely because of the possibility of overdosing which manifests days after injection of botulinum toxin. Especially in generalized tetanus, the main obstacle to the use of botulinum toxin for tetanus may prove to be the cost of treatment, in which large doses may be needed to reduce rigidity and spasms of large muscles.

SUMMARY

Tetanus toxin, which is produced by *C. tetani*, is the cause of tetanus symptoms. It is transported axonally to the spinal cord and/or brainstem after taken up into terminals of lower motor neurons where vesicular release of inhibitory neurotransmitters becomes blocked leading to disinhibition of lower motor neurons. Muscle rigidity and spasms occur, often manifesting as trismus/lockjaw, dysphagia, opisthotonos, or rigidity and spasms of respiratory, laryngeal, and abdominal muscles, which may cause respiratory failure. Botulinum toxin may reduce tetanus symptoms as botulinum toxin largely remains in lower motor neuron terminals, inhibiting acetylcholine release and muscle activity. Botulinum toxin can be injected into the masseter and temporalis muscles to treat the trismus. Botulinum toxin treatment should be started early in the course of tetanus to reduce the risk of pulmonary aspiration, involuntary tongue biting, anorexia, and dental caries. Botulinum toxin treatment can be helpful in other muscle group involvement.

Use of botulinum toxin for the treatment of muscle rigidity and spasms in tetanus has limited clinical experience. However, from a few published reports it would seem that such treatment is useful. The treatment of trismus with botulinum toxin is probably a fairly safe procedure, since injection into the masseter and temporalis muscles can be achieved without endangering the neighboring vital structures.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Dengue Fever

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INTRODUCTION

Dengue fever is a vector-borne disease comprising fever, joint pain, skin rashes, headache, nausea, vomiting, and abdominal pain. The causative organism is dengue virus DENV, with serotypes 1–4 isolated in India and the vector is *Aedes aegypti*. Dengue fever poses a major threat to public health, especially in tropical and subtropical parts of India and worldwide. The other arboviral diseases in India include Japanese encephalitis, West Nile virus, chikungunya fever, Crimean–Congo hemorrhagic fever, and Kyasanur forest disease.

EPIDEMIOLOGY

The first case of dengue fever was reported in 1780 in Madras (now Chennai) and the first outbreak in 1963 in Calcutta (now Kolkata). Following this outbreak, many such outbreaks have been reported in different parts of India. There has been a significant rise in the total number of dengue-positive cases ever since. In the beginning of 2000, southern states, such as Maharashtra, Karnataka, Tamil Nadu, and Puducherry, and Northern States, such as Delhi, Rajasthan, Haryana, Punjab, and Chandigarh, were declared endemic areas for dengue.

On the global front, there has been an increase of 30-fold of the total number of dengue cases over the past five decades. Dengue is responsible for an estimated 50 million infections annually, and it is endemic in over 100 countries. In Southeast Asia, dengue outbreaks were recorded as early as in late 1940s, and it has been identified as a hyperendemic region for decades with the highest reported incidences. 87% of the total population in Southeast Asian countries are at a potential risk of dengue. In comparison to other Asian countries, India did not have widespread cases of dengue until the 1990s.

MODES OF TRANSMISSION

The development of dengue cases in India is dependent on various factors, such as unplanned urbanization, overcrowding, rising population, living in unsanitary conditions, decreased access to clean drinking water, storage of water in large tanks and containers for domestic and commercial use, changes in environment factors, interactions between host and pathogen, and immunological factors. In India, both *A. aegypti* and *A. albopictus* are adept vectors for dengue virus.

Temperature and precipitation: Temperature plays an ideal role for providing favorable conditions for breeding of mosquito and transmission of disease. In regions of warm temperatures and higher humidity, there is a decrease in the incubation period of dengue virus within the vector and during blood-feeding intervals. This leads to a faster process of replication of virus and intensity of transmission. However, the relation between virus transmission and weather is varied across different geographical conditions and socioeconomic conditions. Precipitation provides the mosquito an adequate source of breeding ground and habitat for larvae and pupae.

Urban region: Unlike the rural areas, drier regions, such as cities with a large population density, are prone to be infected by the dengue virus. Due to overcrowding in small areas of accommodation, there is always a tendency to store water in unprotected reservoirs inside or near their households. This may also be seen in areas with limited supply or limited hours of supply water. This leads to collection of water over a long period of time. This source of water attracts *A. aegypti,* which is anthropophilic and therefore increases the chances of transmission.

Inadequate vector control measures: Adequate vector control measures should be undertaken in endemic areas, especially during early monsoon and late monsoon phases. Failure to accommodate such activities within societies, districts, or parts of the city can benefit the transmission of dengue virus further. The lifespan of *A. aegypti* survives best between 16° and –30°C and a humidity of 60–80%. Altitude is a limiting factor for the mosquito as it is distributed between the sea level and 1,000 ft above the sea level. Since its anthrophilic, they have a high tendency to rest in and around cool shady places. Breeding is mostly seen in domestic man-made water receptacles in and around households, construction sites, and factories; natural

habitats are tree holes, leaf axils, and coconut shells. Other sites include unused tires, flowerpots, and desert coolers.

Dengue fever is a complex pathological condition dependent upon three important factors and their relationship between them:

1. *Host*: Man and mosquito
2. *Agent*: Dengue virus
3. *Environment*: Abiotic and biotic factors

TRANSMISSION

Dengue virus (DENV): It is a single-stranded RNA virus consisting of four serotypes DEN1 to DEN4. These serotypes are closely related and belong to the genus *Flavivirus* of family *Flaviviridae*.

Vector

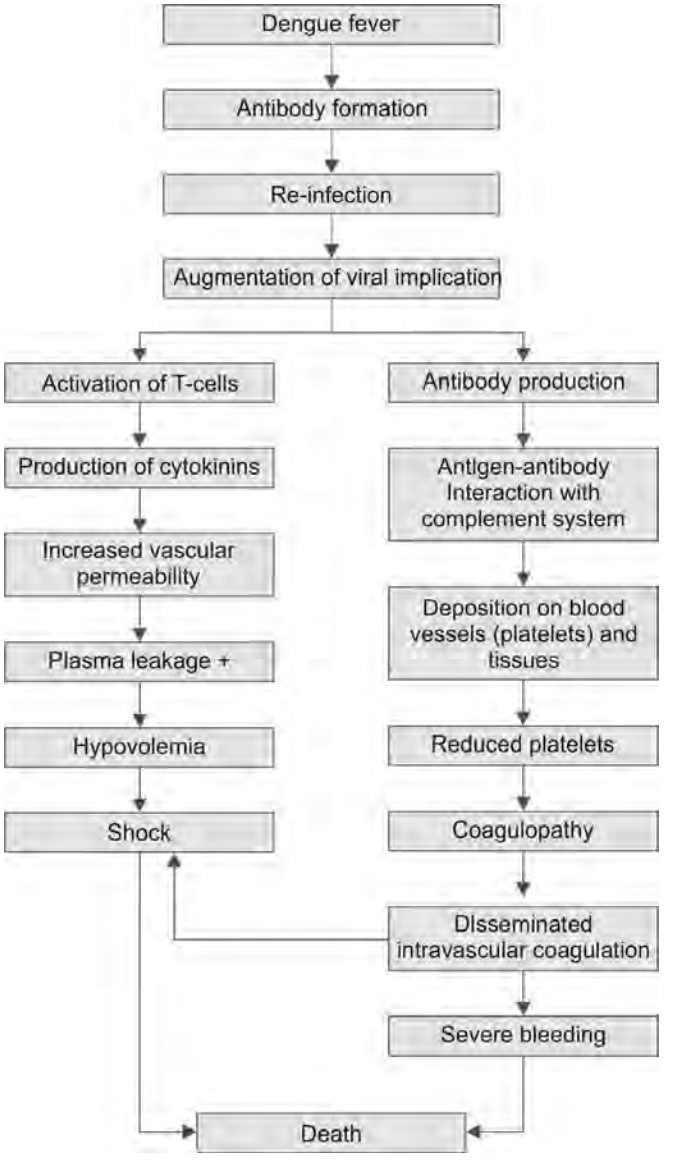
The bite of a female *Aedes* mosquito causes the infestation of DEN virus from mosquito to human. *A. aegypti* is the most potent vector, whereas other species, such as *A. albopictus*, *A. polynesiensis*, and *A. niveus* are secondary vectors. In urban areas of India, *A. aegypti* is the main vector while in some areas of Southern India, *A. albopictus* is a potent vector. A female *Aedes* mosquito lays its eggs on the damp surface just above the water line. The lifecycle of the aquatic stage of the mosquito involving the time taken from hatching to emergence as an adult can be as short as 7 days. The eggs can survive without water up to a year. At low temperatures, it may require several weeks for them to emerge. The average adult survival of *Aedes* mosquito is 15 days. In rainy season or late monsoon, the risk of transmission is higher and survival increases. To get one food meal, the mosquito must feed on several persons. Hence, the infection is transmitted to several persons at a time.

IMMUNOPATHOGENESIS

The infection starts primarily with dengue fever. The severity of infection goes uphill by subsequent infections by different serotypes progressing toward dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). The clinical picture of DHF/DSS is much more severe and life threatening compared to dengue fever. The prognosis of DHF and DSS includes sudden-onset shock, capillary leakage, and hemorrhagic thrombocytopenia occurring at the time of active symptoms of fever (**Flowchart 1**).

CLINICAL PICTURE

After an incubation period of 4–10 days, primary infections may be subclinical or asymptomatic and can produce a spectrum of clinical manifestations. It will provide lifelong immunity to the infecting serotype. The individual infected with the infection is protected from the illness with a different serotype after 2–3 months from the onset of primary infection; however, there is no cross protective immunity in long term. Infection carried over to the next progeny of mosquitoes through eggs, called as transovarian transmission, is a more complicated form of transmission. DEN1 and DEN2 serotypes are widespread in India.



FLOWCHART 1: Pathogenesis of dengue fever.

CLINICAL MANIFESTATIONS

Dengue fever has an acute and sudden onset. It comprises three phases: (1) Febrile, (2) Critical, and (3) Recovery.

Febrile Phase

- It lasts for 2–7 days with the development of high-grade fever suddenly. It is accompanied by facial flushing, skin erythema, generalized body ache, myalgia, retro-orbital pain, arthralgia, rash, hemorrhagic manifestations, such as petechiae and mucosal membrane bleeding, and headache.
- Other symptoms include sore throat, anorexia, nausea, and vomiting which are common.
- *Uncommon symptoms*: Women in childbearing age may develop massive vaginal bleeding. Gastrointestinal bleeding, hematemesis, or melena can also be present.
- A positive tourniquet test is indicative of dengue fever.

- Liver and spleen may be enlarged after a few days of primary infection.
- The earliest manifestation in complete blood count is a decreased count of white blood cells which shows a higher possibility of dengue fever.
- It is an initial phase and too early to have a definite diagnosis of dengue fever, and one must pay careful consideration to rule out differential diagnosis of febrile illness. In addition, it is a precedent of hemorrhagic fever and DSS.

Tourniquet test: The test is performed by inflating a blood pressure cuff up to a midpoint between systolic and diastolic pressure for 5 minutes. A positive test is indicated by the presence of 10 or more petechiae per 2.5 cm^2 of area over the surface of skin. In DHF, the test is usually positive with the presence of 20 petechiae or more. However, in DSS, it may be negative or mildly positive during the heightened period of shock. In the event of a negative result, repeated tests must be taken to ensure confirmation of diagnosis. This is clearly a clinical finding and must be correlated with hematological values. In early stages of DSS/DHF, a timely diagnosis of the ailment has helped in reducing fatality risks and in aiding recovery to an immunocompetent system.

Critical Phase

- At 3–7th day from the onset of symptoms, there is an increased permeability of capillaries along with raised hematocrit levels. There is a drop in temperature of fever between 37.5 and 38°C and less.
- The leakage from capillaries is predominant and usually lasts for 24–48 hours. It is a denotable fact that plasma leakage follows as a result of a decreased level of white blood cells and platelets levels. This stage decides the prognosis of the patient. In case vascular permeability improves, there is a subsequent improvement in the immune system of the patient. This decreases the chances of further progression of leucopenia and thrombocytopenia. However, patients with increased leakage within capillaries tend to worsen and symptoms deteriorate due to loss of plasma volume.
- *Other clinical features are*: depending upon the degree of leakage from capillaries and the vigorous fluid therapy, it is likely to lead to pleural effusion and or ascites. Chest X-ray and USG of abdomen should be done to confirm the diagnosis. Note that the increase of hematocrit from baseline of >20% is directly related to the severity of plasma leakage. This may lead to shock progressively with warning signs and critical loss of plasma volume. There is a change of body temperature to subnormal (signs of hypothermia). The risks of prolonged symptoms of shock lead to decreased perfusion to vital organs and tissues. This leads to progressive organ impairment, metabolic acidosis, and disseminated intravascular coagulation. The progressive stages involve further decrease in plasma volume. In addition to the existing symptoms and the succession of these events, the white blood cells will increase in patients with severe hemorrhage and bleeding. This is contrary to leucopenia that was present in the febrile phase.
- Warning signs include abdominal pain and tenderness, persistent vomiting, fluid accumulation, signs of mucosal bleed, lethargy, restlessness, and hepatomegaly (liver enlargement > 2 cm). Laboratory findings include an increase in hematocrit along with decreased platelet count < 1,00,000/mm^3.
- Other organ involvement leads to severe hepatitis, encephalitis, or myocarditis.
- Cases with active signs of warning can be treated with adequate fluid resuscitation.

Recovery Phase

Once the patient has crossed the 24–48-hour critical phase, the physiological response involves a gradual re-absorption of fluid from the extravascular compartment in the next 48–72 hours. The patient's condition improves, appetite returns to normal, gastrointestinal symptoms resolve, and diuresis ensues.

Characteristic appearance of multiple petechial rashes over upper and lower extremities, back, neck, and chest are also seen. In the first 24–48 hours from the onset of symptoms, patients present with an erythematous macular rash all over the extremities, torso, and back. These rashes blanch upon applying pressure and may present only for a transient period. About 2–3 days after defervescence, the convalescent rash may appear. These are generalized petechial rashes and do not blanch upon applying pressure. They are surrounded by thin, round islets of normal skin, appearing like "isles of white in the sea of red." These rashes disappear after the recovery of symptoms, usually after 7 days. Other symptoms include bradycardia, electrocardiogram eliciting changes in cardiac activity, and pruritis.

On the resolving phase of symptoms, it is evident that the white blood cell count increases much faster when compared to platelet count. The hematocrit levels may be low due to the dilution effect as a result of the reabsorbed fluid. Respiratory distress may be aggravated due to pleural effusion and ascites along with excessive fluid intervention. In the recovery and/or critical phase, the degree of excessive fluid administered can lead to pulmonary edema or congestive heart failure.

SEVERE DENGUE

The clinical features are progressively life threatening with a prolonged critical phase. Depending upon the condition of the patient and progression of symptoms, the presence of one or more of the following is defined as severe dengue:

- Plasma leak from capillaries into the extra-vascular compartment—rise in hematocrit count that may progress to shock
- Signs of respiratory distress secondary to fluid overload
- Fluid overload in pulmonary or gastrointestinal system—pleural effusion/ascites
- Signs of bleeding due to thrombocytopenia
- Decreased adequate perfusion leading to severe organ impairment

The increased permeability of vascular blood vessels increases hypovolemia and progresses to shock. This begins around defervescence, during the 3–7th day of illness. One must look out for the warning signs as they are a precedent of shock. In the initial phase of shock, due to the loss of plasma volume to leakage, there is a compensatory system that maintains normal blood pressure with tachycardia and vasoconstriction, especially in the peripheries. This leads to decreased skin perfusion and capillary refill time. This leads to cold and clammy extremities. Due to the increased vasoconstriction, the diastolic pressure rises toward a normal systolic pressure. This results to a narrow pulse pressure. One must not be fooled by reading a normal systolic pressure as progression into

TABLE 1: Hemodynamic status in hypotensive shock.

Parameters	*Stable circulation*	*Compensated shock*	*Hypotensive shock*
Hypotensive shock	Clear, lucid	Clear, lucid	Altered mental status
Capillary refill time	Brisk <3 sec	Prolonged >2 sec	Delayed further, mottled skin
Extremities	Warm and pink extremities	Cool peripheries	Cold, clammy extremities
Peripheral blood volume	Good volume	Weak and thread	Feeble or absent
Heart rate	Normal	Tachycardia	• Severe tachycardia • Bradycardia in late shock
Blood pressure	Normal blood pressure	• Normal systolic pressure but increased diastolic pressure • Narrow pulse pressure • Postural hypotension	• Narrow pulse pressure <20 mm Hg • Hypotension • Unrecordable blood pressure
Respiratory rate	Normal	Tachypnea	• Metabolic acidosis • Hyperpnea • Kussmaul breathing

later stages of shock will lead to abrupt disappearance of both pressures. The clinical appearance of the patient appears to be lucid and often remains conscious. It is a combination of hypoxia and hypotensive states that leads to multiorgan failure.

Hypotension is defined as systolic blood pressure (SBP) of <90 mm Hg or mean arterial blood pressure (MAP) of <70 mm Hg or a systolic blood pressure decrease of >40 mm Hg. In children up to 10 years of age, the 5th percentile of SBP is calculated by the formula 70 + [(age in years) × 2] mm Hg (**Table 1**).

The patient progressively leads to shock if the pulse pressure is ≤20 mm Hg in children and/or in the presence of signs of poor capillary perfusion. The signs of poor capillary perfusion include delayed capillary refill time, cold or clammy extremities, and tachycardia. The pulse pressure of ≤20 mm Hg indicates a severe form of shock. It is evidently present that hypotension is usually present in later stages of shock associated with severe bleeding. In cases of severe dengue, as discussed in pathophysiology of dengue fever, coagulation disorders may present due to thrombocytopenia. However, it may not lead to bleeding in all cases. It leads to bleeding only in the presence of severe shock along with thrombocytopenia, acidosis, and hypoxia further leading to multiorgan failure and advanced disseminated intravascular coagulation. In some cases, ingestion of aspirin, ibuprofen, or corticosteroids may cause bleeding without precedent prolonged shock or hypotension.

Other manifestations include acute liver failure, cardiomyopathy, encephalitis, and encephalopathy, even present in the absence of severe plasma leakage or shock.

Fatality risk is higher when the clinical condition of the patient progresses to later stages of shock. This can be avoided if the patient is diagnosed and treated at an earlier stage.

A person should be considered for severe dengue with a history of fever for 3–7 days and living in endemic areas along with one or more of the following findings (**Table 2**):

- *Increased hematocrit*: Note that the higher the rise of level from baseline, the greater the severity of the disease
- Signs of respiratory distress to rule out pleural effusion or ascites

TABLE 2: Grading for dengue fever and dengue hemorrhagic fever based on severity of symptoms

Grade	*Signs/Symptoms*	*Laboratory findings*
Dengue fever (DF)	High-grade fever onset 3–7 days, retro-orbital pain, myalgia, arthralgia	Leucopenia, thrombocytopenia
DHF-I	Above symptoms + positive tourniquet test + plasma leakage	• Thrombocytopenia <100,000/mm^3 • Hematocrit 20% or more
DHF-II	Above symptoms + signs of bleeding from skin and IV sites + epistaxis, black tarry stools, mucosal bleeding (gums) + abdominal pain	• Thrombocytopenia <100,000/mm^3 • Hematocrit 20% or more
DHF-III	Above symptoms + weak, rapid pulse + narrow pulse pressure ≤20 mm Hg + high diastolic pressure + hypotension + cold extremities + altered sensorium (restlessness, lucid, confused)	• Thrombocytopenia <100,000/mm^3 • Hematocrit > 20%
DHF-IV	• Profound shock • Unrecordable blood pressure • Feeble pulse • Decreased pulse blood volume	• Thrombocytopenia <100,000/mm^3 • Hematocrit >20%

(DHF: dengue hemorrhagic fever)

- *Capillary compromise or signs of shock*: Tachycardia, cold clammy extremities, delayed capillary refill time >3 seconds, feeble pulse pressure or unrecordable blood pressure in later stages of shock
- *Signs of bleeding*: In mucosal membranes, ears, nose, and massive vaginal bleeding in woman of childbearing age
- *Altered level of consciousness*: Unresponsive, lucid, lethargy, coma, or convulsions
- *Severe gastrointestinal symptoms*: Persistent vomiting, intense abdominal pain, signs of jaundice
- *Signs of organ impairment*: Acute liver failure, acute renal failure, encephalopathy or encephalitis, or unusual symptoms such as cardiomyopathy

STEP-WISE APPROACH TO TREATMENT

1. *Initial assessment*:
   - History
   - Physical examination
   - Investigation
2. Diagnosis
3. Management: In pertinence with the severity of the clinical condition of the patient, management of the patient can be divided into:
   - *Group A*: Stable, may be discharged
   - *Group B*: Requiring hospital admission and intervention
   - *Group C*: Emergency resuscitation and intensive care stay

Initial Assessment

History

A complete and discreet history covers all areas of concerns and doubts. It aids in ruling out other differential diagnoses with a similar onset of febrile illness. It comprises:

- Onset and duration of first symptom
- Associated symptoms
- Frequency of symptoms within 24 hours
- Aggravating or relieving factors
- History of outside food consumption or travel to an endemic area
- Look out for warning signs
- *Change in mental sensorium*: Signs of dizziness, decreased level of consciousness, confusion
- History of trauma, fall from height, intoxication levels
- *Coexisting medical ailments*: Obesity, diabetes mellitus, pregnancy, hypertension
- History of last meal
- Check for decreased urine output and frequency since the onset of symptoms
- History of recent adventurous sports such as trekking, camping in forests, swimming in waterfall (rule out typhus, malaria, leptospirosis)
- *Recent unprotected sexual intercourse*: Rule out acute HIV seroconversion illness
- History of past medical and surgical interventions
- *Current medication history*: Use of aspirin, clopidogrel, heparin, warfarin

Physical Examination

It includes:

- *Head-to-toe examination*: Hydration status, signs of pallor, icterus, clubbing, cyanosis, lymphadenopathy, and pedal edema
- *Change in mental sensorium*: Signs of dizziness, decreased level of consciousness, confusion
- Assessment of hemodynamic status
- Signs of tachypnea, dyspnea, acidotic breathing
- Signs for abdominal tenderness, location of tenderness, rule out hepatomegaly, splenomegaly, signs of ascites
- *Signs of petechial rashes*: Over the upper and lower limbs, abdomen, chest,
- *Signs of bleeding*: Over mucosal membranes, ear, nose, throat, excessive vaginal bleeding in women
- *Tourniquet test*: Can be repeated in previously negative reading
- *Changes in hemodynamic status*: Look for signs of hypotensive shock

Investigation

- *Complete blood count with peripheral smear*: Hematocrit count is evaluated at the initial hours of febrile phase to maintain as baseline, in order to compare with in subsequent testing. An increased level of hematocrit count with a parallel decrease in platelet levels is an early indication of the critical phase of dengue fever.
- *Additional tests*: Arterial blood gas analysis in cases of sudden breathlessness, dyspnea on exertion, chest discomfort, desaturation status, liver function test, random blood glucose, serum electrolytes, serum urea, serum creatinine, bicarbonate levels, lactate count, cardiac enzymes, urine routine, and examination
- *Radiological studies*: Chest X-ray, ultrasound abdomen/CT abdomen

Dengue fever should be differentiated from other diseases (**Table 3**) and those presenting with similar features, such as fever and rashes.

DIAGNOSIS

Early diagnosis of febrile illness can prevent the progression to a more severe and critical phase of the disease and eventually in some cases death. During the initial 5 days of illness, viral isolation in cell cultures and nucleic acid amplification test (NAAT) can be done to confirm dengue. It can also be confirmed by virus antigen by enzyme-linked immunosorbent assay (ELISA) or rapid tests. Virus isolation requires a higher level of expertise and infrastructure and maybe expensive. In order to cultivate virus, it is ideal to cool and preserve the viability of virus after collection of samples from the patient and delivery to the laboratory. It usually requires several days for confirmation of virus cultivation whereas nucleic acid amplification detection assays can be used to detect dengue within 24–48 hours. Both virus isolation and NAAT need to be maintained at adequate quality assurance, controlled procedures, and done by experienced technicians. The NS1 antigen test can be done with antigen detection kits. Results from dengue NS1 can be obtained as early as an hour. After the

TABLE 3: Differential diagnosis of dengue fever.

Flu-like symptoms	*+/– Rash*	*Infectious diseases*	*Malignancy*	*Clinical features*
• Chikungunya • Influenza • Measles • HIV seroconversion illness • Mononucleosis	• Rubella • Measles • Scarlet fever • Meningococcal infection	• Malaria • Acute gastroenteritis • Leptospirosis • Typhus • Typhoid • Viral hepatitis • Bacterial sepsis • Septic shock	Acute leukemia	• Diabetic ketoacidosis • Lactic acidosis • Leukopenia ± thrombocytopenia • Platelet disorders • Renal failure • Respiratory distress (Kussmaul breathing) • SLE • *Acute abdomen*: Acute appendicitis, acute cholecystitis, perforated viscus

(SLE: systemic lupus erythematosus)

initial 5 days, there is a decrease in antigens and appearance of viruses may have disappeared. The NS1 antigen may be present in some cases. For serology, decreased or absence of immunoglobulin M (IgM) in response to a febrile phase affects diagnostic ability. A fourfold increase or a higher increase in antibody levels by IgG ELISA or by hemagglutination inhibition (HI) testing is indicative of an acute flavivirus infection.

MANAGEMENT

Group A (Patient Stable, may be Discharged)

- This includes patients who are able to take oral fluids in order to maintain adequate hydration and are able to void urine every 6 hours. Additionally, patients with no warning signs and with a decrease in frequency of vomiting, diarrhea, or fever episodes are included in this group. It also includes patients who are ambulatory and are not severely dehydrated. They need to be evaluated serially until the critical phase is over with complete blood count to monitor white blood cells and platelet count. In the event of a stable hematocrit and adequate hydration status, the patient can be sent home for rest and adequate oral rehydration with fluids is recommended.
- Oral fluids can be increased with oral rehydration solution (ORS), fruit juices, and electrolyte-rich water with sugar. One must be aware of possible hyperglycemia due to physiological stress in the febrile phase.
- Tablet paracetamol 500 mg for high fever is adequate at an interval of 6 hours. In order to reduce body temperature, tepid sponging can be done. Avoid use of acetylsalicylic acid (aspirin), ibuprofen, and nonsteroidal anti-inflammatory drugs (NSAIDs) as these may aggravate risks of bleeding with underlying thrombocytopenia.
- The patient and family need to be counseled regarding signs and symptoms of bleeding, rashes, severe abdominal pain, persistent vomiting, deterioration of mental status, cold clammy extremities, lethargy, irritability, restlessness, black stools, coffee ground vomiting, and decreased urine output. The patient should be monitored at home by family members for increased frequency of symptoms, temperature pattern, volume of intake fluids, urine output, and warning signs and reviewed after 4 days in the hospital. If any of the symptoms arise, the patient should be brought back to the hospital for critical intervention.

Group B (Patient Requiring Hospital Admission and Intervention)

This group includes patients who are in need of in-hospital management for close observation and approach to a critical phase. Coexisting medical conditions, such as pregnancy, diabetes mellitus, old age, infancy, renal failure, and immunosuppressed individuals, such as those chronic hemolytic disease and HIV, make the treatment more complicated and require careful close observation within the hospital. In the event of one or more signs of warning symptoms, the treatment module should be initiated at the earliest.

- *An initial hematocrit level must be obtained before starting fluid therapy*. Start with isotonic fluid solutions such as 0.9% saline, Ringer's lactate, or Hartmann's solution at 5–7 mL/kg/h for the first 1–2 hours. Then reduce it at a rate of 3–5 mL/kg/h for the next 2–4 hours and further maintain at 2–3 mL/kg/h or less according to the clinical response of the patient. Reassess the hydration status of the patient every half hourly in order to rule out early signs of pleural effusion or fluid overload. Repeat hematocrit level and watch for increase in levels despite fluid therapy. If the hematocrit level remains the same with minimal increase, continue with the same rate at 2–3 mL/kg/h for the next 2–4 hours. In case of increased hematocrit levels, increase the rate of fluid administration to 5–10 mL/kg/h for 1–2 hours. Repeat the hematocrit levels every 2 hourly and adjust the rate of fluid therapy accordingly.
- Maintain a minimum intravenous fluid in order to maintain an adequate urine output at 0.5 mL/kg/h. Initial fluid therapy is required during the initial 24–48 hours in order to replenish the loss of blood volume. The intravenous fluid should be tapered according to a decrease in the hematocrit level, stable hemodynamic status, and adequate urine output.
- Constant monitoring should be done for all patients until the critical phase is over. Parameters that need constant monitoring include vital signs and peripheral perfusion every 1–4 hours, urine output every 4–6 hours, and

hematocrit levels before and after fluid replacement and then every 6–12 hours. According to the hemodynamic status of the patient, serial investigations, such as liver function test, renal function test, and coagulation levels, should be done.
- *For correction in serum electrolyte imbalances*: Start sodium bicarbonate at 1–2 mEq/kg
- *Dengue patient without warning signs*: Encourage oral fluids in the absence of persistent vomiting. In the absence of oral tolerance, start intravenous fluids of 0.9% saline or Ringer's lactate.

Maintenance fluid can be calculated by using the Holliday–Segar formula: 4 mL/kg/h for the first 10-kg body weight + 2 mL/kg/h for the next 10-kg body weight + 1 mL/kg/h for subsequent body weight.

Group C (Emergency Resuscitation and Intensive Care Stay)

- It includes a patient requiring emergency and critical care intervention in the event of severe plasma leakage or respiratory distress due to fluid overload, severe hemorrhage, and organ impairment. Initial resuscitation with fluid is the sole essential requirement. The choice of fluid should be isotonic and volume should be sufficient to maintain adequate and effective circulation during the critical phase of plasma leak. It should be avoided by replacement with isotonic crystalloid solution or colloid solutions in hypotensive shock. During aggressive resuscitation, careful consideration to look out for hyperchloremic acidosis is evident in use of 0.9% saline and is often confused with lactic acidosis with prolonged shock.
- Blood grouping and matching should be done in the event of possible blood transfusion in patients with severe bleeding and decreased platelet count.
- Fluid resuscitation should be not confused with simple fluid administration. Resuscitation is defined as administration of large volume of fluids in boluses for a limited amount of time and close monitoring for signs of fluid overload and pulmonary edema. Ideal resuscitation with isotonic fluids should aim to restore central and peripheral circulation with decrease in tachycardia, improving blood pressure, pulse volume, decreased capillary refill time, and warm pink extremities. Hemodynamic status with a stable conscious level, decreasing metabolic acidosis, and urine output at ≥0.5 mL/kg/h would be expected after fluid resuscitation.

COMPLICATIONS IN SEVERE DENGUE

Electrolyte imbalances: These mostly occur due to excessive vomiting and diarrhea or due to use of hypotonic solutions for fluid therapy for resuscitation and treatment of dehydration. Hyponatremia, hypokalemia, metabolic acidosis, hyperkalemia, and hypercalcemia are most commonly present.

In the presence or absence of diabetes mellitus, hypoglycemia or hyperglycemia can occur.

Treat the underlying diseases, including nosocomial infections or coinfections resulting to high-grade fever.

Supportive and adjuvant treatment: It includes vasopressors and inotropes if required to prevent life-threatening hypotension and/or while endotracheal intubation. Treatment of organ impairment, such as encephalopathy or encephalitis, should be done. Renal replacement therapy and/or continuous venovenous hemodialysis can be initiated in adverse cases.

COMPLICATION: COMPENSATORY SHOCK

Initiate fluid resuscitation at the rate of 5–10 mL/kg/h with isotonic crystalloid solution (**Flowchart 2**). Reassess the condition of the patient and note the deterioration of symptoms. If the symptoms are resolving, intravenous fluids can be gradually decreased to 5–7 mL/kg/h for the next 1–2 hours. Further, on improvement of the patient's condition, the rate of fluid administered can be decreased to 2–3 mL/kg/h for the next 3–4 hours. Depending upon the patient's response, the maintenance rate can be continued for the next 24 hours.

However, if the patient's condition does not improve after initial fluid resuscitation, re-evaluate the hematocrit levels after bolus fluid is administered. In the event of persistent increased hematocrit levels of >50%, the second bolus fluid can be administered at 10–20 mL/kg/h for 1 hour. If there is improvement in hemodynamic status, a decreased rate at 7–10 mL/kg/h can be given for the next 1–2 hours. Further, it can be gradually tapered on improvement of vital signs and reduction of symptoms. In case of a decrease in hematocrit levels below the initial baseline hematocrit, it is indicative of bleeding. Preparation for possible blood transfusion must be done and transfusion should be started after cross checking with the serum blood count. In case of bleeding, serial administration of isotonic crystalloid or colloid solutions may need to be given for the next 24–48 hours.

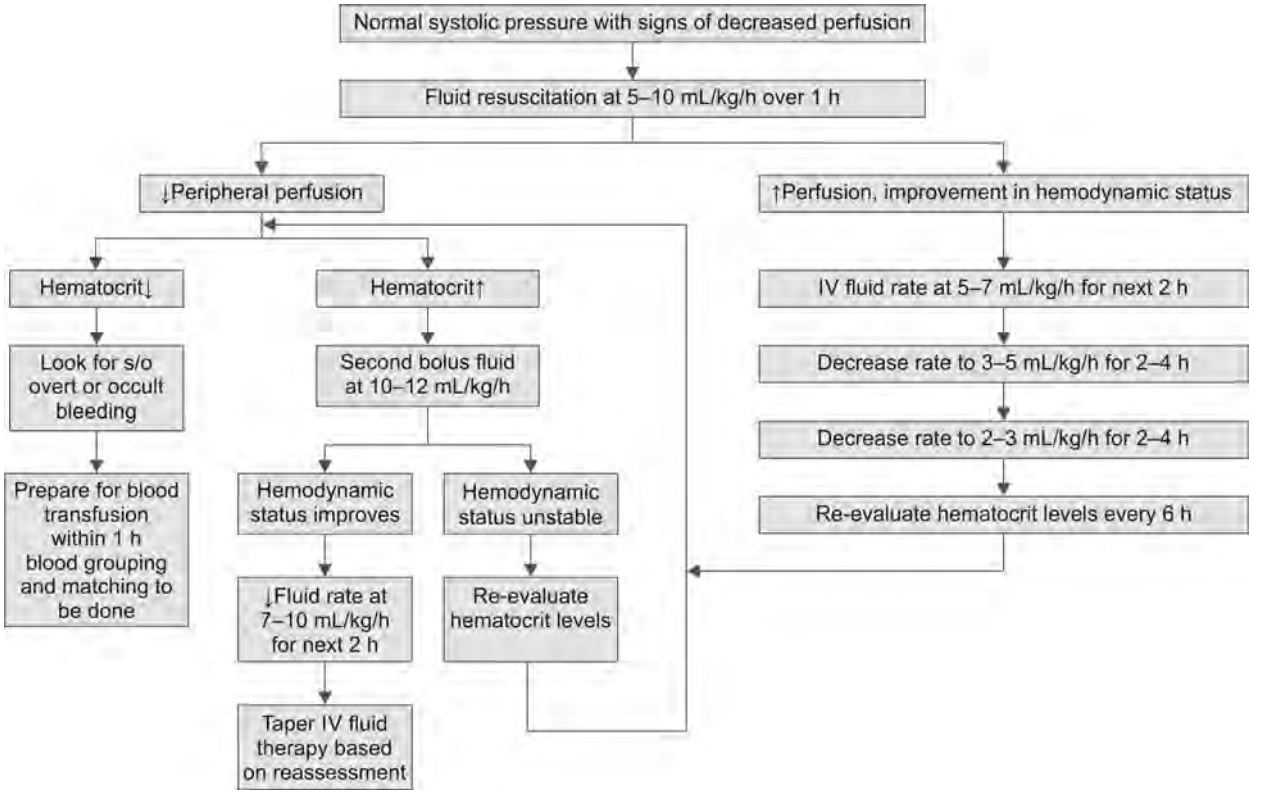
COMPLICATION: HYPOTENSIVE SHOCK

A more vigorous fluid therapy must be initiated for hypotensive shock (**Flowchart 3**). Fluid resuscitation with crystalloid or colloid solution at 20 mL/kg as bolus dose must be administered as fast as possible. This is to ensure that excessive plasma leakage can be reversed and the patient can be reverted from shock at the earliest.

In the event of improvement, follow with intravenous fluid administration at 10 mL/kg/h for the next 1 hour. Continue with crystalloid infusion and reduce the rate to 5–7 mL/kg/h for the next 1–2 hours. Then reduce to 3–5 mL/kg/h for the next 2–4 hours and then to 2–3 mL/kg/h or less maintained for the next 24–48 hours. In the event of unstable hemodynamic vitals, re-evaluate hematocrit levels and compare the results with the previous hematocrit prior to bolus administration. If the hematocrit level is below 40% in children and adult female, and below 45% in adult males, it indicates an underlying bleeding within the systemic circulation. The need for blood cross match and transfusion is evident and should be started as soon as possible.

If hematocrit is higher than baseline levels, shift to colloid solution IV fluids at a rate of 10–20 mL/kg as a second bolus over 30 minutes to 1 hour. Reassess the patient after the second bolus; if vitals improve, decrease the rate of IV fluids to 7–10 mL/kg/h for 1–2 hours. Change back to crystalloid solution later and reduce the rate of fluid administration gradually as mentioned above in the event of improving the patient's condition.

In the event of an unstable condition, repeat hematocrit levels. If the hematocrit reduces compared to the previous


Normal systolic pressure with signs of decreased perfusion
Fluid resuscitation at 5–10 mL/kg/h over 1 h
↓Peripheral perfusion
↑Perfusion, improvement in hemodynamic status
Hematocrit↓
Hematocrit↑
IV fluid rate at 5–7 mL/kg/h for next 2 h
Look for s/o overt or occult bleeding
Second bolus fluid at 10–12 mL/kg/h
Decrease rate to 3–5 mL/kg/h for 2–4 h
Decrease rate to 2–3 mL/kg/h for 2–4 h
Prepare for blood transfusion within 1 h blood grouping and matching to be done
Hemodynamic status improves
Hemodynamic status unstable
Re-evaluate hematocrit levels every 6 h
↓Fluid rate at 7–10 mL/kg/h for next 2 h
Re-evaluate hematocrit levels
Taper IV fluid therapy based on reassessment

FLOWCHART 2: Depicting fluid therapy in compensatory shock.

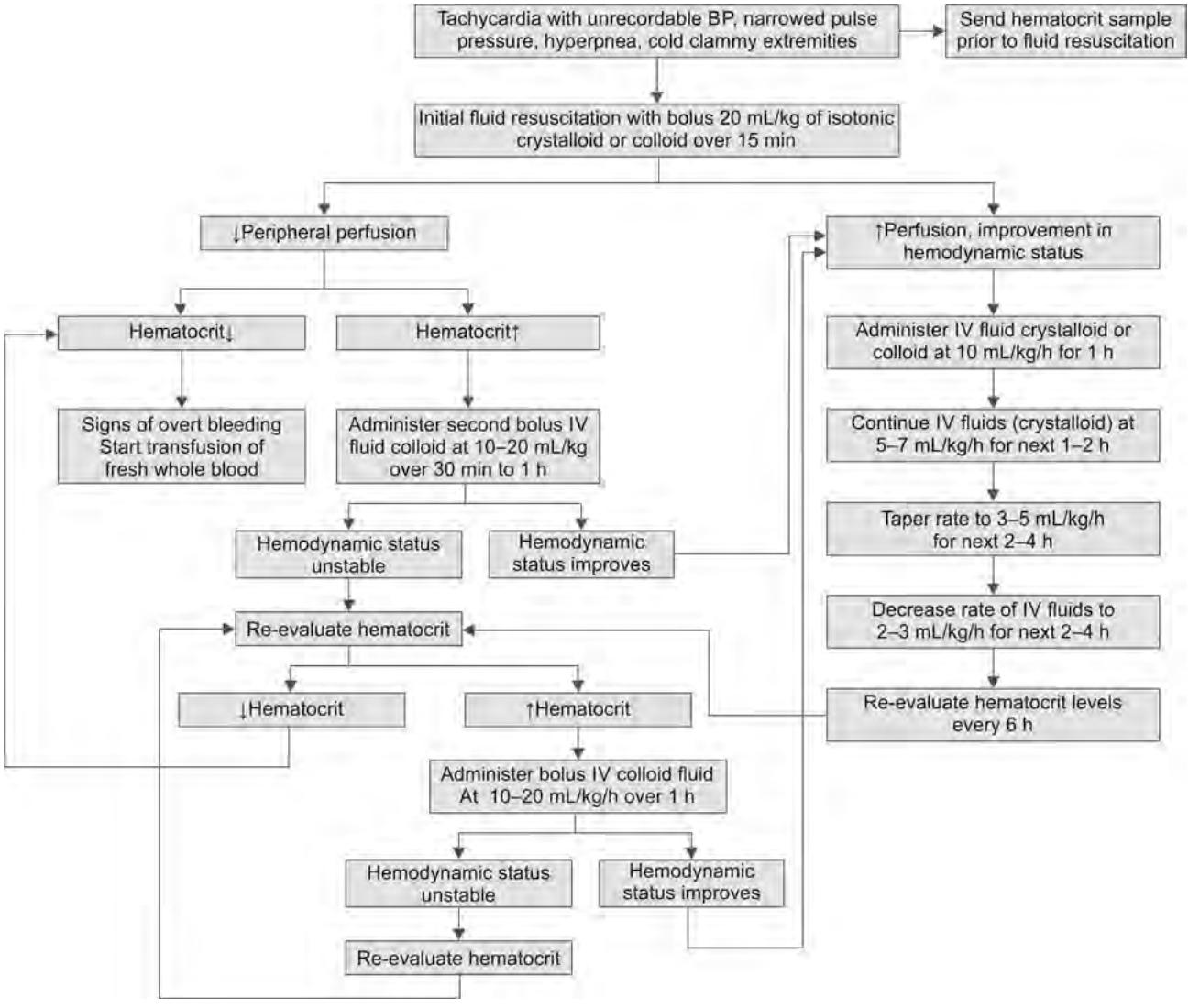
result, it indicates bleeding and requires immediate blood transfusion. If the hematocrit level increases to >50%, continue colloidal solution at 10–20 mL/kg infusion over 1 hour. After the bolus dose, decrease the rate of IV fluid to 7–10 mL/kg/h for the next 1–2 hours. Shift to crystalloid solution IV fluid and taper the rate of administration with respect to the patient's response.

Over the next 24 hours, serial doses of bolus IV fluid may be required depending upon the patient's response. Titrated doses need to be administered over the first 24 hours. In cases of severe dengue, the patient needs to be admitted to a high dependency unit or intensive care unit for intervention and constant monitoring until the critical phase is over and signs of shock are resolved.

A detailed input and output fluid chart should be maintained. Monitor vital signs and peripheral perfusion every 15–30 minutes during the critical phase and every 1 hour once the patient is out of shock phase. It is evident that vigorous fluid administration leads to increased risks of fluid overload and therefore needs more careful and regular monitoring in order to ensure adequate fluid replacement. In cases of severe dengue, acquire an arterial line as soon as possible in order to measure arterial blood pressure. Blood pressure measured by cuff may not be accurate in hypotensive shock. The arterial line can provide more accurate pressure readings and easier access to obtain a frequent sample of blood. ECG is taken to monitor cardiac activity changes and serial ECG to compare improvement or deterioration of the patient. Urinary catheterization should be done to monitor constant urine output, ideally at 0.5 mL/kg/h. Until the patient is stable, the hematocrit level should be evaluated prior and after bolus fluid administration and then every 4–6 hours. In addition, arterial or venous blood gas analysis should be done as soon as patient treatment begins. Evaluate bicarbonate, lactic acid levels, and total pCO_2 every 30 minutes in the initial critical phase until the patient's condition is stable. Random blood glucose should be checked before fluid resuscitation and repeat as indicated. Other investigations such as renal function test, liver function test, and coagulation profile prior to fluid resuscitation and after 1 hour of fluid resuscitation should be done.

The hematocrit level can be used as a guide to treatment along with changes in the patient's vital signs including peripheral extremities, pulse pressure, blood pressure (systolic and diastolic), heart rate, respiratory rate, and capillary refill time. An event of rising hematocrit along with unstable vital signs including narrow pulse pressure indicates active plasma leakage and can be treated well with a second dose of bolus replacement. An event of rising or persistently high hematocrit along with stable vital signs and adequate urine output does not require a more aggressive approach of fluid resuscitation and requires close monitoring of hematocrit levels for the next 24 hours. Hematocrit levels are more likely to reduce to baseline within 24 hours.

An event of decreased hematocrit levels with unstable vital signs including narrow pulse pressure, tachypnea, tachycardia, metabolic acidosis, decreased or no urine output shows an increased risk of bleeding, and blood transfusion should be initiated immediately. However, in an event of a hematocrit level with normal vital signs and adequate urine output is an indication of decreased plasma leakage and reabsorption of extravasated fluids. In this case, IV fluids must be decreased and finally stopped in order to prevent fluid overload and pulmonary edema.


Tachycardia with unrecordable BP, narrowed pulse pressure, hyperpnea, cold clammy extremities
Send hematocrit sample prior to fluid resuscitation
Initial fluid resuscitation with bolus 20 mL/kg of isotonic crystalloid or colloid over 15 min
↓Peripheral perfusion
↑Perfusion, improvement in hemodynamic status
Hematocrit↓
Hematocrit↑
Administer IV fluid crystalloid or colloid at 10 mL/kg/h for 1 h
Signs of overt bleeding Start transfusion of fresh whole blood
Administer second bolus IV fluid colloid at 10–20 mL/kg over 30 min to 1 h
Continue IV fluids (crystalloid) at 5–7 mL/kg/h for next 1–2 h
Hemodynamic status unstable
Hemodynamic status improves
Taper rate to 3–5 mL/kg/h for next 2–4 h
Re-evaluate hematocrit
Decrease rate of IV fluids to 2–3 mL/kg/h for next 2–4 h
↓Hematocrit
↑Hematocrit
Re-evaluate hematocrit levels every 6 h
Administer bolus IV colloid fluid At 10–20 mL/kg/h over 1 h
Hemodynamic status unstable
Hemodynamic status improves
Re-evaluate hematocrit

FLOWCHART 3: Fluid therapy in hypotensive shock.

HEMORRHAGIC COMPLICATIONS

Minor bleeding may occur in mucosa in any patient with dengue and recovers during the recovery phase. However, in patients with severe thrombocytopenia, bed rest and trauma should be avoided to prevent any bleeding. Careful consideration should be given in acquiring venous access and catheterization during this phase. Avoid use of intramuscular treatments for hematomas. In addition, in order to treat severe thrombocytopenia, there is no effective correlation with the use of prophylactic blood transfusion and is not indicated. In case of severe bleeding, it is more overtly present in the gastrointestinal tract and vagina in adult females. Patient with increased risk of bleeding are mentioned below.

- Persistent prolonged shock
- *Associated organ impairment*: Renal failure, liver failure
- Persistent metabolic acidosis
- Administration of nonsteroidal inflammatory agents
- *Underlying conditions*: Peptic ulcer disease
- Anticoagulant therapy
- Recent history or active complaints of trauma
- Hemolytic conditions are at risk of acute hemolysis with hemoglobinuria

Precursors to Bleeding

- Reduced level of hematocrit along with unstable hemodynamic state even after fluid resuscitation
- Refractory shock—not responding to consecutive fluid resuscitation at 40–50 mL/kg
- Persistent and overt bleeding with unstable hemodynamic status, with or without a decrease in hematocrit
- Hypotensive shock with a normal or low hematocrit level prior to fluid resuscitation
- Worsening metabolic acidosis with or without normal systolic blood pressure
- Persistent acidosis with or without abdominal tenderness and distension

Transfusion of blood should be initiated at the earliest; however, careful consideration should be taken to prevent acute fluid overload. A decreased level of hematocrit <30% is not indicated for blood transfusion as bleeding is a postplasma leakage phenomenon in the presence of prolonged shock. During the plasma leak phase, hematocrit levels exceed to 45% or more prior to onset of bleeding. When bleeding starts, hematocrit levels drop from these high levels to low and critically low hematocrit levels. Hence, the hematocrit levels may not be reduced due to plasma leak.

Treatment of Hemorrhagic Complications

Initial blood transfusion at 5–10 mL/kg of fresh packed red cells or 10–20 mL/kg of fresh whole blood at an appropriate rate should be started. Stored blood contains lower levels of 2,3-diphosphoglycerate (2,3-DPG) which decrease the oxygen-releasing capacity of hemoglobin that causes functional tissue hypoxia. An ideal clinical response includes improvement in hemodynamic status and acid–base balance. Repeat blood transfusion is considered in patients with continued signs of bleeding or no rise in hematocrit after the first blood transfusion. Insertion of a nasogastric tube (NG) should be performed with caution as severe bleeding may lead to occlusion of airway. A lubricant must be applied over the NG tube vigorously in order to prevent trauma. Central venous catheterization must be done under USG guided by experienced personnel.

COMPLICATION: FLUID OVERLOAD

In cases of severe dengue, fluid overload causes pleural effusions bilaterally and/or ascites is the main predisposing factor for acute respiratory syndrome. Acute pulmonary edema and severe persistent metabolic acidosis from severe shock are the other factors predisposing to acute respiratory distress syndrome (ARDS). Factors leading to fluid overload are aggressive administration of IV fluids; incorrect use of hypotonic solution in place of isotonic solutions; use of large volumes of intravenous fluid in patients with no severe bleeding; inappropriate transfusion of fresh frozen plasma, platelet concentrates, and cryoprecipitate; and intravenous fluids continued beyond the resolved plasma leakage phase (after defervescence). Primary comorbid diseases include congenital or ischemic heart disease and chronic lung or renal disorders.

Clinical Features

- *Respiratory insufficiency*: Due to fluid overload, leads to acute respiratory distress, difficulty in breathing
- *Tachypnea*: Increased respiratory rate
- Wheezing >> crepitations
- *Abdominal distension*: Ascites
- Raised jugular venous pressure
- *Signs of pulmonary edema*: Cough with pink or frothy sputum
- Crepitations
- Cyanosis
- *Signs of irreversible shock*: In heart failure with predisposing hypovolemia

Investigations

- *Chest X-ray*:
  - Pleural effusion
  - Cardiomegaly
  - Upward displacing of diaphragm—due to ascites
  - Varying degrees of bat's wing appearance
  - Kerley B lines
- ECG—detection of arrythmias, ischemic changes
- Arterial blood gas analysis
- *ECHO-2D*: In order to elicit regional wall abnormality, presence of clots, vegetations, hypokinesia, ventricular hypertrophy
- Cardiac enzymes

Management

In order to relieve respiratory distress, oxygen therapy should be started immediately. Intravenous fluids must be stopped to allow redistribution of fluid into the intravascular space from pleural and peritoneal cavities. This enables dieresis and reverts pleural effusion, thereby decreasing ongoing respiratory distress. Fluids can be stopped when signs of decreased or nil plasma leakage is evident with stable hemodynamic vitals including systolic blood pressure, normal pulse pressure, and adequate peripheral perfusion. Fluid therapy can be stopped when hematocrit levels decrease to baseline with good pulse volume, adequate urine output, and no signs of fever for 24–48 hours.

- IV fluids can be stopped if the patient is maintaining normal blood pressure, pulse pressure, and hematocrit levels after 24–48 hours. If required, oral or intravenous furosemide can be started at 0.1–0.5 mg/kg/dose once or twice daily or an infusion of 0.1 mg/kg/h. Evaluate serum potassium levels and treat any abnormalities mainly ongoing hypokalemia.
- In case a patient is maintaining stable vitals during the first 24–48 hours, it is advisable to regulate the intravenous fluids according to the patient's response. Gradual and timely tapering of fluids must be followed. Avoid use of diuretics during this period as they cause decrease in intravascular volume.
- Patients with unstable vitals and persistent decreased hematocrit levels elicit signs of occult bleeding. Immediately start fresh whole blood transfusion at an adequate rate.
- Patients with unstable vital signs and elevated hematocrit levels should obtain small doses of bolus of colloid fluid solution.

SUMMARY

Over the past 50 years the world has seen large increases in the rates of dengue fever. Dengue fever is a mosquito-borne infection caused by the dengue virus commonly a disease of the tropics and subtropics geographic area and many cases are diagnosed among returning travelers in all areas of the world. Symptoms include fever, headache, muscle and joint pains, and a characteristic skin rash. Sometimes the disease may progress into life-threatening dengue hemorrhagic fever, which manifests as bleeding, thrombocytopenia, and leakage of blood plasma, or into dengue shock syndrome, in which life-threatening hypotension occurs.

Most cases can be managed by supportive therapy with oral rehydration and close follow-up. Judicious use of intravenous fluids is required to maintain perfusion and sufficient urinary output. Dengue may progress to severe disease requiring blood transfusions and admission for intensive care. Prevention currently depends upon reducing the habitat of the vector; *Aedes aegypti*, and avoiding its bite. Habitat reduction involves decreasing mosquitoes access to stagnant bodies of water or, if that is not possible, applying insecticide. While efforts are being made to develop a vaccine.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Malaria

Sahanya Ramesh Shetty, Neeraj Mangla, Devendra Richhariya

INTRODUCTION

Malaria is a parasitic infection that is preventable and treatable. In some cases, severe malaria progresses into cerebral malaria and sometimes death. Malaria is a clinical condition affecting the immune system causing hemolytic changes in systemic circulation. Malaria has been a major disease affecting large sections of society for a long time. Reference to protozoan infections can be traced back to writings from Hippocrates and numerous mythological and biblical passages. The main objective of treatment includes the removal of the parasite from the patient's blood rapidly and effectively. This will further help in prevention of progression of the disease and its severity. Complete cure is not determined; however, early prevention and diagnosis can provide aid in recovery and complete remission. Some critical cases, due to lack of medical care attained, may progress to uncomplicated malaria and to severe disease or death. In chronic states of long-standing malaria, due to prevalent malarial transmission around, malaria-related anemia develops. Although treatment is definitive and clear, malaria has been a cause of serious concern among developing and developed countries.

INCIDENCE

According to the World Health Organization (WHO) studies, there has been a global decline from 71 to 57 cases at risk per 1,000 population at risk during the period of 2010–2018. Between 2014 and 2018, the rate of decline slowed down dramatically reducing to 57 cases per 1,000 population at risk in 2014 and remained at a stagnant level till 2018. However, the Southeast Asian region has shown a fall in incident rate from 17 cases of disease per 1,000 population at risk in 2010 to 5 cases in 2018. This accounted for a total of 70% decrease in the number of malarial cases per 1,000 population. In the African region, the case incidence decreased from 294 in 2010 to 229 in 2018, with a 22% reduction. In the region of Americas, a rise was observed during this period due to increase in malaria transmission in the Bolivarian Republic of Venezuela. During 2015 and 2018, there were only 30 countries which were endemic. This also marked a reduction in case incidence by a large number and progressing to a reduction of 40% or more by 2020. Of the four subtypes, *Plasmodium falciparum* is the most prevalent parasite for malaria in African region, accounting for 99.7% of estimated malarial cases in 2018. In the South-eastern Region, it accounted for 50% of the total malaria cases, 71% in the Eastern Mediterranean Region, and 65% in the Western Pacific Region. In the South-east Asian region, when compared on the global front, there is a huge *Plasmodium vivax* burden with majority being in India at 47%. In the American region, it accounts for 75% cases.

CAUSATIVE AGENT, TYPES, AND LIFE CYCLE

Malaria is caused by protozoa of the genus *Plasmodium*. *Vector*: Mode of transmission is by the bite of a female mosquito of the genus *Anopheles* on humans. It comprises four species that affect the human population:

1. *P. falciparum*
2. *P. vivax*
3. *P. ovale*
4. *P. malariae*

Among the four species of *Plasmodium*, *P. falciparum* and *P. vivax* account for the majority of the cases, of which *P. falciparum* leads to causation of the most severe form of the disease.

Life Cycle

The life cycle of *Plasmodium* incudes two host (mosquito and human) and various stages.

Infective: The uninucleate, lancet-shaped sporozoite (~1 × 7 μm). Sporozoites are produced as a result of sexual reproduction in the midgut of vector *Anopheles* mosquitoes and migrate to the salivary gland. During a blood meal of an infected *Anopheles* mosquito, there is transmission of sporozoites from the saliva of vector to the small blood vessels of the human. On entering the systemic circulation of human (second host), there is uptake of protozoans to liver parenchymal cells. This occurs within 30 minutes of inoculation. After the uptake, the parasite develops into a multinucleate spherical schizont within the liver, comprising 2,000–40,000 uninucleate merozoites. This process is called exoerythrocytic schizogony (liver phase). This period takes 5–21 days and is dependent on the type of *Plasmodium*.

In *P. vivax* and *P. ovale*, the maturation phase can take up to 1–2 years and at this time dormant parasites are called hypnozoites. The life cycle of *Plasmodium* is summarized in **Flowchart 1**. Microscopic features of early trophoblast (*vivax and falciparum*) and mature stages of *vivax and falciparum* are shown in **Figures 1A** and **B**.

PATHOPHYSIOLOGY

The inevitable nature of the mature schizonts results in their eruption and release of large numbers of merozoites into systemic circulation. When the merozoites enter the blood stream, they infect the red cells. There is a development or maturation of merozoites into either an erythrocytic stage schizont or a spherical or banana-shaped uninucleate gametocyte. This mature erythrocytic schizont contains few merozoites. This schizont further ruptures and releases merozoites that further infect other erythrocytes. This enables to determine a time period between the release of merozoites and further infestation of erythrocytes and can help in classic periodicity of fever in malaria. The spherical or banana-shaped gametocyte presents the sexual stage of *Plasmodium*. It is highly infectious when mosquitoes ingest it during their blood meal. During the cycle within the mosquito, gametocytes develop into females (macrogametes) and males (microgametes). They further mature after 2–3 weeks into sporozoites that are infectious to human. It can be concluded that the time interval between development of sporozoites and infection of a mosquito must be 2–3 weeks and that is essential for the mosquito to be alive to infect.

CLINICAL FEATURES

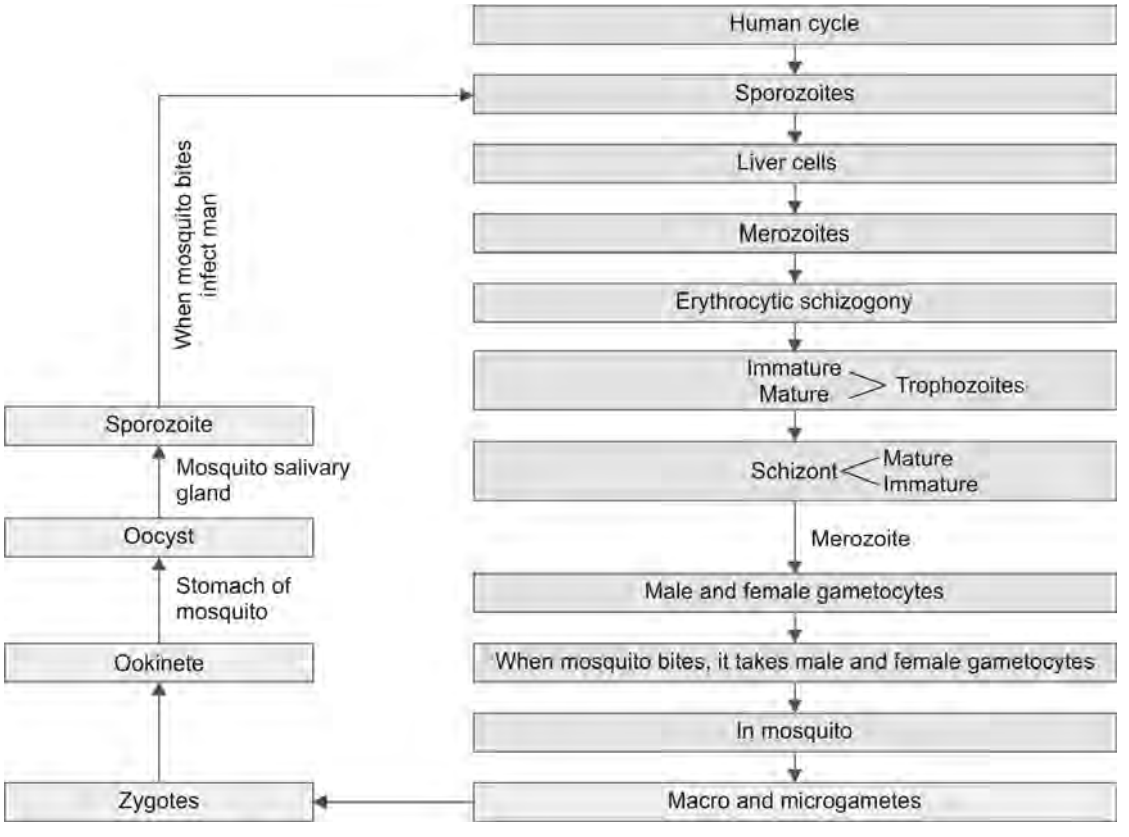
Nonspecific: Lack of sense of well-being, headache, fatigue, abdominal discomfort, muscle ache, nausea, vomiting, and orthostatic hypotension.

Classic malaria paroxysm: Fever spikes with chills and rigors at a regular interval (often >40°C). Other than fever, there are many clinical features such as mild anemia and splenic enlargement (splenic enlargement is common in otherwise healthy people living in malaria-endemic areas; it reflects repeated infection). Mild jaundice common in uncomplicated malaria resolves in 1–3 weeks.

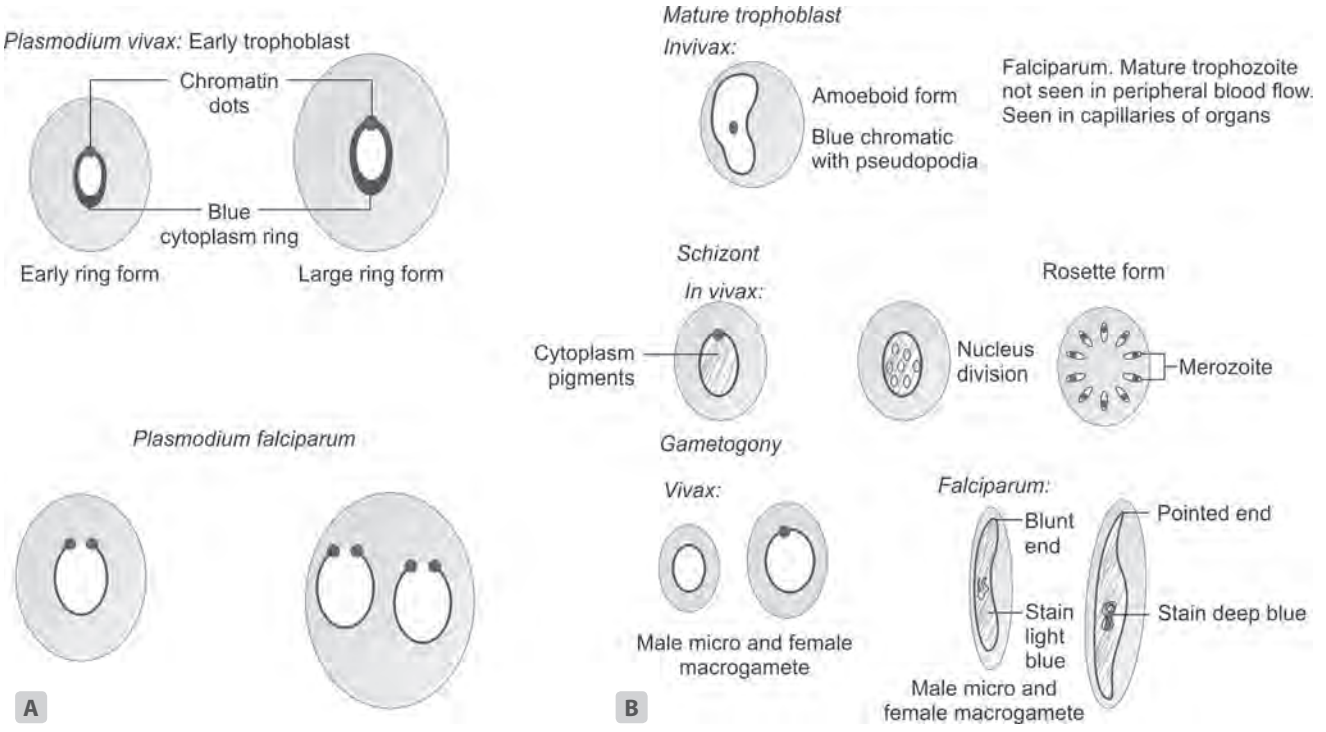
Severe falciparum malaria: Criteria for defining severe malaria are: unarousable coma (cerebral malaria), acidosis, severe normochromic normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome (ARDS), hypoglycemia, hypotension, shock, disseminated intravascular coagulation (DIC), convulsion, hemoglobinuria, others (hyperparasitemia-parasitemia >5%), jaundice (serum bilirubin >3 mg/dL). Clinical features of malaria are summarized in **Table 1**.

INVESTIGATION AND DIAGNOSIS

A large spectrum of diseases are present in differential diagnosis of febrile illness. One must always consider the possibility of malaria in patients with a history of travel even if the patient has been on prophylaxis for malaria. This can help reduce the morbidity and mortality rates in patients with



FLOWCHART 1: Life cycle of *Plasmodium*.



FIGS. 1A AND B: (A) Microscopic features of early trophoblast (*vivax* and *falciparum*); (B) Mature stages of *vivax* and *falciparum*.

TABLE 1: Clinical features of malaria.

Type of malaria	*Uncomplicated malaria*	*Severe malaria*	*Malaria relapses*
	Classical (but rarely observed) malaria attack lasts for 6–10 h	Severe malaria is a medical emergency and should be treated urgently and aggressively. It occurs when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism	In *P. vivax* and *P. ovale* infections, patients having recovered from the first episode of illness may suffer several additional attacks ("relapses") after months or even years without symptoms. Relapses occur because *P. vivax* and *P. ovale* have dormant liver stage parasites ("hypnozoites") that may reactivate. Treatment to reduce the chance of such relapses is available and should follow treatment of the first attack
Stages of febrile illness	• A cold stage (sensation of cold, shivering) • A hot stage (fever, headaches, vomiting, seizures in young children) • Finally a sweating stage (sweats, return to normal temperature, tiredness)		
Clinical presentation	• Fever • Chills • Sweats • Headaches • Nausea and vomiting • Body aches • General malaise	Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities	Neurologic defects may occasionally persist following cerebral malaria, especially in children. Such defects include trouble with movements (ataxia), palsies, speech difficulties, deafness, and blindness

Continued

Continued

Type of malaria	*Uncomplicated malaria*	*Severe malaria*	*Malaria relapses*
Physical findings	• Elevated temperatures • Perspiration • Weakness • Enlarged spleen • Mild jaundice • Enlargement of the liver • Increased respiratory rate	• Cerebral malaria, with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities • *Severe anemia* due to hemolysis (destruction of the red blood cells) • *Hemoglobinuria* (hemoglobin in the urine) due to hemolysis • *Acute respiratory distress syndrome* (ARDS), an inflammatory reaction in the lungs that inhibits oxygen exchange, which may occur even after the parasite counts have decreased in response to treatment • *Abnormalities in blood coagulation* • *Low blood pressure* caused by cardiovascular collapse • *Acute kidney injury* • *Hyperparasitemia*, where more than 5% of the red blood cells are infected by malaria parasites • *Metabolic acidosis* (excessive acidity in the blood and tissue fluids), often in association with hypoglycemia • *Hypoglycemia* (low blood glucose). Hypoglycemia may also occur in pregnant women with uncomplicated malaria or after treatment with quinine	• Recurrent infections with *P. falciparum* may result in severe anemia • Malaria during pregnancy (especially *P. falciparum*) may cause severe disease in the mother and may lead to premature delivery or delivery of a low birth weight baby • On rare occasions, *P. vivax* malaria can cause rupture of the spleen • *Nephrotic syndrome* (a chronic, severe kidney disease) can result from chronic or repeated infections with *P. malariae* • *Hyper-reactive malarial splenomegaly* (also called "tropical splenomegaly syndrome") occurs infrequently and is attributed to an abnormal immune response to repeated malarial infections. The disease is marked by a very enlarged spleen and liver, abnormal immunologic findings, anemia, and a susceptibility to other infections (such as skin or respiratory infections)
Diagnosis	Demonstration of parasites in the blood, usually by microscopy. Additional laboratory findings may include mild anemia, mild decrease in blood platelets (thrombocytopenia), elevation of bilirubin, and elevation of aminotransferases		

a decreased immune response, such as children, pregnant women, or patients undergoing chemotherapy. Complete history and primary evaluation are essential to determine the source or route of transmission. *There is often a confusion between P. knowlesi and P. falciparum or P. malariae* at different stages. Clinical correlation is helpful in these stages as *P. malariae* infection is not generally severe and may cause only uncomplicated malaria. However, *P. falciparum* and *P. knowlesi* are determinants of severe malaria. According to updates from the National Vector Borne Disease Control Programme (NVBDCP), India, it is recommended to start the first loading dose of chloroquine only for the areas where neither microscopy nor rapid drug test is available for the first 24 hours.

Diagnosis of malaria is based on clinical suspicion and laboratory confirmation of parasitemia and microscopic examination of peripheral blood smear (PBS). Confirmation is done by thin and thick film (more reliable when parasitemia is very low). Nothing is found better than direct examination of smear, but it is time consuming, needs infrastructure, and single negative PBS cannot rule out malaria. To improve the measures for diagnosing malaria, various rapid diagnostic testing are available for malaria (**Table 2**).

TABLE 2: Rapid diagnostic tests for malaria.

Microscopic methods	• Acridine orange staining • QBC testing
Molecular methods	• DNA and rRNA probes • Polymerase chain reaction (PCR)
Antigen detection	• HRP2 antigen detection • Parasite F test • Parasite LDH detection
Other methods	• Immunochromatographic test

(HRP2: histidine-rich protein 2; LDH: lactate dehydrogenase; PCR: polymerase chain reaction; QBC: quantitative buffy coat)

TREATMENT OF UNCOMPLICATED MALARIA

Mostly early intervention and treatment have proven to improve the prognosis of the patient (**Table 3**).

P. vivax: Chloroquine for 3 days followed by primaquine (PQ) for 2 weeks. PQ is contraindicated in infants, patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and pregnant women. Ask patients to watch out for dark-colored urine or hematuria, discoloration of peripheries, and any signs of cyanosis. In such events, primaquine must be withheld.

Treatment of *P. vivax* Malaria

The drug schedule for treatment of *P. vivax* malaria is as follows:

- *Chloroquine*: 25 mg/kg body weight divided over 3 days, i.e., 10 mg/kg on day 1, 10 mg/kg on day 2, and 5 mg/kg on day 3.
- *Primaquine*: 0.25 mg/kg body weight daily for 14 days. PQ is contraindicated in infants, pregnant women, and individuals with G6PD deficiency. A 14-day regimen of PQ should be given under supervision.

Treatment of *Plasmodium falciparum*

Treatment involves a combination of artesunate (AS) for 3 days with sulfadoxine–pyrimethamine (SP) for 1 day. In addition, a single dose of PQ is added on day 2.

Artemisinin-based combination therapy with sulfadoxine–pyrimethamine (ACT-SP): Artesunate (AS), available as 50-mg tablet, is given for 3 days, and SP tablets, containing 500-mg sulfadoxine and 25-mg pyrimethamine, are given for 1 day. In addition, PQ large tablets should be given on the second day. ACT-SP—AS 4 mg/kg body weight daily for 3 days plus sulfadoxine (25 mg/kg body weight) and pyrimethamine 1.25 mg/kg body weight on the first day.

Pregnant women with uncomplicated *P. falciparum* should be treated as follows:

- *First trimester*: Quinine—quinine salt 10 mg/kg, three times daily for 7 days; pregnant female should eat regularly, to avoid hypoglycemia while on quinine treatment. Artesunate-based combination therapy is not to be given in the first trimester of pregnancy.
- *Second and third trimesters*: Artesunate-based combination therapy is indicative.

Note: PQ is contraindicated in pregnant woman. In cases where timely diagnosis of malaria and/or rapid diagnostic testing, suspected cases of malaria are to be treated with a course of chloroquine, until confirmatory reports are awaited. In the North-Eastern states of India, it is recommended to use co-formulation of tablet artemether 20 mg and lumefantrine 120 mg as per the age-specific dose schedule. It is recommended to use the co-formulated tablet of artemether (20 mg) and lumefantrine (120 mg) (ACT-AL) as per the age-specific dose schedule.

Treatment of Mixed Infections

P. vivax + *P. falciparum cases*: All mixed infections should be treated with a full course of ACT and PQ 0.25 mg/kg body weight daily for 14 days. In the north-eastern states, treat with age-specific ACT-AL for 3 days + PQ 0.25 mg/kg body weight daily for 14 days. In other states: ACT-SP for 3 days + PQ 0.25 mg/kg body weight daily for 14 days.

Treatment of P. ovale and P. malariae: In India, these species are very rarely found in few places. *P. ovale* should be treated as *P. vivax*, and *P. malariae* should be treated as *P. falciparum*.

Treatment of mixed infections: All cases of mixed infection are to be treated as *P. falciparum* as per the drug policy applicable in the area plus PQ for 14 days.

TABLE 3: Summary of treatment of malaria.

Drug-sensitive malaria		
	Oral treatment for uncomplicated malaria	Parenteral treatment for severe malaria
Chloroquine	10-mg base/kg followed by 5 mg/kg at 12, 24, 36 hours. Total 25 mg/kg. Add primaquine 0.25 mg/kg or 15 mg/day for 14 days for radical cure	3.5 mg/base/kg IM or subcutaneously every 6 h. Total dose 25 mg/kg
Sulfadoxine– pyrimethamine	• 20 mg/kg sulfadoxine, 1 mg/kg pyrimethamine (single oral dose—three tablets) • 1 tablet = 500 mg sulfadoxine + 25 mg pyrimethamine	
Drugs-resistant malaria		
Mefloquine	15 mg/kg single dose, second dose 10 mg/kg	
Quinine	10 mg/kg every 8 hourly with tetracycline 4 mg/kg QID or doxycycline 3 mg/kg OD for 7 days	20 mg/kg IV loading dose over 4 h followed by 10 mg/kg over 2–8 hours every 8 hourly
Artesunate	In combination with total 25 mg of mefloquine per kg, give a total of 10–12 mg/kg in divided doses over 3–5 days	2.4 mg/kg IM or IV followed by 1 mg/kg. Artesunic acid 1 ampoule = 60 mg dissolved in 5% dextrose given by IV/IM bolus
Artemether	Orally the same regimen as artesunate	3.2 mg/kg IM. Then 1.6 mg/kg daily, not to be given IV (1 ampoule = 80 mg)
Halofantrine	8 mg/kg repeated at 6 and 12 h, repeat regimen 1 week later in an immunodeficient patient	

Drug Resistance

Drug resistance is the ability of a parasite stain to survive or multiply despite administration and absorption of drugs given in the doses equal to or higher than those recommended but in the limit of the tolerance of the subject.

WHO Grading of Drug Resistance

- Sensitive—clearance of parasitemia within 7 days of initiation of therapy.
- Low grade—clearance of parasitemia with recrudescence.
- High grade (R-I)—75% but <100% parasites are clear within 7 days of initiation of therapy.
  High grade (R-II)—parasite count does not fall by >75%.

Drug failure: Absence of drug action after administration of a normally effective dose caused by improper ingestion or deficient absorption or unusual rate of rapid excretion.

RADICAL TREATMENT

Radical treatment: Radical treatment is primaquine administration to all confirmed cases of malaria. Tissue schizonticidal activity of primaquine therapy (a 2-week therapy in *P. vivax* malaria) completely cures the infection in the host and thereby prevents relapses. A single dose of primaquine destroys the gametocytes in *P. falciparum* malaria, thereby preventing the spread of the infection into the mosquito.

All proven cases of malaria (a 2-week course in *P. vivax* malaria and a single dose in *P. falciparum* malaria) should be given primaquine. In the event of uncomplicated cases of *P. falciparum* and *P. vivax* malaria, it is preferred to follow treatment per orally. Hence, it is imperative that primaquine is started in all proven cases of malaria. It is advisable to maintain a 2-week course for *P. vivax* malaria and a single-dose therapy in *P. falciparum* malaria.

CHEMOPROPHYLAXIS TO TRAVELERS

Travelers who are planning to visit a malaria-endemic area should start taking an antimalarial drug 1 week before departure and continue for 4 weeks after leaving the endemic area. Recommended prophylactic drugs depend on the knowledge of the local pattern of *Plasmodium* drug sensitivity. Chemoprophylaxis is never entirely reliable. Malaria should be taken into consideration as a differential diagnosis of fever in a patient who has traveled to an endemic area and even if he/she has been taking prophylaxis. Mefloquine remains the prophylactic agent of choice. Doxycycline (can be used in <8 years and in pregnant women) and atovaquone + proguanil combination are used as an alternative to mefloquine. Chloroquine remains the drug of choice in preventing drug-sensitive malaria. It is safe in pregnancy also. Pregnant women should avoid traveling to an endemic area (chloroquine or proguanil or intermittent SP):

- Chloroquine—300-mg base (500 mg salt) orally once a week
- Mefloquine—228-mg base (250 mg salt) orally once a week
- Doxycycline—100 mg orally once a day
- Primaquine—start only after testing G6PD deficiency 15 mg base daily for 14 days
- Atovaquone + proguanil 250/100 mg once daily
- Pyrimethamine-sulfadoxine—in areas of chloroquine-resistant malaria. Three tablets single dose (75 mg + 1,500 mg).

TREATMENT OF SEVERE MALARIA

Severe malaria is considered an emergency, and treatment should be started as per the severity and associated complications which can be best decided by the treating physicians. A blood smear sample should be taken. Give a parenteral dose of artemisinin derivative or quinine in suspected severe/cerebral malaria cases before admitting or referring patients, and send the case sheet, details of treatment history, and blood slide with the patient to the higher center. Parenteral artemisinin derivatives or quinine should be used irrespective of the chloroquine-resistance status of the area with one of the options given in **Box 1**. After parenteral artemisinin therapy, patients should receive a full course of oral artesunin-based combination therapy for 3 days. After parenteral quinine therapy, the patient should continue with oral quinine 10 mg/kg body weight three times a day for 7 days plus doxycycline 3 mg/kg

BOX 1: Treatment of severe malaria.

Initial parenteral treatment for at least 48 hours: Choose one of the following four options:

1. *Quinine*: 20-mg quinine salt/kg body weight on admission (IV infusion or divided IM injection) followed by a maintenance dose of 10 mg/kg 8 hourly; the infusion rate should not exceed 5 mg/kg/h. Loading dose of 20 mg/kg should not be given, if the patient has already received quinine
2. *Artesunate*: 2.4 mg/kg IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day or
3. *Artemether*: 3.2 mg/kg IM given on admission, then 1.6 mg/kg per day or
4. *Arteether*: 150 mg daily IM for 3 days in adults only (not recommended for children)

Supportive treatment:

- Plasma exchange
- Measure blood sugar every 4–6 hourly
- Parasite count and hematocrit every 6–12 hourly
- Blood transfusion
- Management of fluid balance

Follow-up treatment, when the patient can take oral medication following parenteral treatment:

- Quinine 10 mg/kg three times a day with doxycycline 100 mg once a day or clindamycin in pregnant women and children under 8 years of age, to complete 7 days of treatment
- Full oral course of area-specific ACT
- *In north-eastern states*: Age-specific ACT-AL for 3 days + PQ single dose on the second day
- *In other states*: Treat with ACT-SP for 3 days + PQ single dose on the second day

(ACT-AL: co-formulated tablet of artemether and lumefantrine; ACT-SP: artemisinin-based combination therapy with sulfadoxine–pyrimethamine; PQ: primaquine)

body weight once a day or clindamycin 10 mg/kg body weight 12-hourly for 7 days (doxycycline is contraindicated in pregnant women and children under 8 years of age). Pregnant women (any trimester) of severe malaria can be treated with artemisinin derivatives (do not have a risk of hypoglycemia like quinine). Continue with parenteral treatment for a minimum of 48 hours and then switch to oral therapy (if the patient accepts orally). Mefloquine is associated with neuropsychiatric complications and should be avoided in cerebral malaria.

CHRONIC COMPLICATIONS OF MALARIA

Tropical splenomegaly (Hyperreactive malarial splenomegaly)—chronic and repeated malaria infection causes splenomegaly and hepatomegaly, and the patient presents with abdominal mass and dragging sensation of abdomen. Sharp abdominal pain is suggestive of peri-splenitis. Anemia and pancytopenia in blood picture is significant findings. The patient is vulnerable to respiratory and skin infections.

Quartan malaria nephropathy—chronic and repeated malaria infection by *P. malariae* gives rise to an immune complex-mediated injury to renal glomeruli and histologically presents as focal and segmental glomerulonephritis with a slit in the capillary basement membrane.

Burkitt's lymphoma and Epstein–Barr virus (EBV) infection—immunosuppression induced by malaria infection may give rise to infections of lymphoma virus. Burkitt's lymphoma is strongly associated with EBV infection.

CEREBRAL MALARIA

Cerebral malaria is a manifestation of severe falciparum malaria. The condition is described in *P. vivax* or mixed infection of *P. falciparum* and *P. vivax*. Incidences are increasing in India in the areas (northeast region, Gujarat, Andaman, and Rajasthan) where chloroquine-resistant malaria is highly prevalent. Three benign forms of malaria—*vivax*, *ovale*, and *malariae*—invade only old red cells and reticulocytes and are able to produce parasitemia not >2%. On the other hand, *falciparum* invades/infects erythrocytes of all ages. A high level of parasitemia and a large number of merozoites are released to infect hepatocytes. In *falciparum* malaria, only younger ring forms are present in peripheral blood. Other stages of life cycle remain sequestrated in the internal organ of body (escape the host defense mechanism). Thus, severe and complicated malaria is produced only by *P. falciparum*.

Criteria for Diagnosing Cerebral Malaria

Unarousable coma after exclusion of encephalitis and bacterial meningitis: Persistence of coma for >6 hours after generalized seizure and confirmation of *P. falciparum* parasitemia, along with the presence of features of severe malaria, such as severe normocytic anemia, hemoglobin < 9 g, parasitemia > 10,000/μ, renal failure, pulmonary edema, circulatory collapse, DIC, metabolic acidosis, and hemoglobinuria. Partial or generalized tonic-clonic seizures (GTCS) are common. Whenever cerebral malaria is suspected, confirm with parasitological diagnosis. Cerebral malaria can be suspected even if PBS is negative. Presence of malaria pigments in monocytes is a useful indicator of diagnosis of malaria, especially in the absence of peripheral parasitemia and in an anemic child. In a patient with severe *falciparum* malaria, >2% of total erythrocytes are parasitized.

Neuro-ophthalmological Signs in Cerebral Malaria

Disorders of conjugate gaze nystagmus are common findings. Papilledema is rare. Corneal and conjunctival reflexes remain intact. Pupils are symmetrical and react to light. Motor system examination findings—upper motor signs, increase in muscle tone and deep tendon reflexes, and presence of patellar and ankle clonus—are observed. In advanced stages, opisthotonos posturing may be observed; posturing may be decerebrate or decorticate. Deep breathing hypoventilation with extensor posturing with periodic respiration features is suggestive of transtentorial herniation. Other commonly associated conditions are summarized in **Box 2**. The mortality rate for severe malaria and cerebral malaria is high (15–20%); deep coma is an important indicator for adverse prognosis. Other prognostic indicators are given in **Table 4**. The patients who survived developed long-standing neurological sequelae and postmalaria neurological syndrome (**Table 5**).

BOX 2: Common associated conditions with severe and cerebral malaria and suggested antimalarial drugs.

Commonly associated conditions:

- Hypoglycemia
- Raised intracranial pressure
- Anemia
- Lactic acidosis
- Hypoxia
- Renal failure
- Bleeding disorders
- Chest infections
- Gram negative sepsis

Associated systemic complications and their management:

- Blood transfusion/blood products for anemia, coagulopathy
- Correction of hypovolemia for shock
- Paracetamol sponging fanning for hyperpyrexia
- Dialysis for renal failure
- Bolus glucose followed by infusion for persistent hypoglycemia
- Fluid and electrolyte maintenance
- Fluid restriction and diuretics for pulmonary edema

Suggested antimalarial and doses:

- *Quinine*: 20 mg/kg bolus infusion over 4–6 h followed by 10 mg/kg IV (over 6 h) every 8 hourly
- *Artesunate*: 2.4 mg/kg IV or IM given on admission (time = 0), then at 12 and 24 h, then once a day
- *Artemether*: 3.2 mg/kg IM given on admission, then 1.6 mg/kg per day for 6 days
- *Quinidine*: 10 mg/kg IV over 1 hour followed by 0.1 mg/kg/min IV with ECG monitoring

TABLE 4: Poor prognostic indicators or cerebral malaria.	
Clinical indicators of poor prognosis	• Deep coma • Repeated convulsion • Absent corneal reflexes • Decerebrate rigidity • Organ dysfunction • Retinal hemorrhage • Age < 3 years
Laboratory indicators of poor prognosis	• Parasitemia > 5% • Peripheral schizonts • Leukocytosis • PCV < 20% • Anemia < 7 g • Hypoglycemia < 40 mg • BUN > 60 mg/dL • Total bilirubin > 2.5 • Aminotransferases >3 times

(BUN: blood urea nitrogen; PCV: pneumococcal conjugate vaccine)

TABLE 5: Neurologic sequelae of cerebral malaria.	
Neurologic sequelae	• Hemiplegia • Cortical blindness • Aphasia • Ataxia • Tremors • Hearing defect • Repeated convulsion • Behavioral abnormalities • Spastic quadriplegia
Postmalarial neurologic syndrome	• Acute confusional state or psychosis • Generalized seizures • Action and/or postural tremors • Delayed and self-limiting cerebral ataxia • Severe steroid-responsive encephalopathy • Motor aphasia • Generalized myoclonus • Cerebral ataxia

SUMMARY

Malaria has been a cause of serious concern among developing and developed countries. It has been a major disease affecting large sections of society for a long time. Malaria is a parasitic infection that is preventable and treatable. Treatment is definitive and clear. The main objective of treatment includes the removal of the parasite from the patient's blood rapidly and effectively. This will further help in prevention of progression of the disease and its severity. Early prevention and diagnosis can provide aid in recovery and complete remission. Clinically, malaria damages the immune system. In some cases, severe malaria progresses into cerebral malaria and sometimes death. In some cases, it may progress to severe categories due to lack of medical care and may progress to complicated malaria and to severe disease or death. In chronic states of long-standing malaria, due to prevalent malarial transmission around, malaria-related anemia can develop.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Tuberculosis

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INTRODUCTION

Tuberculosis (TB) tops the list of infections that cause death and is also listed among top 10 causes of death worldwide. More than one-third of the world's population has had TB infection, but disease and death occurs disproportionately in those who are immunocompromised and at extremes of the age spectrum. Rest of the infected but immunocompetent population harbors TB in dormant or latent form for many years. TB can produce disease in any organ of the body and thus has innumerous manifestations. In emergency room (ER), TB can present with acute or chronic manifestations involving almost any organ or system. Therefore, in high-burden countries like India, TB always remains a possibility, either primary or an underlying cause, in all patients. An intelligent and focused investigation often reveals the underlying infection by TB and the newer diagnostic methods have made it possible to diagnose TB in a matter of few hours. If treated before it causes significant damage to the organs or systems, it is curable but the emergence of resistance in TB bacillus to the first- and second-line drugs is a great cause of concern throughout the world.

ETIOLOGY/CAUSES

The agent causing TB is *Mycobacterium tuberculosis* (*Mtb*) an acid-fast bacillus (**Box 1**) and humans are the only natural host for *Mtb*. It is an obligate aerobe and survives in humans by disseminating and then lying dormant in organs with high blood flow and oxygen concentration such as lungs, renal cortices, meninges, vertebrae, and epiphyses of long bones for many years.

BOX 1: Etiological agent for tuberculosis.

Etiological agent: Tuberculosis
Domain: Bacteria
Phylum: Actinobacteria
Class: Actinobacteria
Order: Actinomycetales
Family: Mycobacteriaceae
Genus: Mycobacterium
Species: Mycobacterium tuberculosis

PATHOPHYSIOLOGY

Mycobacterium tuberculosis has developed mechanisms to survive within humans by evading the immune response and lie dormant in humans waiting patiently for decades for an opportunity to overcome the immune system and then spread to the other human hosts. *Mtb* enters the macrophages and alters its functions to survive and replicate inside macrophages. The natural history of TB in humans has four phases; replication, dissemination, latency, and reactivation.

In most humans, the cell-mediated immunity quickly controls the replicating *Mtb* and surrounds them forming "granulomas" or "tubercles". Some of the *Mtb* reach local lymph nodes where also they get surrounded by immune cells. The caseation, necrosis, and calcification is called *"Ghon foci"* while the area of primary scarring and calcification along with the calcified hilar lymph nodes produces what is called the *"Ghon complex"*.

Spread is initiated when *Mtb* proliferates in lungs leading to liquefactive necrosis as a result of immune cells trying to contain the *Mtb*. The liquefied material from lungs escapes to the environment in the form of tiny cough droplets containing *Mtb*. Inhalation of infected droplets may establish *Mtb* in the new susceptible hosts. The liquefactive necrosis in various organs can occur either during primary infection called primary TB or when *Mtb* reactivates after a latent period of dormancy called secondary TB.

CLINICAL PRESENTATION

Mycobacterium tuberculosis can get disseminated widely through infected macrophages and thus can produce disease in any organ or system. Still, the most common organ to develop disease is the lungs because of their higher oxygen content and blood flow. The classical presentation is pulmonary TB (PTB) presenting with prolonged fever (evening rise), productive cough, hemoptysis, night sweats, weight loss, fatigue, and malaise.

TABLE 1: Common extrapulmonary tuberculosis.	
Effusions	Pleural, ascitic, joint, and pericardial
Neurological	Meninges, brain parenchyma, and spinal cord
Musculoskeletal	Bones, joints, muscles, and vertebrae
Urogenital	Kidneys, ureters, bladder, and genital organs
Abdominal	Intestinal, peritoneal, esophageal, mesenteric, and hepatobiliary
Lymphatic	Lymph nodes, splenic, bone marrow, thymic ophthalmological, otorhinolaryngeal, and dermatological

Equally important is the common extrapulmonary tuberculosis (EPTB) presenting as **Table 1**. The clinical presentation of EPTB will be organ specific. The EPTB patients are mostly noncontagious, still they have a high morbidity and mortality and are more likely to present with varied complications in the ER. Early recognition and treatment of classical PTB is important from public health perspective, but diagnosis and treatment of EPTB is also important from the patient's perspective.

Features of Concern (Red Flags)

Although TB requires prompt treatment in all patients, but the following are particularly aggressive presentations of TB where a delay in diagnosis can lead to quick loss of life or organs:

Meningoencephalitis (severe new-onset headache and altered sensorium), vertebrospinal (paraparesis), pericarditis (chest pain, elevated jugular pressure, and hypotension), endocarditis (murmurs and continuous high grade fever), and miliary TB (multiple organ dysfunction), PTB with destroyed lungs (hemoptysis and respiratory failure), and ocular TB (loss of vision).

EVALUATION

History

Salient features in history suggestive of TB include any one or more of the following: Cough persisting for >2 weeks, pyrexia of unknown origin >1 week, any episode of hemoptysis, night sweats, and weight loss. Patients with EPTB will have organ-specific complaints and are often missed in initial analysis. Genital TB in females is an important cause of primary infertility. "Night cries" are typically reported in vertebral TB. The tone of paravertebral muscles decreases during sleep and the resulting movement of vertebrae causes intense pain at night. A high index of suspicion and careful examination followed by focused investigation often reveals the underlying diagnosis of EPTB.

Physical Examination

Whenever a diagnosis of PTB is considered, it is advisable to avoid close contact during examination. Patient should be given a triple layer mask and focused examination to record the vitals and provision of necessary supportive care is needed. EPTB is mostly noncontagious and detailed examination should be done. Elicitation of signs in neurotuberculosis helps localize the lesion in brain, meninges, or spinal cord. Similarly bone and joint TB.

Interpretation of Findings

Some specific physical examination findings that should prompt workup for EPTB include matted cervical lymph nodes (more common in young), unilateral pleural effusion (all ages), ascites (in young), meningitis (all ages), blackish discoloration of skin suggestive of adrenal TB, nonhealing ulcers on skin and mucosa (all ages), abdominal lump (intestinal or mesenteric TB), boggy swelling below umbilicus (psoas abscess), vertebral tenderness with deformity (vertebral TB), blurry vision with red eye or headache (ocular TB), and muffled heart sounds with raised jugular venous pressure (pericardial TB).

INVESTIGATIONS

Diagnosis of Pulmonary Tuberculosis

Since PTB is the most common form and is also responsible for spread of TB in community, it should be diagnosed and treated promptly. Properly collected sputum is used for diagnosis.

Ziehl–Neelsen (ZN) staining is the cheapest method to diagnose TB with the help of an acid-fast stain and a microscope. ZN staining has low sensitivity if bacillary load is <10,000/mL in the sample, so may come false negative in cases that have intermittent shedding of bacilli.

Better staining methods include fluorescent stain (auramine-rhodamine) to detect *Mtb* under fluorescent microscope and is easier to screen large number of samples in a shorter time. Fluorescent microscopy is a better screening tool but can give false positives, so all fluorescence positive samples should be confirmed using ZN staining, culture, or nucleic acid amplification methods.

Cartridge-based nucleic acid amplification tests (CBNAATs) have been developed and are in wide use. They have very high sensitivity and low turnaround time of 2 hours. CBNAAT results are positive at a bacillary load of 131 bacilli/mL. CBNAAT is better than microscopy as it gives diagnosis of TB and rifampicin resistance in the same process and it also has higher sensitivity at low bacillary loads.

Culture methods are the gold standard for diagnosis of TB as they can come positive at 10–100 bacilli/mL, but the turnaround time for cultures is high. Solid cultures show *Mtb* growth at 6–8 weeks and liquid cultures show *Mtb* growth earliest at 12–18 days. Cultures must be done in all cases as they help us in doing drug sensitivity analysis and diagnose drug resistant TB.

Chest X-ray

Some patients of PTB do not shed bacilli but have clinical symptoms and lesions on chest X-ray suggestive of PTB. Findings on chest X-ray that have high likelihood of PTB include cavitary lesions that are most common in upper lobes (**Fig. 1**), but can occur anywhere in the lungs and military TB showing small <3 mm nodules in all lung fields. Chest X-ray showing fibrosis in upper lobes suggest old healed PTB.

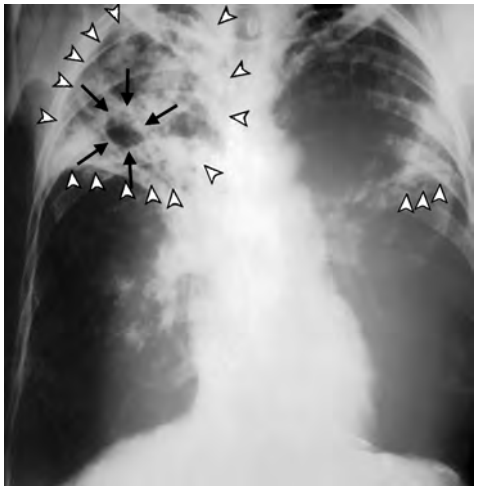


FIG. 1: Chest X-ray showing typical lesions (cavity) in pulmonary tuberculosis involving upper lobes.

Diagnosis of Extrapulmonary Tuberculosis

The samples used for diagnosis of EPTB depend on the site and organ involvement and thus include pus, lymph node aspirate, effusions, tissue, cerebrospinal fluid, urine, synovial fluid, gastric aspirate, and bone marrow.

The methods used to diagnose EPTB are similar to PTB and include ZN staining, fluorescent staining, CBNAAT, and cultures. Since the bacillary load in EPTB samples is not high, CBNAAT has been recommended to be performed in all EPTB samples for a quick diagnosis. CBNAAT can be performed in all samples except urine and blood.

Histopathology

Diagnosis can also be established by examining tissue samples under microscope and presence of caseous necrosis and granulomas on histopathology is highly suggestive of TB.

Imaging in Extrapulmonary Tuberculosis

Radiological investigations such as computed tomography and magnetic resonance imaging has a big role in establishing the diagnosis in many forms of EPTB where bacillary load is less and obtaining sample is not easy, e.g., genitourinary TB, intestinal TB, mesenteric TB, bony TB, suspected tuberculomas, and pericardial effusion.

Adenosine Deaminase in Effusion

If history is suggestive of TB and other causes of effusion are ruled out, presence of elevated levels of adenosine deaminase (ADA) in from pleural or pericardial effusion, ascites, or cerebrospinal fluid is used by many clinicians to establish a diagnosis of EPTB in absence of a definitive diagnosis.

Diagnosis of Latent Tuberculosis

Skin test called *Mantoux test* where we inject 0.1 mL of purified protein derivative intradermally in the forearm and the result is read after 48 and 72 hours by measuring the skin induration at the test site. Induration size of >10 mm is taken as a positive result for Mantoux test, but individuals who have received Bacillus Calmette–Guérin (BCG) immunization for TB prevention are also expected to have positive test. In absence of BCG and active TB, a positive Mantoux test is suggestive of latent TB.

Tuberculosis and Human Immunodeficiency Virus

All patients diagnosed with TB must be worked up for HIV infection. The immune system in HIV-infected individuals does not mount adequate response to TB infection and therefore, the manifestations in these individuals are atypical, e.g., cavitary form of reactivation TB in HIV depends on the CD4 levels and patients with low CD4 levels can have normal chest X-rays with reactivation TB. The Mantoux test is taken as positive at >5 mm induration in HIV-positive patients.

Diabetes and Tuberculosis

All patients of TB must be worked up for diabetes mellitus which is a condition where immune system becomes weak and can lead to reactivation of latent TB.

TREATMENT

Treatment of TB depends upon whether the *Mtb* bacillus is drug sensitive or drug resistant. The drug sensitive forms of *Mtb* infection are treatable using four *primary drugs, i.e., rifampicin (R), isoniazid (H), ethambutol (E), and pyrazinamide (Z)* in a fixed dose combination given on a daily basis for first 2 months followed by rifampicin and isoniazid for next 4 months.

New Case of Tuberculosis

For PTB and most forms of EPTB, 6-month combination therapy 2 (HRZE) + 4 (HRE) of antitubercular [antituberculous treatment (ATT)] drugs is curative unless the *Mtb* is drug resistant. The sputum is tested for presence of *Mtb* at 2 months and at 6 months.

Previously Treated Tuberculosis

Patients who have taken ATT for >1 month in the past and are now diagnosed again with TB. Regimen for treatment of previously treated TB is 2 (HRZES) + 1 (HRZE) + 5 (HRE).

Classification of Resistant Tuberculosis

- *Monodrug-resistant (MR) TB*: Resistance to one of the four first-line drugs H, R, Z, and E
- *Polydrug-resistant (PDR) TB*: Resistance to only one of R or H plus one of Z or E
- *Multidrug-resistant (MDR)TB*: Resistance to both R and H
- *Extensive drug-resistance (XDR):* Resistance to R and H and one of the fluoroquinolones and one of the second-line injectable drugs

If the sputum is found to be resistant to rifampicin at the time of diagnosis using CBNAAT, the sample is then tested using line probe assay (LPA) to detect resistance for both rifampicin and isoniazid. Simultaneously cultures should be established to test sensitivity for second-line drugs. Cultures take few weeks to compete, but LPA can be obtained within hours and can confirm MDR TB.

Treatment of MDR TB includes 6–9 months of intensive phase with injectable kanamycin and oral levofloxacin, ethambutol, pyrazinamide, ethionamide, and cycloserine

followed by 18-month continuation phase with oral levofloxacin, ethambutol, ethionamide, and cycloserine.

Treatment of XDR TB includes 6–12 months of injectable capreomycin, oral moxifloxacin, linezolid, para aminosalicylate, clofazimine, high-dose isoniazid, and co-amoxiclav. The injectables are stopped and 18-month continuation phase contains all other oral drugs.

Bedaquiline and delamanid are new drugs added for drug-resistant TB and have been shown to effectively reduce the total duration of therapy in them.

Additional steroids are needed in some forms of TB, e.g., TB meningitis and pericardial TB.

DISPOSITION

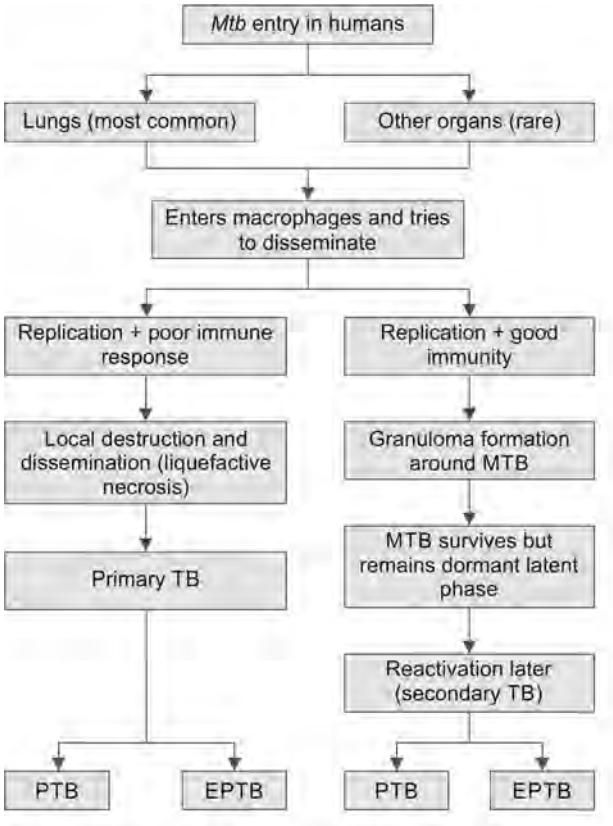
The patients of TB can be diagnosed by two methods:

1. First is by proving the diagnoses using microbiological methods (ZN staining, fluorescent staining, CBNAAT, or culture)
2. Second is clinically diagnosed TB where microbiological diagnosis could not be established. Clinical diagnosis can be based upon history, physical examination, blood investigations, and radiological investigations.

The patients are put on appropriate treatment and then discharged once their condition is stabilized. The duration of ATT should be extended to total 9 months in TB meningitis.

SUMMARY

Tuberculosis is caused by *Mtb* and it is the number one infectious cause of death worldwide. Humans are the only natural host for *Mtb* and its survival mechanism has helped *Mtb* to establish infection in one-fourth of the human population worldwide. In most humans, the infection does not result in disease but the bacillus replicates and disseminates to various organs before the immunity checks its multiplication. The bacillus evades sterilization by the immune system by lying inactive or dormant in multiple organs called latent TB. Later in life when immunity becomes weak, the reactivation TB may occur. To come out of the infected host into the environment, the most common mechanism used by *Mtb* is cough and therefore, lungs are the most commonly infected organs in TB. Liquefactive necrosis in lungs causes cavity formation and the contents of the liquefied parenchyma are expelled out of lungs in cough. These coughed out droplets contain enough bacilli to infect surrounding susceptible hosts. *Mtb* also gets established in various organs during its primary infection which results in EPTB. Almost all organs can show damage due to *Mtb* and is called EPTB. EPTB is an important cause of morbidity and mortality among ER patients. The diagnosis is made after careful history, focused examination, and intelligent investigation. Various methods widely used to detect *Mtb* in human samples include ZN staining, fluorescence microscopy, CBNAAT, and *Mtb* cultures. CBNAAT can detect rifampicin resistance along with the presence of *Mtb* in the samples. LPA can detect rifampicin and isoniazid resistance. To detect resistance to other drugs, we use *Mtb* culture methods but it is takes weeks to months for this process. Diagnosis of TB is not always possible to confirm by microbiological methods and many cases are diagnosed based upon history, physical examination, and investigations like radiology. Once detected the patients should be promptly started on ATT to make them noninfectious. Steroids may be given in addition to the patients of meningitis and pericarditis. The treatment regimen for MDR TB includes one injectable and numerous other second-line drugs and is prolonged for 2–3 years. Newer drugs like bedaquiline and delamanid has reduced the total duration of treatment for up to 1 year in MDR TB. Organ-specific involvements in EPTB need special consideration and red flag signs must be remembered while working in ER so that the diagnosis of TB in life or organ threatening presentations is not missed. **Flowchart 1** summarizes tubercular infection.


Mtb entry in humans
Lungs (most common)
Other organs (rare)
Enters macrophages and tries to disseminate
Replication + poor immune response
Replication + good immunity
Local destruction and dissemination (liquefactive necrosis)
Granuloma formation around MTB
Primary TB
MTB survives but remains dormant latent phase
Reactivation later (secondary TB)
PTB
EPTB
PTB
EPTB
• Diagnosis: Clinical, ZN staining, CBNAAT, and culture or biopsy
• Treatment: Combination chemotherapy
• New case: 6 months 2 HRZE + 4 HRE
• Previously treated case: 2 (HRZES) + 1 (HRZE) + 5 (HRE)

(CBNAAT: cartridge-based nucleic acid amplification test; EPTB: extrapulmonary tuberculosis; MTB: *Mycobacterium tuberculosis*; PTB: pulmonary tuberculosis; TB: tuberculosis; ZN: Ziehl–Neelsen)

FLOWCHART 1: Summary of tuberculosis infection.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Rabies

Ashok Mishra

INTRODUCTION

Management of animal bite cases is mandatory to protect against the risk of rabies which is an acute fatal encephalomyelitis caused by a ribonucleic acid (RNA) virus under the genus *Lyssavirus* and family Rhabdoviridae. It is the most important viral zoonosis of warm-blooded animals such as dogs, cats, and jackals recognized today because of its global distribution, incidence, veterinary, and human health costs and extremely high-case fatality rate.

Most of the mortality due to rabies is from Asia and Africa with 56% of the deaths estimated to occur in Asia and 44% in Africa. Human rabies is mainly caused by dog bites and annual incidence of bite in India is 1.7%. Human rabies is endemic in India. According to a recent the World Health Organization (WHO) estimate, globally 55,000 deaths occur every year; of these, 20,000 (36%) occur in India. In India, there are 17.4 million exposures to animal bites each year. Rabies is transmitted to man usually by bites or licks of rabid animals.

Rabies now features among the 17 identified neglected tropical diseases (NTDs) by the WHO. The acute viral infection is characterized by inflammation of the central nervous system (CNS). When the disease occurs in man, the most characteristic symptom is fear of water (hydrophobia) which develops due to painful spasms of the muscles of deglutition. Rabies is an extremely dangerous disease with a frequently long incubation period, highly distressing symptoms, and as a rule, a lethal outcome. The violent symptoms associated with the illness and usual inevitability of death make it one of the most terrifying diseases.

Rabies or hydrophobia is probably the oldest recorded infection of mankind. Even today it is as frightening a disease as it was in the past. Sushrut, the famous Indian physician observed this condition in dogs, foxes, etc., which manifests as a state of confusion, drooping of tail and lower jaw, and profuse salivation. He emphasized that this condition was fatal, once clinical symptoms became apparent.

Dr Louis Pasteur in 1885 developed the first antirabies vaccine which was first administered on July 6, 1885 to Joseph Meister, the young boy who had been severely bitten 14 times by a rabid dog. After Jenner and his concept of protection against smallpox, rabies vaccine was the third vaccine developed in history, long before recognition of the nature of viruses.

CURRENT SCENARIO

September 28 is being observed as World Rabies Day. This viral disease which is almost invariably fatal kills 50,000–70,000 people per year. Around the world, rabies kills around 100 children every day because they cannot afford the vaccine. In Africa and Asia alone, the disease threatens 3.3 billion people—just under half the world's population.

More than 99% of all human deaths from rabies occur in the developing world, and rabies still remains a neglected disease throughout most of Asia. Asia accounts for >90% of all rabies deaths with nearly 31,500 deaths and 40–60% of all animal bites occurring in children under 14 years. Dog bites are the primary source of human infection in all rabies endemic countries in the region and account for 96% of human rabies cases. The annual incidence of suspect bites from rabid dogs is 6.5 per million humans in Asia. India, Bangladesh, and Myanmar are high rabies endemic among the Southeast Asian countries. The estimated number of human rabies deaths in Asia is approximately 30,000–40,000 annually (20,000 in India, 2,000 in Bangladesh, and remainder in the rest of Asia).

In India, about 15 million people are bitten by animals, mostly dogs (91.5%) every year and need postexposure prophylaxis (PEP). The incidence of animal bites in 17.4 per 1,000 population. A person in bitten every 2 seconds and someone dies from rabies every 30 minutes. Cats are the second most common source of human rabies exposures in Asia and virus samples collected from Asian rabid cats and other domestic animals revealed only canine street virus strains.

Causative Agent

The causative agent (*Lyssavirus* type 1) is a very small (size 120 × 80 nm), bullet shaped, i.e., round at one end and flat at another, neurotropic RNA-containing virus (**Fig. 1**). The virus is present in the saliva of rabid animals, in the saliva of human rabies patients, and also in the urine in low titers. Upon biting, scratching or licking on broken skin and intact mucous membrane, the virus enters the body, multiplies locally in the tissues and muscles, and then travels to brain at the speed of 3–10 mm/h via neurotropic nerves. There it affects the brainstem function, causing hydrophobia (fear of water), aerophobia (fear of breeze), and/or photophobia (fear of light)

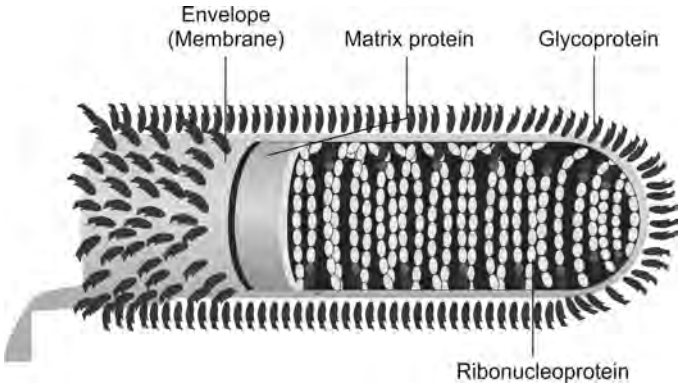


FIG. 1: *Lyssavirus* type 1—causative agent of rabies.

and finally resulting in respiratory paralysis and death. Virus is highly resistant against cold, dryness, and decay, and can remain infectious for weeks in dead bodies.

The virus recovered from naturally occurring cases of rabies is called "street virus". It is pathogenic for all mammals and shows a long variable incubation period (20–60 days in dogs). Serial brain-to-brain passage of the street virus in rabbits modifies the virus such that its incubation period is progressively reduced until it becomes constant between 4 and 6 days. Virus isolated at this stage is called a "fixed virus''. A fixed strain of virus is one that has a short, fixed, and reproducible incubation period (4–6 days) when injected intracerebrally into suitable animals. It does not form Negri bodies. The fixed virus is used in the preparation of antirabies vaccine.

Reservoirs of Infection

Rabies exists in three epidemiological forms.

1. *Urban rabies*: The transfer of infection from wildlife to domestic dogs results in the creation of urban cycle while is maintained by dog and is responsible for 99% of human cases in India. Cats can also be the source of human infection.
2. *Wildlife rabies*: Wildlife or sylvatic rabies is perpetuated by the jackal, fox, hyena, etc. In South Africa, the disease is enzootic in the mongoose. These animals maintain a cycle among themselves and transmit the infection to dogs and domestic animals. Man may contract rabies through intrusion into this wildlife cycle of rabies.
3. *Bat rabies*: In some Latin American countries such as Brazil, Venezuela, Mexico, Trinidad, Tobago, and parts of USA, the vampire bat is an important host and vector of rabies. They can transmit rabies to animals and humans. This form of rabies is responsible for killing hundreds of thousands of cattle annually. Humans are affected while sleeping outdoors. Recently, rabid bats have been found in Germany, Denmark, and Holland but not reported in India. Rabies virus is probably transmitted between vampire bats by either bite or aerosol.

Source of Infection

The source of infection for man is the saliva of rabid animals. In dogs and cats, the virus may be present in the saliva for 3–4 days (occasionally 5–6 days) before the onset of clinical symptoms and during the course of illness till death. Only half of rabid animals have virus in saliva so the probability of getting rabies following the bite of a rabid canine is 50%.

Carrier States

In rare cases, carrier states have also been reported where the animal although apparently healthy, has transmitted the disease.

Host Factors

All warm-blooded animals including man are susceptible to rabies. Incidence of rabies is maximum in children aged <15 years. Bites around head and neck are most dangerous. Veterinary workers, animal handlers, forest staff, hunters, field naturalists, and laboratory staff working with rabies virus are much more vulnerable for exposure to rabies virus.

Mode of Transmission

- *Animal bites*: In India, most of the human rabies cases occur due to bite of a rabid dog. There is also possibility of contracting rabies through the bites of cats, monkey, horses, sheep, goat, etc. As a prerequisite to transmission, the saliva of the biting animal must contain the virus at the time of bite.
- *Licks*: Licks on abraded skin and mucosa (abraded or unabraded) can transmit the disease. In rare instances, the disease may be transmitted through bone splinter or other object contaminated with saliva of a rabid animal.
- *Aerosols*: Aerosol (respiratory) transmission can occur in two ways, either in caves harboring rabid vampire bats or in the laboratory where aerosols created during homogenization of infected animal brains can infect laboratory workers.
- *Person-to-person*: Man-to-man transmission although rare, is possible either through bite by a hydrophobia patient or through corneal or organ transplants.

Incubation Period

The incubation period in man is highly variable, commonly 3–8 weeks following exposure (may be up to 3 months). But it may vary from 4 days to many years.

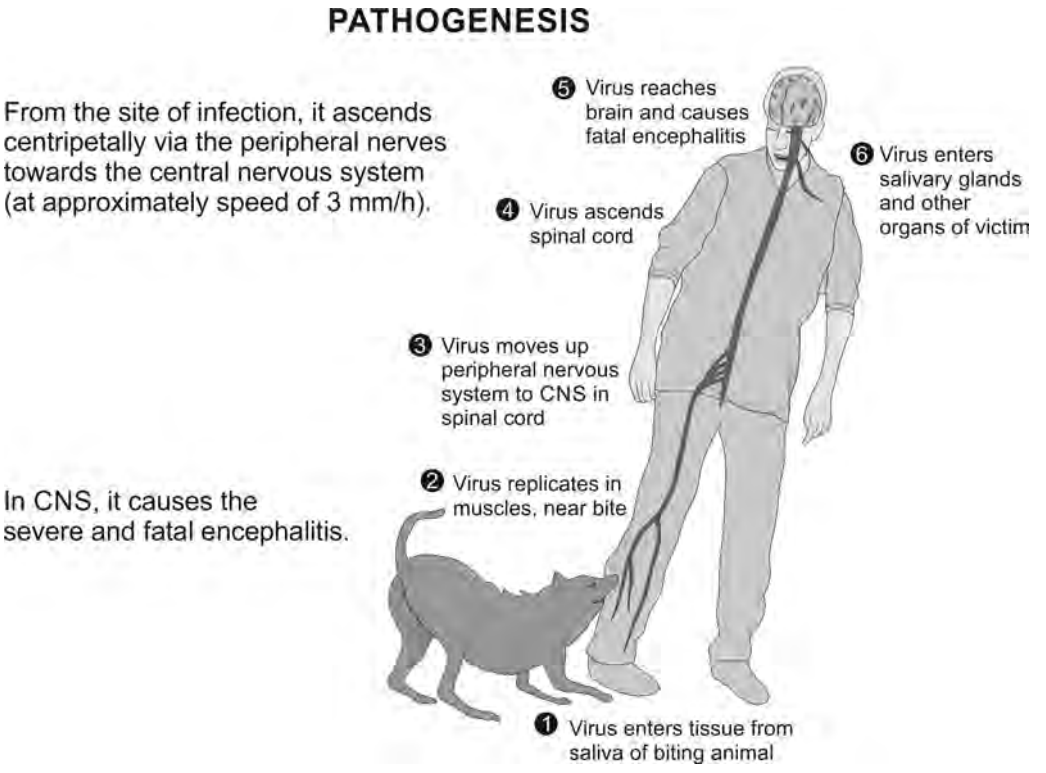
The incubation period depends on number of factors: (i) site of the bite, (ii) severity of the bite, (iii) number of wounds, (iv) amount of virus injected, i.e., virus inoculum, (v) species of the biting animal, (vi) protection provided by clothing, and (vii) treatment undertaken, if any.

In general, incubation period is shorter in severe bites, bites on head and neck region, upper extremities, and also bites by wild animals. In no other communicable disease, the incubation period is not so variable and dependent on so many factors as in rabies.

PATHOGENESIS

The live virus, once introduced through the epidermis or mucous membrane, multiplies and ascends centripetally up the peripheral nerves to the CNS resulting in generalized encephalomyelitis (**Fig. 2**). Once the virus reaches the CNS, it multiplies exclusively in the grey matter and then spreads centrifugally along autonomic nerves to other tissues including salivary glands and cornea.

The pathognomonic lesion is an intracytoplasmic eosinophilic inclusion body commonly known as Negri bodies. These Negri bodies are seen only with infection of


PATHOGENESIS
From the site of infection, it ascends centripetally via the peripheral nerves towards the central nervous system (at approximately speed of 3 mm/h).
In CNS, it causes the severe and fatal encephalitis.
5 Virus reaches brain and causes fatal encephalitis
6 Virus enters salivary glands and other organs of victim
4 Virus ascends spinal cord
3 Virus moves up peripheral nervous system to CNS in spinal cord
2 Virus replicates in muscles, near bite
1 Virus enters tissue from saliva of biting animal

(CNS: central nervous system)

FIG. 2: Pathogenesis of rabies.

"street virus" and not with "fixed virus". So far the virus has not been isolated from the blood of rabies patients and hence, the hematogenous route of spread is ruled out. In rabies, there is no initial viremia and the virus is not accessible to the normal immune mechanism of the body. The viremia or the stimulation of the normal immune mechanism is only during the end stages of the fatal disease therefore the role of naturally acquired infection is practically nonexistent.

CLINICAL PRESENTATION

Rabies in man is known as hydrophobia in general. The disease can be divided into different stages:

- *Prodromal stage*: The disease begins with prodromal symptoms such as fever, headache, myalgia, sore throat, and vomiting. There is pain and tingling or numbness at the site of bite in about 80% of cases. It is the most important complaint at this time and is related to the multiplication of virus at the local site. This stage may last for 3–4 days.
- *Stage of acute encephalitis*: This stage is characterized by excessive motor activity and agitated behavior. There is widespread excitation and stimulation of nervous system involving the sensory, the motor, the sympathetic, and the mental systems. There are symptoms of confusion, hallucination, muscle spasms, and convulsions. There is exaggerated sensitivity to noise, light, touch, or currents of air. Autonomic symptoms such as increased perspiration, salivation, lacrimation, pupillary dilatation, and hypotension are present. Hypoxia and hyperventilation progress to hypoventilation and repeated apnea.
- *Stage of brainstem dysfunction*: Now the characteristic symptom of hydrophobia appears which is pathognomonic of rabies and is absent in animals. This fear of water is due to painful, violent, involuntary contraction of diaphragm, respiratory, laryngeal and pharyngeal muscles, and initiated by swallowing of liquids. Progressively, even the sight, smell, or sound of liquids can precipitate spasm of muscles of deglutition. More than 80% patients succumb to the disease during this stage. Death is due to respiratory arrest, convulsions, or choking. Rest of the patients may progress to next stage.
- *Stage of paralysis*: Paralytic symptoms can occur at any time during the course of illness. Now the muscle spasms cease and there is apathy, stupor, coma, and generalized flaccidity. Death occurs due to hypoxia or heart failure. Occasionally, rabies may present as Guillain–Barré type of ascending paralysis. This may be seen with bite of a vampire bat or in patients who have received PEP against the disease.
- *Death*: Once the symptoms develop, the disease is fatal and the patient dies within two weeks. There are no quarantine restrictions for a rabies patient. However, since the saliva, urine or tears, etc., may contain the virus, all the persons coming in contact should be immunized against rabies. Transmission from man to man, though uncommon is possible.

DIAGNOSIS

The clinical diagnosis can be possible on the basis of classical signs and symptoms. Hydrophobia is pathognomonic of rabies. There is history of animal bite.

Laboratory Diagnosis

The laboratory tests are not routinely done for the management of animal bite cases, as these are not cost effective for

management purposes and have limited availability in specific centers of big cities. Several biological samples such as saliva, cerebrospinal fluid (CSF), skin biopsies containing hair follicles collected at the nape of neck, extracted hair follicles, tears, and urine can be used. Positive results of viral RNA in samples should be confirmed by sequencing to avoid false positives. Sensitivity of testing only one skin biopsy/patient is ≥98% but by collecting and testing three serial daily saliva samples per patient, it is possible to achieve maximal, i.e., 100% sensitivity. Fluorescent antibody test is a very reliable test nowadays and can establish the diagnosis within a few hours. If the brain is negative, by this test a person need not be treated. Fluorescent antibody titers in clinical rabies are >1:10,000 which help to differentiate between rabies and vaccine reaction.

Rabies-specific Enzyme-linked Immunosorbent Assay Technique

Enzyme-linked immunosorbent assay (ELISA) techniques for detection of rabies antigen or antirabies immunoglobulin G (IgG) are rapid, easy to use, and safe. Fluorescent antibody test can be performed on corneal impressions. After 7–10 days of illness, virus neutralizing antibodies appear in the serum and CSF which can be measured by the rapid fluorescent focus inhibition test (RFFIT) or ELISA. Histopathologically, the necrosed ganglia, demyelinated cord sheaths, glial proliferation, and Negri body inclusions are typical feature for a specific encephalomyelitis due to rabies.

Differential Diagnosis

Before the appearance of hydrophobia and in those cases where it does not manifest, rabies needs to be differentiated from other clinical conditions such as tetanus (lockjaw), encephalitis, hysteria, acute polyneuritis, poliomyelitis, and belladonna poisoning.

Rabies in Dogs

Two clinical forms of manifestation are known in dogs:

1. *Furious rabies*: Dog behaves abnormally and becomes very restless. Gradually it becomes dangerously aggressive with a tendency to bite objects, animals, and man indiscriminately and without provocation. There is profuse salivation due to paralysis of muscles of deglutition and tone of bark changes due to partial paralysis of vocal cords. Generalized convulsions followed by muscular incoordination and paralysis of muscles of trunk and extremities are seen at the terminal phase of illness.
2. *Dumb rabies*: It is characterized by predominantly paralytic clinical features. The excitation phase, if present, tends to be very short. Progressive paralysis starts with head and neck region. Animal has difficulty in swallowing. The dog withdraws itself from being disturbed and lapses into a stage of sleepiness and dies in about 3 days.

Once the symptoms of rabies develop in an animal, it rarely survives more than a week.

Observation of an animal for 10 days from the day of biting for signs of rabies is applicable for dogs and cats only and not for other domestic or wild animals. The rationale for observation is that if these animals are having infective saliva with rabies virus, they will show signs of disease in the next 3–5 days and die subsequently in another 3–5 days.

MANAGEMENT OF HUMAN RABIES (HYDROPHOBIA)

Although no specific treatment for rabies is available, a case has to be managed according to following procedure. The patient should be sedated and kept in a quiet room, with shades drawn on windows. No external stimuli such as noise and bright light should be present which may lead to convulsions. Patient should be treated symptomatically and proper hydration and diuresis should be maintained. Intensive respiratory and cardiac therapy is given. The nursing attendants and all persons coming in contact with the patient should be adequately protected as these patients are potentially infectious. The intensive care and nursing support are a must for rabies patients and there are seven cases of human rabies on record who survived this dreaded disease.

PREVENTION OF HUMAN RABIES

Postexposure Prophylaxis for Rabies

Human rabies is essentially a fatal disease once the clinical signs develop, although 100% preventable. Rabies PEP consists of thorough wound care along with administration of modern antirabies vaccine and rabies immunoglobulin (RIG). This is highly effective if carried out systematically and diligently. If a person has received pre-exposure prophylaxis (PrEP), then it eliminates the need for RIG in case of an exposure. The key to survival is administration of PEP as soon as possible. A patient with category III exposure needs thorough wound cleansing and a first dose of vaccine along with RIG on the day of bite or day of reporting (**Table 1**). The vaccination is done according to one of the WHO approved schedules to achieve a serum antibody titer of >0.5 IU/mL which is considered acceptable according to WHO. In case of any confusion regarding exposure it is always better to give over-treatment rather than under-treatment for prevention of rabies.

Assessment of Exposure and Observation Period

Immunization must be initiated immediately after every bite. Observation of dog/cat for signs of rabies for at least 10 days is important as well as valid. We can modify the treatment regimen (from postexposure to pre-exposure) if the dog/cat survives 10 days of observation.

We start the modern antirabies vaccine [cell culture vaccine (CCV)] according to the WHO schedule on the day of bite by dog/cat or as soon as the patient reports. That is considered day "0". Then the vaccine is given on day "3" and "7" as per schedule. If the dog/cat is alive and normal till the 10th day, then the remaining doses are not given. Alternatively, after giving the first and second doses on days "0" and "3", the third dose of day "7" may be deferred if the dog/cat is healthy on day 7. It is further deferred to day 14 if the dog/cat is alive and healthy for 10 days. Then the patient is given the option of converting the present postbite/postexposure vaccination into a modified preventive/pre-exposure vaccination by giving the third dose of vaccine either on day 21 or day 28. As three doses confer immunity for a duration of 1 year, so it is advisable to give a booster dose after 1 year. Thus, we convert the postexposure schedule to pre-exposure schedule. It is further emphasized

TABLE 1: Postexposure prophylaxis in rabies.

Categories	Nature of contact	Recommended treatment	
		Unknown, sick, proven, and wild animal	Healthy animal
I	Touching or feeding animals, licks on intact skin no mucous membrane exposure	None	None
II	Nibbling of uncovered skin, minor scratches, or abrasions without bleeding	• Modern tissue culture • Rabies vaccine	• Modern tissue culture • Rabies vaccine
III	Single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposure due to direct contact with bats	• Modern tissue culture • Rabies vaccine and rabies immunoglobulin (RIG)	• Modern tissue culture • Rabies vaccine and RIG

- Start pre-exposure vaccination particularly in children and others likely to have repeated animal contact, and are at a risk of dog bites
- Start full treatment on first day and discontinue vaccine if animal is alive and well on day 10, or if it has been found rabies negative on reliable laboratory examination. Encourage patient to return for another dose of vaccine on day 21, so that a full pre-exposure series has been completed
- If there is significant delay in presentation or if the patient is immunosuppressed, it may be appropriate to double the first dose of vaccine. Administration of two ampoules of vaccine, one in each arm, on day 0

that the observation period of 10 days is valid for dogs and cats only and not for any other animals because of the variability in the period of infectivity in other animals saliva.

Wound Care and Treatment

Proper wound care is a very important step as it may bring down the risk of infection to the extent of 50–70%. This step is however, often neglected. Our objective is to reduce the virus deposited at the site of bite as much as possible. The wound treatment must be done immediately or as early as possible after the bite. The steps are as follows:

- Gentle washing of the wound using a detergent soap, preferably under running tap water for at least 10 minutes.
- Application of household antiseptics like povidone-iodine, 40–70% alcohol or 0.01% aqueous solution of iodine can be done.
- In some extensive deep wounds the exploration of wound followed by debridement, removal of dirt and dead tissue may be required in a hospital setting and sometimes under anesthesia.
- *Suturing must be generally avoided as a rule*, as it may lead to the risk of inoculation of virus deep into the wound. However, if it cannot be avoided, it should be done as late as possible, from several hours up to 1 or 2 days. The suturing should be loose and minimum possible stitches should be given. Before the suturing equine rabies immunoglobulin (ERIG) or human rabies immunoglobulin (HRIG) should be infiltrated into the wound.
- *Generally animal bite wound should not be dressed or bandaged* and if unavoidable, it should be loose and not occlusive.
- Proper tetanus prophylaxis and wherever necessary, systemic antibiotics to prevent wound sepsis should be given.
- The use of any local applicant or irritant such as turmeric, neem, red chilli, lime, plant juices, coffee powder, coin, etc., should be discouraged or avoided as these will propel the virus deeper into the wound causing nerve infection, encephalitis, and death.

MODERN ANTIRABIES VACCINE

The vaccine against rabies is a liquid or dried preparation of fixed virus inactivated by a suitable method. In India, mainly three types of modern CCVs are available which are:

1. Human diploid cell vaccine (HDCV)
2. Purified chick embryo cell vaccine (PCECV)
3. Purified vero cell rabies vaccine (PVRV)

Dose

About 1 mL intramuscular (IM) for HDCV and PCECV and 0.5 mL IM for PVRV irrespective of age of person.

All CCV can be stored at 2–8°C and never to be stored in freezer compartment.

Indications

All cases of animal bites irrespective of severity of exposure require the same number of injections and dose per injection. The category III requires simultaneous administration of RIGs.

Site for IM Injection

The deltoid region is ideal site for injection (anterolateral aspect of mid-thigh in young children). Gluteal region is not recommended due to the amount of fat present there which retards the absorption of vaccine and interferes with the optimal antibody production and immune response. The use of modern, inactivated, and purified CCV with a potency of at

least 2.5 IU per single IM dose should be done according to one of the following WHO schedules:

- *Intramuscular schedule*: The most widely used is WHO Essen Schedule on day 0, 3, 7, 14, and 28 with an optional dose on day 90. *Abbreviated Multisite IM Schedule* (Zagreb Schedule), i.e., the 2-1-1 regimen (one dose of CCV IM in right arm and one in left arm on day 0, one dose on day 7 and one dose on day 21), although WHO approved is, however, not approved by Drug Controller General of India and hence should not be used in our country.
- *Intradermal (ID) schedule*: This schedule has been recommended by the WHO to reduce the cost of postexposure treatment with CCV. This has been approved by the Government of India also. This should only be used where adequately trained staff is present well versed in technique and maintenance of cold chain and storage of supplies. The regimen currently in use is known as the updated Thai Red Cross Schedule. In this schedule one dose of vaccine in a volume of 0.1 mL is given intradermally at two different lymphatic drainage sites, usually the right and left upper arms, on day 0, 3, 7, and 28. This updated Thai Red Cross Schedule (2-2-2-0-2) has been adopted in India.

It is important to know that the IM dose of PVRV is 0.5 mL and that of PCECV is 1 mL. Still as per the recommendations of the WHO, the ID dosage of all rabies vaccines uniformly is 0.1 mL.

Regarding adverse effects, properly prepared CCV have not been associated with any serious adverse effects. Some people may complain of localized edema and redness, sore arm, headache, nausea, malaise, and fever.

Switch over from one CCV to other is not encouraged as good immune response is best achieved with same brand/type of vaccine. However in case of nonavailability of same type/brand switch over can be done.

RABIES IMMUNOGLOBULIN FOR PASSIVE IMMUNIZATION

The RIGs or antirabies serum (ARS) are readymade antirabies antibodies providing passive immunity and immediate protection. Even the best of modern vaccines take 10–14 days to elicit the protective antibody titer of >0.5 IU/mL of serum and therefore RIGs cover this vulnerable period in category III exposure.

The combination of antirabies vaccine and RIG is almost 100% effective "at prevention" of clinical symptoms and disease; however, attempts to use vaccine or RIG after the onset of symptoms have not been successful. Some salient points related with use of RIG should always be kept in mind. These are:

- RIG should be administered in all individuals with category III exposure and in those with category II exposure who are immunodeficient.
- RIG is administered only once and as soon as possible after the initiation of PEP. RIG is not indicated beyond the seventh day after the first antirabies vaccine dose.
- The dose of human RIG is 20 IU/kg body weight and for equine RIG, 40 IU/kg body weight.
- All of the RIG, or as much as anatomically possible, should be administered into or around the wound site/s.
- Remaining RIG, if any, should be injected IM at a site distant from the site of vaccine administration. RIG may be diluted to a volume sufficient for all wounds to be effectively and safely infiltrated. There are no scientific grounds for performing a skin sensitivity test prior to ERIG administration. So it is not mandatory.

Rabies immunoglobulin should be immediately given after exposure to inhibit viral spread because vaccination needs time to induce a humoral response. RIG can be diluted with normal saline whenever the calculated dose (20 IU/kg body weight for HRIG subject to a maximum of 1,500 IU and 40 IU/kg body weight for ERIG subject to a maximum of 3,000 IU) is inadequate to infiltrate all wounds without previous dilution. However, the overall dose of HRIG or ERIG should not be increased because it may interfere with vaccination and may lead to reduced rate of seroconversion.

SPECIFIC SITUATIONS

Pre-exposure Prophylaxis

It is recommended for high-risk groups such as laboratory staff handling the rabies virus and infected material, physicians and paramedics attending the hydrophobia cases, veterinarians, animal handlers and catchers, wildlife wardens, pet owners, and travelers from rabies-free to rabies-endemic areas.

Pre-exposure prophylaxis should consist of three 1 mL IM or 0.1 mL ID doses of CCV, one dose each given on day 0, 7, and 28 with one booster after 1 year. Persons in high-risk group should have their neutralizing antibody titers checked every 6 months. If it is <0.5 IU/mL, a booster dose of vaccine should be given. These persons after successful PrEP, if get exposed to rabies virus irrespective of time interval between previous vaccination and re-exposure require only two booster doses of CCV on day 0 and 3 without any RIG, whatever be the category of exposure or bite.

Re-exposure Following Pre-exposure or Post-exposure Prophylaxis

In case of re-exposure anytime, if a person has previously received complete PrEP of three doses with one booster after 1 year or PEP of five doses with a potent CCV, should be given only two booster doses, IM or ID on days 0 and 3 but no RIG is necessary in them (WHO, 2002).

Pregnancy and Lactation

There are no contraindications regarding the use of modern CCV for PEP during pregnancy and lactation.

Extremes of Age

The dose of CCV is not dependent on age and weight. The dose is exactly the same from pediatric to geriatric age group.

If a dog is vaccinated against rabies, it cannot suffer from or transmit the disease. But in view of questionable maintenance of cold chain it is very difficult to say that a vaccinated dog is immune against rabies unless it is confirmed by a serological test. However, a modern tissue culture vaccine of adequate potency, if given regularly to dog following strict schedule should prove to be sufficiently protective.

Indications for Doubling the First Dose of Cell Culture Vaccine

In some situations it becomes necessary and appropriate to double the first dose of antirabies CCV, whatever route or schedule is used. These are:

- In patients with underlying chronic disease (e.g., liver cirrhosis)
- In patients who are severely malnourished
- In patients reporting for treatment after a delay of 48 hours or more
- In patients who are congenitally immunodeficient or suffering from acquired immunodeficiency syndrome
- In patients taking immunosuppressive drugs (including corticosteroids, antimalarials, and anticancer drugs)
- In patients with very high degree of exposure or extensive wounds, i.e., on head, neck, face, hands, genitals, etc., following bites by suspect or proven rabid animals or by wild animals such as fox, jackal, and mongoose
- In patients where RIG is indicated but unavailable

CONTROL OF RABIES

As the major source of infection is dog, the control of dog population along with their mass immunization in the shortest possible time remains the most logical approach for the control of this dreaded disease. A canine rabies control program has been launched by the ministry of agriculture. This type of program should incorporate three basic elements:

1. Epidemiological surveillance
2. Control of dog population
3. Mass immunization of dogs

Mass immunization may be considered by giving primary vaccination at 3 months of age and booster 1 year later and then every year. Nowadays, safe oral vaccines have become available and can be used for mass immunization. Oral immunization can cover 75% of dog population. Oral vaccination of wild animals with attenuated as well as recombinant vaccines by using "oral vaccine baits" has successfully reduced and controlled wildlife rabies in foxes in some countries of Europe such as Germany and Switzerland and also in Canada.

Health Education

Health education of public regarding prevention and control of rabies and management of animal bite is crucial to save lives. It is a real tragedy that this disease which is 100% preventable is still a major cause of mortality in developing countries.

Consumption of raw milk of any suspected rabid animal (cow, buffalo, goat, etc.) shall be considered and treated as category III exposure. Boiling of milk destroys the rabies virus.

Proper cooking of meat destroys the virus but raw meat can transmit the virus.

If a person presents after a considerable delay of weeks to months with a history of animal bite, it is mandatory to give complete course of postexposure treatment including infiltration of wound site with RIG in view of the 100% mortality with this disease. It may be appropriate to double the first dose of vaccine.

SUMMARY

- The saliva of rabies patients contains rabies virus and is infective, hence in case of suspicion about contact with saliva of a rabies patient during kissing the contact requires rabies postexposure vaccination. If ulcers are present in the mouth, then immunoglobulins should be advised by IM route.
- Rabies virus is present in the semen and to some extent in vaginal secretions. In some male patients, priapism and in both male and female patients increased libido may be observed. Hence to the healthy contact, a complete course of postexposure vaccination should be given. If abrasion on penis or vagina, RIG is to be given by IM route.
- There have been some instances of failure even after complete course of antirabies treatment. During discussions at WHO and other expert committee meetings it was found that the efficacy and immunogenicity of modern CCV were never in doubt but failures were either due to delay in getting vaccination or RIG was not used or there was already immunosuppression in patients.
- There is no contraindication of giving antirabies vaccine along with Expanded Program of Immunization (EPI)/ pediatric vaccines in case of postexposure vaccination; however, an interval of 3–4 weeks between the two types of vaccines is advisable in case of PrEP.
- Modern antiretroviral (ARV) can be safely given to children having chickenpox, measles, or any other eruptive fevers.
- If during antirabies vaccination any dose is missed, then patient is counseled regarding strict adherence to schedule and schedule is completed as soon as possible.
- No dietary restrictions are required during vaccination but alcohol, tobacco, gutka, and smoking must be avoided.
- There is no single shot antirabies vaccine till date and a full course of antirabies vaccination does not guarantee or provide lifelong immunity against the disease.

Rabies is still a very dreadful as well as dreaded disease. Strict measures to control or eliminate the disease in domestic as well as wild animals must be taken if we are ever to achieve mastery over this deadly virus. In conclusion, cases of human rabies would be extremely rare if all patients knew whom to approach for treatment in case of bite, if antirabies vaccine and serum were readily available and if the postexposure treatment was strictly and diligently carried out following the guidelines.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Skin and Soft Tissue Infections

Javier Saavedra Urbe, Devendra Richhariya

INTRODUCTION

Skin and soft tissue infections (SSTIs) are causes for common outpatient as well as emergency department (ED) visits. SSTIs are common form of infections presenting to ED which includes routine skin infections to rapidly life-threatening SSTIs. Abscess and purulent cellulitis, nonpurulent cellulitis, and necrotizing soft tissue infections (NSTIs) are the most important clinical types of SSTI in clinical practice. SSTIs can be classified as proposed by the Infectious Disease Society of America (IDSA) because it suggests a useful clinical diagnostic approach—in which the first step is to "look for pus" (**Flowchart 1**)—dividing SSTIs according to presence or absence of purulence. If there is purulence, the causative bacterium is likely *Staphylococcus aureus*. Performing good drainage, with an incision and drainage procedure is utmost importance along with antibiotics with activity against methicillin-resistant *S. aureus* (MRSA) are generally indicated. If there is no pus, then consider nonpurulent cellulitis and NSTIs. In nonpurulent cellulitis beta-lactam antibiotics (which do not cover MRSA) can be used as causative agents is β-hemolytic streptococcal species. If a necrotizing infection is suspected, broad-spectrum antibiotics should be administered because etiology may be polymicrobial. In addition to antibiotics, prompt surgical intervention is also indicated. Antibiotics recommended for major SSTIs are summarized in **Table 1**. SSTIs can also be classified on the basis of involvement of skin. Erysipelas is a form of nonpurulent cellulitis limited to the epidermis and impetigo is an infection that affects only the keratin cells of this layer. Furuncles are an infection originating in hair follicles that produce a localized subcutaneous abscess within the hypodermis. Carbuncles, which are a coalescence of multiple furuncles, tend to extend deeper into the hypodermis. Necrotizing fasciitis is an infection of the fascia is the connective tissue layer that lies below the hypodermis; SSTIs can also be classified on the basis of severity of local and systemic symptoms, and recommended management is summarized in **Table 2**.

MICROBIOLOGY

Staphylococcus aureus or one of the β-hemolytic streptococcal species is the major causative agent for community-onset SSTIs presenting to ED. However, in special circumstances after animal bites and water exposure, there are numerous other important pathogens that cause SSTIs. **Table 3** summarizes the special types of SSTI in which the bacteriology includes pathogens other than *S. aureus* and β-hemolytic streptococcal species.

Staphylococcus aureus is a gram-positive coccus that grows in clusters and is a part of the normal human microbiota. It is frequently found on the nasal mucosa, the skin (especially of the axilla and groin), and in the gastrointestinal tract. Classically *S. aureus* causes localized pus-producing lesions, such as furuncles, abscesses, and carbuncles. *S. aureus* has unique quality to survive on fomites; infection control measures should include disinfecting high-touch household surfaces and linen. Finally, the purulent nature of *S. aureus* infections seems to allow transmission from person to person by even brief direct contact with the draining lesion.

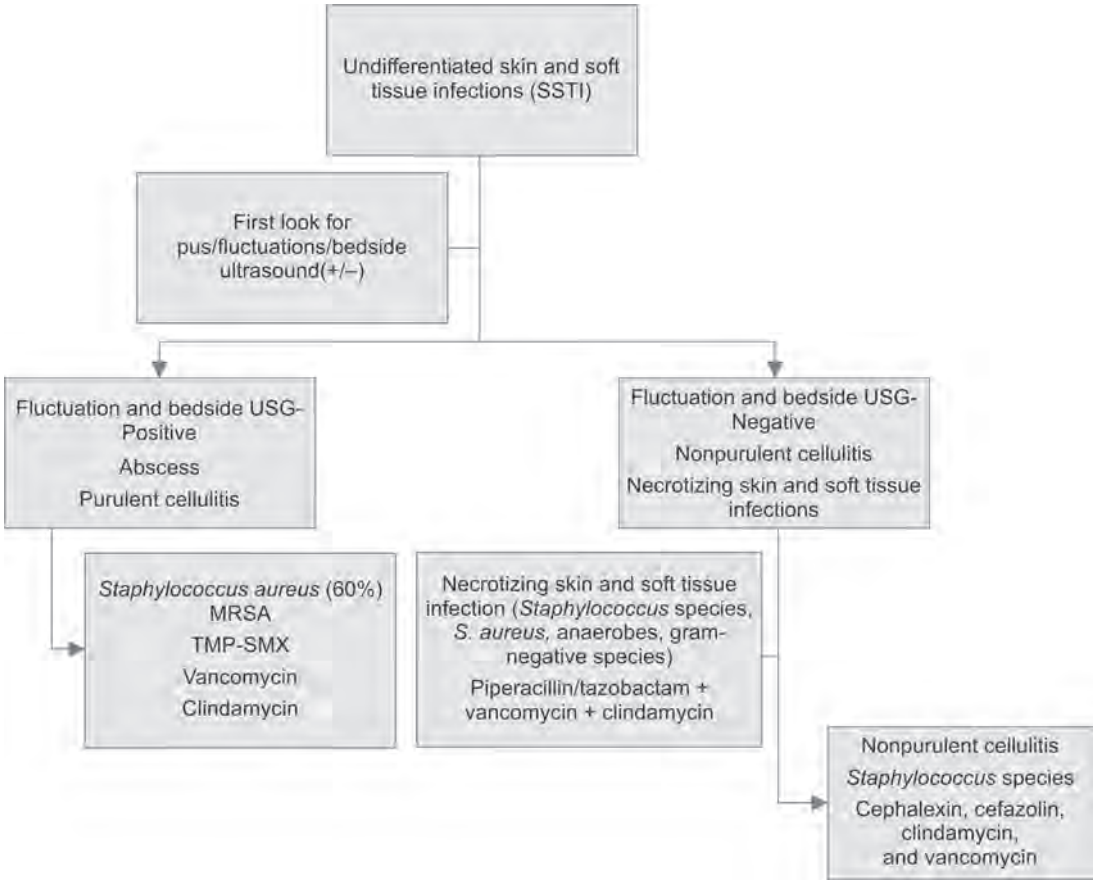
β-hemolytic Streptococcal Species

The β-hemolytic streptococci species are gram-positive cocci that grow in chains and are also part of the normal human skin microbiota. In contrast with *S. aureus*, a characteristics clinical feature of streptococcal SSTIs is lack of purulence. *Streptococcus pyogenes*, also known as group A *Streptococcus* (GAS), is the most common, but other species—groups G, D, and B are identified as etiologies of nonpurulent cellulitis. *S. pyogenes* is one of the preeminent human pathogens, responsible for a range of clinical infections including not only impetigo, lymphangitis, erysipelas, cellulitis, and necrotizing fasciitis, but also pharyngitis, scarlet fever, pneumonia, streptococcal toxic shock syndrome, and the notorious sequelae of infection, rheumatic fever, and glomerulonephritis.

IMPETIGO

Epidemiology and Microbiology

Impetigo is caused by both *S. aureus* and *S. pyogenes* after colonization of the unbroken skin. Colonization further leads to infection at an interval of approximately 10 days. Impetigo mostly occurs in children between ages 2 and 5 years, but may also occur in older children or adults. Poor hygiene and



(MRSA: methicillin-resistant *Staphylococcus aureus*; TMP-SMX: trimethoprim-sulfamethoxazole; USG: ultrasonography)

FLOWCHART 1: Clinical approach to undifferentiated skin and soft tissue infection.

TABLE 1: Antimicrobial therapy for purulent cellulitis, nonpurulent cellulitis, and necrotizing soft tissue infection.

Infections	***Antibiotics***	***Dosage (adult)***	***Comments***
Impetigo (*Staphylococcus* and *Streptococcus*)	• Mupirocin ointment • Cephalexin • Clindamycin • TPM-SMX	• Apply to lesion • 250 mg 6 hourly PO • 300–400 mg 6 hourly PO • 1–2 DS tablet 12 hourly PO	
Abscess and purulent cellulitis (MRSA and MSSA)	• Vancomycin • Clindamycin • Doxycycline • Linezolid	• 30 mg/kg/day in two divided doses IV • 600 mg every 8 hours IV or 450 mg qid PO • 100 mg 12 hourly PO • 600 mg every 12 hours IV or 600 mg bid PO	For penicillin allergic patients; parenteral drug of choice for MRSA
Nonpurulent cellulitis (beta-hemolytic *streptococcus* and MSSA	• Cephalexin • Cefazolin • Clindamycin • Nafcillin • Penicillin VK	• 500 mg every 6 hours PO • 1 g every 8 hours IV • 600–900 mg every 8 hours IV • 1–2 g every 4–6 hours IV • 250–500 mg every 6 hours PO	
Necrotizing soft tissue infection (GAS, *Clostridium* species, MRSA, gram-negative rods, and others)	• Piperacillin • Tazobactam • Aztreonam • Vancomycin + clindamycin	• 4.5 g every 6 hours IV • 2 g every 6 hours IV • 15–20 mg/kg IV every 12 hours IV • 600–900 mg every 8 hours IV	

(DS: double strength; GAS: group A *Streptococcus*; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; TMP-SMX: trimethoprim-sulfamethoxazole)

TABLE 2: Severity classification of skin and soft tissue infections (SSTIs).		
Class	*Description*	*Management*
1	Afebrile and healthy, other than acute SSTI	If required, incision and drainage. If required, oral antimicrobials as an outpatient
2	Febrile and ill appearing, but no unstable comorbidities (e.g., diabetes) that may complicate or delay resolution	Can be treated with oral antibiotics or outpatient IV therapy and may require a short period of observation in hospital
3	Appear toxic and unwell (fever, tachycardia, tachypnea, and/or hypotension)	Likely to require inpatient treatment with parenteral antibiotics
4	Sepsis syndrome or life-threatening infection (e.g., necrotizing fasciitis)	Likely to require admission to intensive care facility for surgical assessment and parenteral antimicrobial agents

TABLE 3: Microbiology of special types of skin and soft tissue infections (SSTI).	
Conditions	***Possible pathogens***
Fresh or salt water exposure	*Vibrio vulnificus*, *Aeromonas hydrophila*, *Erysipelothrix rhusiopathiae*, *Mycobacterium marinum*, and others
Human bites	*Eikenella corrodens*, *Fusobacterium nucleatum*, *Streptococcus anginosus*, and *Staphylococcus aureus*
Cat bites	*Pasteurella multocida; Streptococcus* species, *S. aureus*, *Fusobacterium* species, *Bacteroides* species, and others; and *Bartonella henselae* (cat scratch disease)
Dog bites	*Pasteurella multocida; Streptococcus* species, *S. aureus*, *Fusobacterium* species; *Bacteroides* species; and *Capnocytophaga* (may cause overwhelming sepsis in susceptible patients)
Diabetic foot	*S. aureus* (including MRSA), β-hemolytic streptococcal species, *Pseudomonas aeruginosa*, *Enterococcus* species, *Escherichia coli*, other *Enterobacteriaceae* species, oral anaerobic species, *Bacteroides* species, and *Clostridium* species
Injection drug use	*S. aureus* (including MRSA), *Streptococcus* species, oral anaerobic species, *Clostridium perfringens*, *Clostridium sordellii*, and *Clostridium novyi*
Perirectal abscess	*S. aureus*, *Streptococcus* species, *E. coli*, other *Enterobacteriaceae* species, *Bacteroides fragilis*, and other anaerobic species

(MRSA: methicillin-resistant *Staphylococcus aureus*)

disruption of the epidermal layer by mosquito bites, abrasions, and eczema are the important risk factors for impetigo.

Clinical Features

There are two major types of impetigo: Nonbullous and bullous. Nonbullous impetigo is the more common form and presents as a yellowish crust on the face, arms, or legs. Impetigo begins with a papule, and then progresses to vesicle, and pustule surrounded by an area of erythema. Over a period of 4–6 days the pustule gives rise to the characteristic thick and golden crust. Sores may be pruritic, but not painful. Fever is rare, but regional lymphadenopathy may be present. Touching the sores may result in spread of the infection. Bullous impetigo is a staphylococcal disease common in children <2 years of age. Bullous impetigo clinically present as painless fluid-filled bullae, predominantly on the arms, legs, and trunks. After the bullae break, they may form yellow scabs. If infection extends to the dermis, ulcers covered with a crust or eschar develops. Poststreptococcal glomerulonephritis is a possible complication of streptococcal impetigo.

Diagnosis

The diagnosis of impetigo is made by visual recognition. For differentiating staphylococcal from streptococcal infection, Gram stain and culture may be used. Assays of antistreptolysin O are not useful in the diagnosis or management of impetigo. If poststreptococcal glomerulonephritis is suspected in any patient, assays of antistreptolysin O may be helpful.

Treatment and Prophylaxis

Impetigo treatment involves removing the crust and washing the affected area with soap and water followed by prescribing antibiotic. A topical antibiotic with reliable antistaphylococcal activity is useful. Mupirocin is the most widely recommended topical agent. For more widespread lesions cephalexin and dicloxacillin antibiotics may be used. Good personal hygiene can prevent the spread of impetigo to susceptible individuals.

ABSCESS

Epidemiology and Microbiology

Focal collections of pus located within the dermis and hypodermis are known as cutaneous abscesses and are clinically present as "painful, tender, and fluctuant red nodules, pustule, and surrounded by a rim of erythematous swelling". The definitions and terminology of common types of abscesses and other purulent infections are listed in **Table 4**.

Staphylococcus aureus is responsible for abscess in about 75% of cases, of which mostly MRSA predominates. Injection drug use (IDU)-related cutaneous abscesses may be polymicrobial and contain oral streptococci and anaerobes, because saliva is so often used to dissolve the drug and clean needles and syringes. Recurrent abscesses associated with injectable drug abusers; after shaving of legs, axilla, and pubic hair; and prior colonization of infection.

TABLE 4: Definitions—purulent skin and soft tissue infection.

Conditions	*Description*
Cutaneous abscess (skin abscess)	Subcutaneous collection of pus with a wide spectrum of size and severity
Folliculitis	Tiny, papular abscesses, inflammation and infection of hair follicles
Furuncle	Small, spontaneous, and cutaneous purulent abscess develop around a hair follicle, extending below the epidermis. Patients may be referred as a "spider bite" or commonly called as "boil"
Carbuncle	Multiple furuncles coalesce and of typically involving the deep subcutaneous tissues; base of the neck is common site
Paronychia	Abscess at the base of a finger or toe nail, trapped below the eponychial fold
Hidradenitis suppurativa	An often-inherited form of acute and chronic inflammation of sebaceous and apocrine glands that causes follicular occlusion; abscesses appear purulent but are sterile
Purulent cellulitis	Erythema, induration, and warmth that extends from a purulent focus

Clinical Features

Cutaneous abscesses are easily recognized by their visual appearance. The circular shape erythema, swelling, and induration often associated with a small point of necrosis or signs of spontaneous drainage. There may or may not be significant purulent cellulitis extending radially from the purulent focus (nonpurulent cellulitis, often circumferential around a limb). Fluctuance is a classic hallmark of abscesses; however, it is frequently absent in the early stages of formation and in the case of a deep subcutaneous abscess. In fact, minimal external signs appear of cutaneous abscesses where hypodermis is particularly thick, like the gluteal and thigh region.

Diagnosis

For a cutaneous abscess the first-line "diagnostic test" is palpation for fluctuance examination. When fluctuance is absent or difficult to localize emergency physician may take the help of ultrasound examination as an adjunct to the physical examination. Ultrasound examination findings of abscess cavities are hypoechoic or anechoic and acoustic enhancement deep to the pus collection. In addition, for deep or intramuscular abscesses, ultrasound examination can be invaluable in identifying the best location for incision. A computed tomography scan rarely required and may be used for deep subcutaneous or intramuscular abscesses and helpful to evaluate abscesses around the perineum (scrotum and rectum) and in the neck. Cultures are usually not necessary, because the bacteriology has been well-established and MRSA is endemic. For recurrent abscesses Gram staining and culture of the pus may be required.

Treatment and Prevention

Incision and drainage is strongly recommended for treatment of carbuncles, abscesses, and large furuncles. Incision and drainage traditionally involve a single linear incision followed by blunt dissection. Needle aspiration has been shown to be generally inferior to incision and drainage for drainage of cutaneous abscesses. However, on the face when cosmesis is a major consideration, needle aspiration may be preferred. Incision and drainage is routinely followed by irrigation of the abscess by some practitioners. After incision and drainage, packing the abscess cavity with one-quarter to one-half inch of gauze is another widely accepted routine practice. Antibiotics should be reserved for large or complicated abscesses, defined as those with fever or other systemic inflammatory response syndrome signs, >5 cm of surrounding cellulitis, or occurring in an immunocompromised host. After successful incision and drainage, hospitalization is not required but admission may be considered in the following situation.

- If abscesses drainage is done in the operating room,
- Significant surrounding cellulitis associated with fever requires parenteral antibiotics,
- Evidence of severe sepsis suggesting bacteremia, and
- Immunocompromised patients [including acquired immunodeficiency syndrome (AIDS), end-stage renal disease, and poorly controlled diabetes mellitus]

Discharge instructions aimed at reducing recurrences and spread of *S. aureus* within households. Discharge instructions after abscess incision and drainage should be given to patient are as follows:

- Keep draining wounds covered with a clean bandage.
- Wash hands frequently, especially after touching infected wounds or soiled bandages.
- Wash clothing that is contaminated by drainage.
- Do not share contaminated items such as towel, clothing, bedding, or razors.
- Clean contaminated environment surfaces with bleach, detergent, or disinfectant.

PURULENT CELLULITIS

Purulent cellulitis is associated with a purulent focus such as an abscess, a pustule, ulcer, or purulent wound and also known as culturable cellulitis. Causative pathogens for cellulitis with purulence are likely *S. aureus* with approximately 60% being MRSA. Oral trimethoprim-sulfamethoxazole (TMP-SMX) and intravenous vancomycin and clindamycin (oral or intravenous) are recommended antibiotics. It is very important for physicians to understand the distinction between purulent and nonpurulent cellulitis and the implications regarding etiology and antibiotic choice.

NONPURULENT CELLULITIS

Nonpurulent cellulitis typically occurs when there is a breakdown in the physical skin barrier, immune system, and/or circulatory system. Major risk factors include diabetes mellitus, obesity, venous insufficiency, impaired lymphatic drainage (e.g., trauma or prior surgery), IDU, and old age. Most cases of nonpurulent cellulitis are caused by β-hemolytic *Streptococcus* species includes not only *S. pyogenes*, but also

group C or G streptococci. Local pain, tenderness, swelling, and erythema are common clinical findings in nonpurulent cellulitis. Large areas of skin can be involved rapidly and associated with systemic manifestation such as fever, lymphangitis, or bacteremia. Carefully examine the lower extremities interdigital spaces between the toes for fissures or maceration, which may indicate a fungal coinfection requiring treatment.

ERYSIPYELAS

Erysipelas is a subtype of nonpurulent cellulitis limited to the epidermis. Erysipelas is an acute onset infection, clinically present as fever and mostly involve lower extremity with clear line of demarcation between involved and uninvolved tissue. Facial erysipelas may occur after streptococcal sore throat and classically has a brilliant salmon red color lesion and butterfly-shaped distribution.

Correct diagnosis of nonpurulent cellulitis can be challenging. It is identified as nonpurulent when it is actually purulent (and potentially caused by MRSA) and can lead to initiation of inappropriate treatment. In purulent cellulitis, fluctuance may be absent or underappreciated, especially early in the infection.

In addition, noninfectious processes are often misdiagnosed as cellulitis. Nonpurulent cellulitis should be distinguished from chronic venous insufficiency, gout, large local reactions, bee stings contact dermatitis, deep vein thrombosis, fungal infection, drug rash, vasculitis, malignancy (lymphangitis and carcinomatosis), and herpes zoster. The most important and life-threatening mimic of cellulitis is NSTI.

For diagnosis of cellulitis, imaging is not useful though point-of-care ultrasound examination can be used to evaluate undifferentiated erythema and swelling, such as deep vein thrombosis, superficial thrombophlebitis, bursitis, and acute arthritis (septic joint). Ultrasound findings in cellulitis give rise to a "cobblestone" appearance (subcutaneous edema, with hyperechoic fat lobules and adjacent hypoechoic interlobular septate). All patients with a soft tissue infection with signs of systemic toxicity (fever, hypotension, and tachycardia) should have blood cultures and laboratory tests (complete blood count with differential, serum chemistries, creatine phosphokinase, and C-reactive protein and lactate levels). Marked leukocytosis, hyponatremia, and elevated creatine phosphokinase should raise the concern for an NSTI.

Treatment and Prevention

Empiric antibiotic therapy must cover *Streptococcus* species for uncomplicated nonpurulent cellulitis. Staphylococcal coverage is not needed if there is no purulence. Options include cephalexin, dicloxacillin, clindamycin, and penicillin. For nonpurulent cellulitis with systemic signs of infection such as a high fever, intravenous antibiotics are indicated. Options include cefazolin, ceftriaxone, and clindamycin. In addition, if the patient is immunocompromised, e.g., poorly controlled diabetes, infected with the human immunodeficiency virus, and end-stage renal disease patients with cellulitis should generally hospitalized. In the setting of a traumatic wound and in patients with a history of MRSA infection or IDU, initial MRSA coverage should be considered (in the setting of cellulitis). Options for oral MRSA therapy include addition of TMP-SMX or doxycycline to the beta-lactam, or switching to clindamycin. Elevation of the extremity is considered an important component of cellulitis treatment. Interdigital fissures, scales, and maceration should be treated with a topical azole drug as this is an evidence of an underlying fungal infection. Other underlying predisposing conditions such as edema, eczema, venous insufficiency, diabetes mellitus, and obesity should be identified and treated accordingly.

NECROTIZING SOFT TISSUE INFECTIONS

Necrotizing fasciitis is the commonly used term but fasciitis represents only one aspect of NSTIs. NSTIs are rapidly spreading bacterial infection associated with necrosis of subcutaneous fat, muscle, and fascia. Necrotizing cellulitis, clostridial gas gangrene and myonecrosis, and spontaneous streptococcal myositis with streptococcal toxic shock are the subtypes of NSTIs. These infections are most difficult and high-stakes problems in emergency medicine require prompt surgical exploration and debridement for definitive diagnosis and cure. The diagnosis is on the basis of high suspicion, the patient is taken for surgical exploration and debridement for necrosis, patient survival chances may increase. If NSTIs are not suspected initially and patient condition not improved in spite of antibiotics and resuscitation, chances of survival become less. So management of these infections requires close teamwork and close association between emergency and with surgical team.

Epidemiology, Microbiology, and Pathophysiology

Necrotizing soft tissue infections are not very common. Globally the annual incidence ranges from 1.69 to 15.5 cases per 100,000 persons with mortality rates average 20–30% in the literature, but range widely depending on the pathogen(s) involved, underlying host factors, and how quickly the diagnosis is recognized. It is classically taught that NSTIs occur in the wake of devitalized tissue, such as in the postoperative or battlefield setting. Risk factors associated with NSTI are intravenous drug abusers, diabetic foot ulcers, peripheral vascular disease, malnourished, and alcoholic patient.

Necrotizing soft tissue infections are divided into two broad categories: (1) Polymicrobial infection (type I) and (2) Monomicrobial infection (type II). The proportion of cases that are polymicrobial can vary according to the study setting. Polymicrobial infections can include various bacteria, including streptococcal species, Enterobacteriaceae (gram-negative rods), clostridial species, nonclostridial anaerobes such as *Peptostreptococcus* species, *Staphylococcus* species. Monomicrobial infections classically are caused by GAS, previously called streptococcal gangrene. Any age-group and healthy individual may be affected by these infections. Monomicrobial NSTIs occur after exposure to salt water and fresh water, due to *Vibrio vulnificus* and *Aeromonas hydrophila*. *Clostridium perfringens* is found in both monomicrobial and polymicrobial infections. *Clostridium sordellii* NSTI occurs in individual with intravenous drug users and in the postpartum period. Additionally, community-associated MRSA (CA-MRSA) has been implicated as a cause of monomicrobial necrotizing fasciitis. Certain anatomic areas of the body are more prone for NSTIs like Fournier's gangrene is an NSTI of the

genitourinary region. Ludwig's angina is an NSTI that begins in the floor of the mouth. Both have the potential to spread rapidly along adjacent fascial planes. A summary of terms commonly encountered to categorize NSTI is listed in **Table 5**.

The pathophysiology of NSTIs differs depending on the etiologic pathogen. Bacteria or clostridial spores enter through the wound, inflammation, and necrosis spread from the skin and immediate subcutaneous tissue eventually to deeper muscle and fascia. When the inciting mechanism is the seeding of injured muscle by GAS bacteremia, inflammation, and necrosis spreads from the muscle (at which point pain and hypotension may be the only signs) to the skin, eventually producing visible necrosis and bullae. Vascular occlusion is a key component of NSTI pathophysiology. Virulence factors of *C. perfringens* and GAS produce exotoxins, contribute to lethality. *C. perfringens* alpha toxin causes platelet destruction, hemolysis, and increased capillary permeability, and produces massive circulatory collapse due to direct cardiotoxic effects. Streptococcal pyrogenic exotoxins, which compromise normal immune defenses, act as superantigens and trigger massive cytokine release ("cytokine storm") precipitate toxic shock syndrome. **Figure 1** presents a simplified taxonomy and pathophysiology of NSTI.

TABLE 5: Types of necrotizing soft tissue infections (NSTIs).

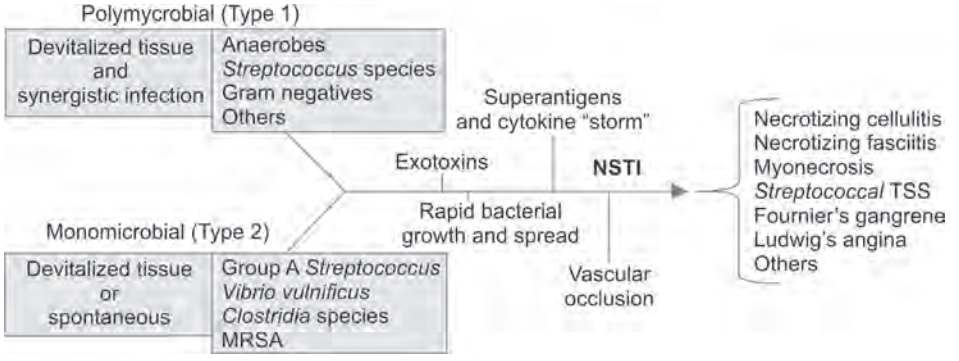
Type	*Description*
Gas gangrene	Associated with contamination of traumatic or surgical wounds by the toxin-producing anaerobe *Clostridium perfringens*, typically involves deep muscle tissue and spreads along facial planes
Fournier's gangrene	Typically, polymicrobial NSTI of the perianal and perineal region, more common in men
Ludwig's angina	Typically, polymicrobial odontogenic infection involving the floor of the mouth, with potential to spread via fascial planes to the neck and mediastinum
Type 1, polymicrobial	Polymicrobial (synergistic) infection, often involving oral and bowel flora. Includes Fournier's gangrene and Ludwig's angina
Type 2, monomicrobial	Typified by group A *Streptococcus* (GAS) and *Vibrio vulnificus*. GAS disease is classically associated with trivial injury and produces streptococcal toxic shock syndrome

Clinical Features

The presence of any of "hard findings" such as bullae, crepitus, necrosis, and cutaneous sensory deficit (from cutaneous nerve necrosis) on physical examination should be considered as NSTI until proven otherwise while the most common presenting signs and symptoms are nonspecific and include fever, pain, tenderness, local swelling, and erythema. In ED, diagnosing NSTIs are challenging as hard findings are absent in early stage of the disease. Massive "woody" soft tissue swelling, referred to as the Michelin Man sign, has been described, and likely is associated with *C. sordellii* and *C. novyi* infections among IDUs. Severe *C. sordellii* infections classically produce no fever. Gastrointestinal symptoms may predominate and be misleading early in cases of streptococcal toxic shock. Myositis may present as isolated and severe deep muscle pain; an elevated creatine phosphokinase, serum lactate, or small hemorrhagic bullae may be the first clues to a serious infection. Certain presentation in ED should raise the suspicion of NSTI. These include the following: diabetic foot infection; perineal infections, especially in men (Fournier's gangrene); odontogenic infections involving extension into the floor of the mouth (Ludwig's angina; any skin infection or poorly differentiated soft tissue complaint in an IDU; and unexplained, severe deep muscle pain).

Diagnosis

Laboratory testing may be useful in distinguishing NSTIs from other SSTIs, particularly from nonpurulent cellulitis. White blood cell count of >15.4/mm^3 and sodium of <135 mmol/L in the setting of a skin or soft tissue complaint should be considered an NSTI until proven otherwise. Elevated creatine phosphokinase can suggest infection involving deep muscle or fascia. Wong and colleagues derived the laboratory risk indicator for necrotizing fasciitis score based on laboratory tests including white blood cell count, sodium, and C-reactive protein. Moderate-to-high risk for NSTI is considered if score of 6 or higher (**Table 6**).



(MRSA: methicillin-resistant *Staphylococcus aureus*; NSTI: necrotizing soft tissue infection; TSS: toxic shock syndrome)

FIG. 1: Simplified taxonomy and pathophysiology.

TABLE 6: Laboratory risk indicator for necrotizing fasciitis score.

Laboratory parameters	*Range*	*Points*
C-reactive protein (mg/L)	≥150	4
White blood cell count (per mm^3)	15–25	1
	>25	2
Hemoglobin (g/dL)	11–13.5	1
	<11	2
Na (mmol/L)	<135	2
Creatinine (mg/dL)	>1.6	2
Glucose (mg/dL)	>180	1

Note: A score of >6 should prompt further evaluation (imaging) and surgical consultation.

Source: Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004;32(7):1535-41.

Plain radiographs helpful in demonstrating the subcutaneous gas in a stippled pattern (25% of NSTIs). Initial imaging modality of choice in most cases of NSTI is computed tomography scanning. It can demarcate the extent of inflammation and identify asymmetric thickening of the deep fascia and fluid adjacent to fascia, and is more sensitive than plain radiography for detecting tissue gas. Hemodynamically unstable patients in ED can be evaluated by bedside ultrasound examination. Specific ultrasound findings in NSTI include tissue gas, irregular fascia thickening, and perifascial fluid. Surgical exploration and debridement remains the definitive diagnostic test for NSTI, as well as the definitive treatment. The gold standard is a constellation of surgical findings that includes nonbleeding tissue, nonadherent muscular fascia on blunt dissection, greyish appearance of the fascia, and so-called dishwater pus. A Gram stain of the surgical specimen should be performed and result can be used to guide empiric antibiotic treatment.

Treatment

Prompt surgical debridement is considered the cornerstone of effective treatment. Surgical treatment involves wide debridement down to bleeding, and repeated inspection and debridement during the hospitalization is often necessary. The most critical supportive care is early goal-directed treatment of sepsis, resuscitation with crystalloid fluid, tissue perfusion monitoring, use of norepinephrine, and pain management when indicated. Because the bacterial etiology is almost never known at the time, NSTI is first suspected in the ED. Broad empiric antimicrobial coverage (piperacillin/tazobactam, vancomycin, and clindamycin) is required, targeting GAS, *Clostridium* species, gram-negative bacteria, and MRSA. Survival is likely inversely correlated with how soon antibiotics are started, as it is in septic shock. For suspected *Aeromonas hydrophila*, the recommended treatment is doxycycline plus either ciprofloxacin or ceftriaxone, and for *Vibrio vulnificus* it is doxycycline plus either ceftriaxone or cefotaxime.

SUMMARY

Skin and soft tissue infections are among the most common infections encountered in the ED and emergency physicians should be expert in their diagnosis and management. The emergence of CA-MRSA at the turn of the millennium greatly increased the incidence of purulent SSTIs and forced a change in antibiotic treatment. The first step in approaching an undifferentiated skin infection should be carefully assessed for purulence, which generally indicates a staphylococcal (often MRSA) infection. Drainage is required for abscesses and adjuvant antibiotics active against MRSA provide additional benefit. Nonpurulent cellulitis can be reliably treated with beta-lactam antibiotics alone. Antibiotic choice is best guided by a hospital antibiogram. Potentially deadly NSTIs require prompt recognition and surgical treatment, yet they are difficult to diagnose. A prudent approach is to consider NSTI every time one encounters a diabetic foot infection, an infection involving the perineum or the floor of the mouth, a skin or soft tissue complaint in an IDU, or any patient with unexplained severe muscle compartment pain.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Musculoskeletal Infections

Avdi S Tahiri, Artan Bejta

INTRODUCTION

Bone and joint infections are relatively uncommon cause of musculoskeletal complains among patients seeking care in emergency department (ED). Musculoskeletal infections such as osteomyelitis (OM) and septic arthritis can have long-term, devastating consequences for children and adolescents, if they are not diagnosed and promptly treated. The classic presentation for these infections is a child with fever and difficulty bearing weight or refused to walk. They management is challenging. Challenges include not only eradicating the infection but also managing other orthopedic complications such as joint destruction, bone loss, pathologic fracture, angular deformities, and limb length discrepancy. The importance of nutritional supplementation as an adjuvant treatment of these infections cannot be overemphasized. A systematic approach to OM, spondylodiscitis, spinal, epidural abscess, and antibiotic prophylaxis for an open fracture, septic arthritis, and periprosthetic joint infection (PJI) is essential in emergency department. For further evaluation and management lab investigations and radiology are also required.

OSTEOMYELITIS

Osteomyelitis (OM) is an infection of bone respectively inflammatory reaction of the bone due to infection most often bacterial in nature, is a rare but serious condition which included all parts of bone (bone marrow and periosteum) and all surrounding structures such as soft tissues and skin, thus as come to damaging all of these structures.

Epidemiology

The exact incidence is unknown. A study from Glasgow, Scotland, covering the period 1990–1999, suggests that it is less than three cases per 100,000 per year (Blyth et al. 2001). Incidence increase by age, especially over 60 years of age and diabetes-related OM.

Etiology and Causes

The causal organism in both adults and children is usually *Staphylococcus aureus* (found in over 70% of cases), and less often one of the other gram-positive cocci, such as the group A beta-hemolytic *Streptococcus* (*Streptococcus pyogenes*) which is found in chronic skin infections, as well as group B *Streptococcus* (especially in newborn babies) or the alpha-hemolytic diplococcus *S. pneumoniae*. But OM can be caused by other organisms as well. *Pseudomonas aeruginosa* often appears in patients using intravenous drugs. Immunocompromised patients are at risk for infection on one wide number of microorganisms such as mycobacteria and fungi (*Candida*) (**Table 1**).

TABLE 1: Organism involved in osteomyelitis.

Age group	***Most common organisms***
Newborns (younger than 4 months)	*S. aureus, Enterobacter* species, and group A and B *Streptococcus* species
Children (aged 4 months to 4 years)	*S. aureus*, group A *Streptococcus* species, *Kingella kingae*, and *Enterobacter* species
Children, adolescents (aged 4 years to adult)	*S. aureus* (80%), group A *Streptococcus* species, *H. influenzae*, and *Enterobacter* species
Adult	*S. aureus* and occasionally *Enterobacter* or *Streptococcus* species
Unusual osteomyelitis organism	
Organism	*Patient characteristic*
Salmonella	Sickle cell anemia patients (*S. aureus* is still most common)
Pseudomonas	IV drug use with AC or SC joint infection or puncture wound through rubber soled shoes
Bartonella	HIV/AIDS patient following cat scratch or bite
Fungal osteomyelitis	Immunosuppressed, long-term IV medications, or parentarel nutrition
Tuberculosis	Manifestations include Potts disease

(AC: acromioclavicular; AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; IV: intravenous; SC: sternoclavicular)

Risk Factors

Certain conditions and behaviors that weaken the immune system increase a patient's risk of OM, including diabetes mellitus (most cases of OM), sick cell disease, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), rheumatoid arthritis, intravenous drugs use, alcoholism, long-term use of steroids, hemodialysis, poor blood supply, recent injuries, and bone surgery replacements.

Pathophysiology

Bacteria may reach the bone via the bloodstream by direct inoculum caused by, e.g., trauma or surgery or by direct spread from an adjacent soft tissue infection (diabetic foot ulcer or periodontal disease). Whatever the route of access, bacteria must be able to subsequently adhere to components of the bone matrix in order to start the infection. Hematogenous OM results either from the introduction of microorganism into the bloodstream (e.g., via intravenous drug use or infected central venous catheter) or an infection elsewhere has a primary focus [e.g., endocarditis] (**Fig. 1**). Patients with OM will often have one or more pathologic risk focus associated with these mechanisms. OM can be acute and chronic OM. An acute OM progresses over days or weeks and is characterized by inflammation of viable bone. Chronic OM evolves over weeks to months or even years and is distinguished by progression to osteonecrosis with the formation of sequestrum, often in the setting of recurrent of refractory infection. In children, the infection usually starts in the vascular metaphysis of a long bone, most often in the proximal tibia or in the distal or proximal ends of the femur. In adults, hematogenous infection accounts for only about 20% of cases of OM, mostly affecting the vertebrae.

Several classification systems exist to categorize OM. The Waldvogel classification system divides OM into the categories of hematogenous, contagious spread, and vascular insufficiency (mechanism of pathogenesis). Cierny–Mader staging system is based of status of disease process, not in etiology, chronically or other factors (**Table 2**). This classification is based by the extent of host anatomic involvement, physiological status, and comorbid factors than can have influence in clearance of infection successful antibiotic therapy and other treatments.

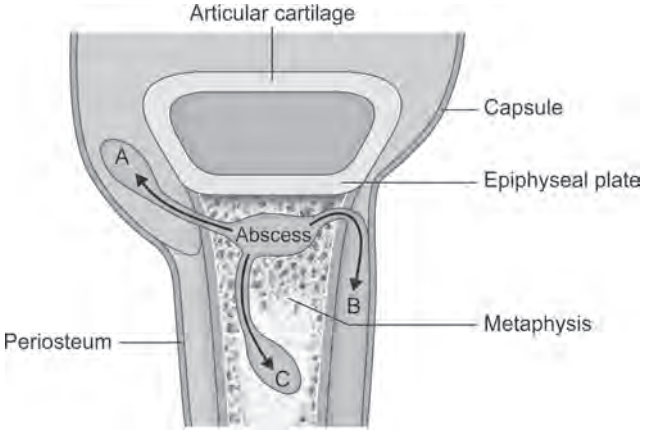


FIG. 1: The spread of pus from a metaphysical focus of osteomyelitis (A) directly into the joint, (B) into a subperiosteal abscess, and (C) into the medullary canal.

Clinical Presentation and Physical Examination

The most common anatomic locations of OM correlate with their mechanism of pathogenesis. Acute hematogenous OM occurs predominantly in children, with the metaphysis of long bones the most common location (e.g., femur and tibia). Contiguous spread is usually in lower extremities, especially in feet (diabetes and other vascular ulcers). Patients usually present within several days to weeks after the onset of symptoms. In addition to local sings of inflammation and infection, patients have sings of systemic illness, including fever, irritability, and lethargy. The subacute and chronic forms usually occur in adults. Generally, are secondary, to an open wound, most often an open wound injury to bone or surrounding soft tissue. Localized bone pain erythema and drainage around the affected area are frequently present. The cardinal sings of subacute and chronic OM include draining sinus tracts, deformity, instability and local sings of impaired vascularity, range of motion, and neurologic status. The incidence of deep musculoskeletal infection from open fractures has been reported to be as high as 23%. Other patients' factors such as altered neutrophil defense, humoral immunity, and cell-mediated immunity can increase the risk of OM. In diabetic and other patients with chronic wounds, certain physical exanimation findings specific to and highly suggestive of OM are easily identified at the bedside. Typical clinical findings include tenderness over the involved bone and decreased range of motion in adjacent joints.

Diagnosis

The diagnosis of OM is based primarily on the clinical findings, with data from the initial history, physical exanimation, laboratory testing, tissue sampling, and imagery. Due to non-specific constellation of sing and symptoms often associated with OM, emergency physicians must have a high index to suspicion for this disease.

Initial laboratory testing in ED should include a complete blood count (CBC), erythrocyte sedimentation, and C-reactive protein (CRP) at the minimum. Blood cultures are positive in up to one-half of children with acute OM. Patients with OM can have or not a leukocytosis. In OM of the extremities plane film and bone scintigraphy remain the primary investigative procedures.

Radiographic evidence of bone destruction by OM may not evident until approximately 2 weeks after the onset of

TABLE 2: Cierny–Mader classification of osteomyelitis.

Anatomic location	
Stage I	Medullary
Stage 2	Superficial
Stage 3	Localized
Stage 4	Diffuse
Host type	
Type A	Normal
Type BL	Locally compromised
Type BS	Systemically compromised
Type C	Treatment is worse to the patient than infection

infection. These radiologic tools help to rule out other potential pathology (e.g., fracture) and provide a baseline for future comparison. A bone abscess found during subacute or chronic stage of hematogenous OM is known as a Brodie's abscess. Computer tomography (CT) can demonstrate periosteal reaction, cortical/medullar bone destruction, and/or adjacent soft tissue infection in great detail.

Magnetic resonance imaging (MRI) can be extremely helpful in unclear situations. This imaging modality is particular useful when a patient is suspected of having an OM and discitis septic arthritis involving the axial skeleton and pelvis. MRI is the most sensitive (90%) and specific (83%) imaging modality available for diagnosing OM, often as early as 3–5 days after the initial onset of infection.

Histologic and microbiologic exanimation of bone is the gold standard for diagnosing OM. Cultures of sinus tract samples are not reliable for identifying causative organisms. Therefore, biopsy is advocated to determine the etiology of OM. Isolation of the infecting microorganism from bone followed by antibiotic susceptibility testing (antibiogram) are important in directing treatment.

Treatment

After the initial evaluation, staging, and establishment of microbial and susceptibilities, treatment includes antimicrobial therapy, debridement with management of dead space, and, if necessary, stabilization of bone. In the most patients with OM, early antibiotic therapy produces the best results. Eradicating a deep-seated infection of the bone can be difficult and successful treatment of OM often requires a combination of medical and surgical therapies. Emergency physician must determine first in caring of a patient with OM is to decide whether antibiotic therapy needs to be initiated ED or not. It depends on the hemodynamic condition of the patient. If the patient's condition appears stable, this allows us to wait a little time until the results of the bone biopsy comes and where we get an information about the type of antibiotic therapy which indicated by antibiogram. However, if the patient is unstable or has sing and symptoms of sepsis every antibiotic therapy is justified. In suspected cases for active OM, blood samples for blood culture should be taken before the antibiotic therapy.

Antibiotic Therapy

Acute hematogenous OM is best managed with careful evaluation of microbial etiology and susceptibilities and a 4–6-week course of appropriate antibiotic therapy. After cultures have been obtained, an empiric parenteral therapy regimen (nafcillin) plus ceftriaxone is initiated to cover clinically suspected organisms. Children with acute OM should receive 2 weeks of initial parenteral therapy before they are given an oral antibiotic therapy.

Chronic OM in adults is more refractory to therapy and is generally treated with antibiotics and surgical debridement. Depending on the type of chronic OM patient may be treated with parenteral antibiotic therapy for 2–6 weeks. Oral therapy using fluoroquinolone antibiotics for gram-negative organisms is presently being used in adults with OM. Other antibiotics that can used to gram-negative agents, such as *P. aeruginosa*, can be achieved with cefepime or meropenem. Gram-positive agents can be covered with vancomycin. Metronidazole can be used to anaerobic agents. Use of vancomycin in combination with piperacillin-tazobactam should be avoided due to risk of nephrotoxicity.

Debridement and Surgical Therapy

The indications for surgical treatment of OM will depend on many factors, including the anatomic location, duration of symptoms, mechanism of pathogenesis, and patient comorbidities. The quality of debridement is the most important and critical factor in successful management. After debridement with excision of bone, removing all infected soft tissues, it is necessary to obliterate the dead space created by the removal of tissue. Dead space management includes local free tissue transfers (e.g., flap coverage) and the use antibiotic impregnated beads. Soft tissue procedures have been developed to improve the local blood flow and antibiotic delivery.

Special Situations

Diabetes mellitus: Diabetes is a significant contributing factor in OM, particularly when patients have concomitant neurologic or vascular abnormalities. *P. aeruginosa* is most frequently isolated from these infections. Initial hospitalization to these patients for vascular supply, identify the agents, and debridement and drain tissue may be necessary.

Follow-up

During treatment, patients with OM should be followed closely for signs and symptoms of worsening infection. After the treatment, follow-up should be based on the response of therapy and the overall health of the patient.

SPONDYLODISCITIS (VERTEBRAL OSTEOMYELITIS)

Spondylodiscitis is an infectious inflammation that affects the vertebrae, vertebrae disk, and adjacent structures. Commonly referred as vertebral OM, spondylodiscitis has an annual incidence of 2.4–4.8 cases per 100,000 individuals. All ages can be affected, but the appearance mostly increases with age. Men are up to three times more than women; this is probably because of higher frequency of comorbidities in men. Spondylodiscitis is the most common complication of sepsis or local infection, usually in the form of an abscess. It usually affects two contiguous vertebrae and space between them. The most common site of infection is the lumbar spine (58%) followed by thoracic (30%) and cervical spine (11%).

Etiology

The main causative organisms are staphylococci and *Mycobacterium tuberculosis*, but potential organisms include a large number of bacteria (*Escherichia coli*, *P. aeruginosa*, and *Proteus mirabilis*), fungi, and rarely zoonosis. Spinal infections can be described etiologically as pyogenic, granulomatous tubercular, fungi, and parasitic. Pyogenic spinal infections include spondylodiscitis, spondylitis, and discitis.

The predisposing and triggers for this infection are diabetes mellitus, age, cardiovascular disorders, drug abuse and longtime steroid intake, alcoholism and nicotine abuse, spinal abnormality, bacteremia (endocarditis), injection drug use, serious trauma, impaired immune competence (chemotherapy and HIV), anemia, cancer, organ failures (renal, liver, or cirrhosis), and rheumatic diseases.

Clinical Presentation

The symptoms of spondylodiscitis are nonspecific and diffuse. More than 90% of patients will complain of localized back or neck pain that is often worse at night and not alleviated by rest and analgesics. Most of them complain an radicular pain which spread to the chest and abdomen. Most of them have fever (less common in patients with tuberculous spondylodiscitis, half of the cases) and neurologic symptoms such as sensory deficit, leg weakness, paralysis, radiculopathy, and sphincter loss. With progression of disease to adjacent structure patient may complain of motor deficit such as limb weakness i.e., paraplegia and quadriplegia. Weight loss may also occur in tubercular or other chronic infections. Lumbar spine infection can precipitate abscesses of the psoas muscle.

Diagnosis

Medical history; often is not characteristic. Either acute fulminant development of symptomatology with localized pain and high fever or gradual insidious onset. The clinical examination includes inspection concentrating on local changes and taking a detailed neurological status. There is typically pain on heel strike, impaction, and percussion, but little local pain on pressure. Diagnosis can delay due to misdiagnosing because symptoms are nonspecific. The laboratory parameters be determined are leukocytes, CRP, and erythrocyte sedimentation rate (ESR). In patients with acute disease, there are a massive increase in the inflammation parameters and in ESR. CRP is typical in chronic cases. Conventional X-ray is the first investigative procedure for diagnosing but is unreliable in early phase of spondylodiscitis (abnormalities cannot be detected until 2–8 weeks). The main methods to diagnose a spondylodiscitis are MRI, biopsy, and microbiological tests such as polymerase chain reaction (PCR) to determine an infectious cause.

An MRI is the diagnostic procedure of choice if spondylodiscitis is suspected. MRI with gadolinium imaging method has a highest sensitivity (93–96%) and specific (92–97%). This provides an image of the whole length of the spinal column so that infection be detected. CT scan can identify cortical destruction and adjacent soft tissue when MRI is contraindicated. The definitive diagnosis of spondylodiscitis is made by bone biopsy with multiple specimens submitted for microbiological culture and pathologic review.

Treatment

Empiric antibiotic therapy can be initiated in emergency department only for severe infection, otherwise antibiotic should be planned after and according to culture and sensitivity report. Antimicrobic therapy for spondylodiscitis should to continue for at least 6 weeks, tuberculosis should take 12 months (consult the infectious disease specialist). Rest and brace use.

Follow-up

Laboratory and X-ray every 6 weeks.

Surgical Treatment

Debridement may be necessary in the setting of epidural or paravertebral abscesses, persistent pain, vertebral destruction/instability, and deformity (consult spine surgeons).

SPINAL EPIDURAL ABSCESS

A spinal epidural abscess (SEA) is an accumulation of pus in the epidural space that can mechanically compress the spinal cord. SEA can develop independently of spondylodiscitis and usually occur in thoracic or lumbar regions. Overall, the incidence of SEA is 1.8 cases per 100,000 persons per year.

Etiology

The most common bacteria that causes SEA come from *Staphylococcus* and *Streptococcus* bacteria followed by *E. coli* and mixed anaerobes. Occasionally the cause is a tuberculosis come from thoracic spine (Pott's disease). Other possible causes of SEA include boils that develop on skin, especially on the scalp and back, septicemia, injury, foreign objects (bullet and knife), and complications from back surgery or puncture procedures. The risk factors who help to develop the SEA are using an anticoagulant agents and blood thinners, a weakened immune system, and a ruptured gallbladder.

Clinical Presentation

Patient with SEA can present to the ED anywhere along a continuum of disease with a wide range of signs and symptoms. The symptoms of an epidural abscess depend on the location of the abscess. Epidural abscess symptoms are headache, disturbed consciousness, fever, movements problems, trouble walking, weakness, (i.e., cauda equina, conus medullaris), inability to control bowels and bladder, erectile dysfunction. A high index of clinical suspicion followed by timely diagnosis of SEA is essential to prevent complications of cord compression and irreversible sensory loss or paralysis.

Diagnosis

Laboratory (CBC, ESR, and CRP). Blood cultures are positive approximately in 60% of patients with SEA. Imaging include X-ray and noncontrast radiology are not much helpful. MRI and CT myelography are highly sensitivity (>90%). Consider MRI to diagnose SEA if patient has unexplained pain. Lumbar puncture is contraindicated because it may trigger cord herniation.

Treatment

If abscess causes neurologic compromise, immediate drainage. Antibiotics with or without aspiration may be sufficient. If the abscess developed after a neurosurgical procedure or urologic instrumentation, an aminoglycoside is added to cover gram-negative bacteria. An epidural requires immediate treatment. Symptoms can include headache, fever, changes in consciousness, vomiting, changes in sensitive, moving or walking, loss of bladder or bowel control, and erectile dysfunction. *Treatment* is with strong antibiotics. Surgery might be needed to drain the fluid from abscess completely.

SEPTIC ARTHRITIS

Septic arthritis is an infection in the fluid and tissues in the joint. It is usually caused by bacteria but occasionally by viruses or fungi. Infectious arthritis can affect people of all ages and genders. The incidence is reported as two to eight cases per 100,000 of general population. In ED, from total number of patients, septic arthritis presenting with 0.01% of all visits.

Acute infectious arthritis caused by bacteria begins quickly. Most cases of septic arthritis are acute, and can affect healthy people as well as people with risk factors. Cartilage within the joint, which is essential with normal joint function, can be destroyed or damaged within hours or days and called as reactive arthritis. In reactive arthritis, the join can be inflamed but not actually infected. Chronic infectious arthritis begins gradually over several weeks. Very little cases of arthritis are chronic and most often affects individuals with risk factors (**Figs. 2A** to **D**).

The joints most commonly infected are the knee, shoulder, wrist, hip, elbow, and the joint of fingers. Most cases of septic arthritis occurs from hematogenous seeding of a joint in the setting of bacteremia. Less frequently, overlying soft tissue infections can spread contiguously to the joint. Direct inoculation of bacteria into a joint can occur through a traumatic arthrotomy, open fracture with dislocation, arthrocentesis or intraarticular injection, and animal bites, e.g., dog cat. Common risk factors are similar as other musculoskeletal infections such as older age, diabetes mellitus, rheumatic arthritis, joint surgery, prosthetic tissue infection, skin infection, injection drug use, alcoholism, sexually transmitted diseases, hemophilia, dialysis, and sickle cell disease (acute septic arthritis).

Etiology

Acute septic arthritis is usually caused by bacteria and viruses. As in other musculoskeletal infections most causative bacteria are *Staphylococcus aureus* and streptococci, but can be caused by other bacteria such as *E.coli* and other gram-negative bacteria Neisseria *gonorrhoeae*. Viruses such as HIV hepatitis B and C can also be causative agent at any age. Spirochetes that cause Lyme disease and syphilis can infect joints. *Candida* septic arthritis may be associated in patients with impaired immune systems. Chronic septic arthritis is usually caused by *Mycobacterium tuberculosis* and fungi. Risk factors for chronic septic arthritis include rheumatoid arthritis, HIV infection, steroid long-time use, chemotherapy, and patients with cancer, an artificial joint.

Clinical Presentation

In acute infectious, symptoms usually begin over hours to a few days. Joint pain associated with warmth, swelling, redness, and restricted movement are the primary presenting features of septic arthritis. Moving and touching is very painful. Fluids collects in the infected joint causing it so swell and stiffen. Symptoms sometimes also include fever and chills. Fever is not diagnostic symptom. In chronic arthritis, symptoms are usually gradual swelling, mild warmth and mild or no redness of the affected joint area, and aching pain that may be mild and less severe than in acute septic arthritis. Usually, a single joint is affected. Unrecognized septic arthritis can progress to joint destruction, OM, and sepsis, with an overall mortality approaching 10%. Early and timely recognition of septic arthritis by the emergency physician is necessary to improve outcomes.

Diagnosis and Differential Diagnosis

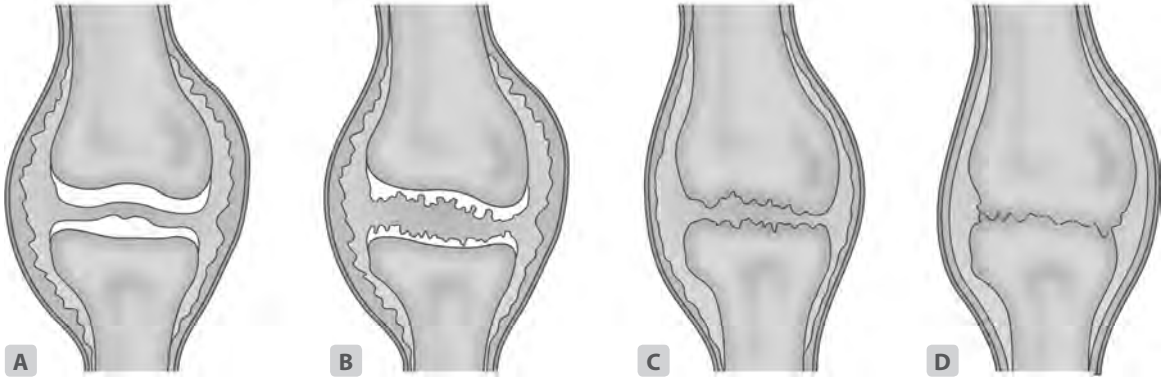
A through history and physical examination are essential of diagnosis, but diagnostic evaluation includes blood tests (CBC, ESR, and CRP), analysis and culture of joint fluid, sometime sputum, spinal fluid, and urine tests. Imaging such as X-ray, CT scan, ultrasonography, and MRI are helpful for diagnosing septic arthritis. Usually a sample of joint fluid (joint aspiration) is essential. Synovial fluid should be submitted for cell count with differential, Gram stain, and microbiological (aerobic and anaerobic) culture. The higher the synovial white blood cell (WBC) count, the greater the chances of septic arthritis. Multiple sets of blood tests and cultures also should be obtained when hematogenous septic arthritis is suspected to improve the chances of identifying a causative microorganism. Imaging helps well such as plain radiography of the infected joint may reveal joint destruction. CT and MRI help in evaluation of septic arthritis also and ultrasonography is done to identify accumulations of fluid or collections of pus (abscesses). Differential diagnosis for septic arthritis includes rheumatic arthritis, Reiter's syndrome, psoriatic arthritis, ankylosing spondylitis, and osteoarthritis.

Therapy

Successful treatment depends on antibiotics, antifungal drugs, removal of the pus, and splinting of the joint, followed by physical therapy.

PERIPROSTHETIC JOINT INFECTION

Performing joint aspirations can identify patients with infection who were erroneously categorized as "aseptic failures". PJIs are one of most challenging and frequent complications after lower extremity joint (hip and knee) arthroplasty.



FIGS. 2A TO D: Acute suppurative arthritis. (A) Pathology in the early stage; (B) There is an acute synovitis with a purulent joint effusion; (C) Soon the articular cartilage is attacked by bacterial and cellular enzymes. If the infection is not arrested, the cartilage may be completely destroyed; (D) Healing then leads to bony ankylosis.

Anywhere from 0.5–2.0% of primarily total hip or knee arthroplasty procedures are complicated by PJI.

Based on the proposed criteria, definite PJI exists when: (1) There is a sinus tract communicating with the prosthesis, (2) a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint, (3) four out of six criteria exist [elevated ESR and CRP, elevated synovial WBC, elevated synovial fluid neutrophil, presence of purulent fluid in the affected joint, isolation of microorganism in one culture of periprosthetic tissue or fluid, and >5 neutrophils per high-power field (HPF)]. PJI may be present if fewer than four criteria are met. Risk factors include male gender, tobacco use, elevated body mass (>30 kg/m^2), diabetes mellitus, rheumatic arthritis, corticosteroid use, previous joint surgery (including revision arthroplasty), and depression.

Pathogenesis

Foreign body devices are covered by host proteins (e.g., fibronectin) after implantation favoring bacterial adherence. Absence of implants causes impairment of activation and degranulation of the granulocyte.

Clinical Manifestations

- *Acute exogenous PJI*: Local sign of inflammation (wound dehiscence, secretion, erythema, warmth, swelling, and tenderness in affected joint and surrounding soft tissue).
- *Acute hematogenous PJI*: Pain after implantation without sing for infection and new onset articular effusion.
- *Chronic PJI*: Pain because of early loosening, local inflammation, sinus tract, and chronic articular effusion.

Microbiology

Most frequent microorganisms are *Staphylococcus aureus* and streptococci and *Propionibacterium acnes* (most important microorganism in periprosthetic shoulder infection).

Treatment

Cornerstone of successful treatment is early recognition and diagnosis. Cure is only possible with adequate surgery combined with long-term antibiotic therapy. Appropriate surgical intervention. The total duration of antibiotic treatment following revision surgery should not exceed 12 weeks.

SUMMARY

Patients with musculoskeletal infections can have heterogeneous presentations, as the signs and symptoms are often occult and nonspecific. *Staphylococcus aureus* is the most common microorganism associated with bone and joint infections. Clinical presentations of musculoskeletal infection in patients presenting to emergency care can range from chronic wounds and nonspecific bone or joint pain to functional debilitation, and even neurologic compromise when the spine is involved. Definitive diagnosis requires sampling of affected tissue for Gram stain and microbiologic culture. Emergency physicians play a critical role in early recognition, evaluation, and management of these infections. Appropriate collection of microbiologic cultures (e.g., blood and synovial fluid) before empiric therapy in the ED has significant implications for isolating causative microorganisms and guiding downstream treatment. Antibiotic therapy may even be safely withheld to pursue bone biopsy and culture if the patient is clinically stable. The mainstay of treatment for bone and joint infections is antibiotic therapy, but surgical consultation for irrigation and/or debridement may be necessary in certain clinical situations. A low threshold should adopt to seek orthopedic surgery and infectious disease specialist consultation in patients presenting with bone and joint infections in the ED and many will require hospitalization for definitive care, combing medical and surgical approaches.

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195 CHAPTER

Management of Sexually Transmitted Infection

Shahbaz Anees, Durre Aden

INTRODUCTION

Management of patients especially those who are at the highest risk for sexually transmitted infections (STIs) can be challenging at times because of the delay in the diagnosis and disease being asymptomatic many times. Thus, there is a need for proper investigations, management, and follow-up of patients with STIs.

EPIDEMIOLOGY

Sexually transmitted infections include human papillomavirus (HPV), *Neisseria gonorrhoeae* (GC), *Chlamydia trachomatis* (Ct), herpes simplex virus (HSV), syphilis, human immunodeficiency virus (HIV), and pelvic inflammatory diseases (PIDs). The number of cases of STIs has increased and is seen more commonly in young adults, pregnant females, and high-risk groups such as homosexual males. The number of cases of syphilis has increased from 17.6% from 2015 to 2016. Generally, most of the patients are either asymptomatic or go for regular outpatient treatment, but still few patients can come to the emergency department (ED) if health care access is limited or patient has some kind of complications. Around 7–16% of STIs are treated in the ED.

A study done by Pearson et al. in 2017 showed that STI visits to the ED have increased. STI treatment without testing impairs the determination of prevalence and incidence of STIs.

ROLE OF THE EMERGENCY DEPARTMENT

Most of the patients with STIs are either asymptomatic or present with nonspecific symptoms. Screening for STIs in an ED can be difficult and challenging as the healthcare personnel are busy treating other acute emergency medical conditions.

So, most of the patients who are treated for STIs are treated symptomatically in the ED based on their chief complaints, such as vaginal/penile discharge or painful urination. Thus, a significant number of patients with STIs remain either undiagnosed or untreated.

Therefore, emergency care providers must be aware of the prevalence of the disease and can have a high index of suspicion of patients with STIs. Testing for STIs should be done even when test results are not immediately available for any patient coming with symptoms such as vaginal or penile discharge or dysuria and STIs are a differential.

Among the various available test, nucleic acid amplification tests (NAATs) are highly specific and sensitive and can help in diagnosis, management, and follow-up of the patients in different ways.

Once the patient is aware that their test results are positive for an STI, they are less likely to acquire an STI in the future. Reed et al. in 2015 in a study on adolescent women also found that those who were aware of their test results had a reduced number of a subsequent visit to the ED for the diagnoses of STI. Many times symptoms of STIs resolve without treatment and leads to permanent sequelae like infertility or PID. NAAT is especially important in patients with recurrence of symptoms and can help in the appropriate management and drug-resistant case. Once the confirm diagnosis of STI is made, patients can more precisely direct their partners to proper therapy which is known as expedited partner therapy (EPT). A diagnosis of STI may help provide pre-exposure prophylaxis (PrEP) against HIV infection.

RISK FACTORS

Young patients with age <25 years, history of sexual contact with multiple partners, not using proper barrier conceptions, drugs, and exchanging sex for drugs and money are high-risk groups for STIs.

EVALUATION

A proper history including sexual history and complete physical examination should be conducted to narrow down the diagnosis.

INVESTIGATIONS

Gold standard testing for most STIs is NAATs and cultures. This is the delay in test results that leads to a primarily syndromic approach to STI diagnosis and frequent empiric treatment. In one study, patients who tested positive for *Chlamydia* or gonorrhea were more likely to have received appropriate

antibiotics than those patients who were negative for either demonstrating that ED providers use symptoms or clinical findings to avoid overtreatment. ED providers treat about 50% of patients with an STI at the time of visit. Follow-up for these patients with an untreated STI is essential, and challenges can be met with focused follow-up planning. In this chapter, we will be dealing with some of the commonly encountered STIs in the emergency room (ER), their management, and empiric treatment.

CHLAMYDIA

Pathophysiology

Chlamydia is a sexually transmitted disease (STD) caused by Ct, a gram-negative obligate intracellular bacterium. Some serotypes of Ct can cause lymphogranuloma venereum (LGV), which are seen especially in patients that participate in anal sex, specifically among men who have sex with men (MSM). They infect columnar epithelial cells in the cervix, urethra, rectum, and oropharynx.

Adolescent females are predisposed to *Chlamydia* due to continued presence of columnar epithelium in ectocervix.

Clinical Presentation

Most of the patients are asymptomatic; however, some can present with vaginal or urethral discharge, rectal discharge, dysuria, abdominal pain, testicular pain, or symptoms of PID.

Special attention should be paid to patients presenting with rectal pain or discharge who are suspected to have *Chlamydia*.

Physical Examination

An examination may show a watery urethral discharge in men or clear endocervical discharge in women. LGV acquired from receptive anal sex can present with proctocolitis, and the associated lymphadenopathy can cause discomfort. All patients with Ct need instructions to abstain from sex for 7 days after treatment and to seek retesting in 3 months (1 month if pregnant) along with prevention counseling. All sex partners in the previous 60 days should also be tested and treated. Some state laws allow for EPT, which is prescribing treatment to partners of patients with proven Ct via a prescription given to the patient for the partner. Large-scale randomized controlled trials have shown that EPT reduced rates of recurrent infections in patients, but EPT is often not available in the ED setting.

Diagnosis

Gram stain of the sample can be done however culture and NAAT are more specific tests.

Treatment

Chlamydia can be treated with azithromycin 1 g PO single dose or doxycycline 100 mg PO twice daily for 7 days. However, LGV can be treated with doxycycline 100 mg orally twice a day for 3 weeks. All patients should be counseled for abstinence from sex for 7 days after treatment and to come for retesting in 3 months (1 month if pregnant). All sex partners of the patient within the last 60 days should also be evaluated and treated. EPT reduces the rate of recurrence, but it is not available at ED.

GONORRHEA

Epidemiology

Gonorrhea is the second most common STI in the US, after *Chlamydia*.

Pathophysiology

It is caused by *N. gonorrhoeae*, gram-negative intracellular diplococcus. They also infect columnar epithelial cells in the cervix, urethra, rectum, and oropharynx and the risk factors are similar to that of *Chlamydia*.

Clinical Presentation

Patients present with symptoms similar to Ct. Urethral discharge in males is more mucopurulent than clear in appearance.

Diagnosis

The urethral discharge is sent for Gram stain. The organism can be isolated by culture technique in Thayer-Martin media. The gold standard for diagnosis is NAAT, but it is not available at many centers.

Treatment

Drug resistance is seen in GC, thus dual therapy is needed. Both ceftriaxone and azithromycin are used to reduce the development of cephalosporin resistance in GC.

A single dose of ceftriaxone 250 mg intramuscular (IM) with 1 azithromycin 1 g PO once is given. In patients with allergy to cephalosporin or severe penicillin allergy, gentamicin 240 mg IM 1 plus azithromycin 2 g orally is the recommended treatment with later follow-up.

Follow-up for patients with GC is similar to Ct.

Complications

Neisseria gonorrhoeae can disseminate and can present with septic arthritis, polyarticular arthritis, and/or pustular skin lesions and fever. Such patients require hospitalization and treated initially with intravenous (IV) ceftriaxone 1 g TDS for 7 days.

TRICHOMONAS VAGINITIS/BACTERIAL VAGINOSIS

Epidemiology

It is caused by *Trichomonas vaginalis* (TV), a protozoan parasite. Bacterial vaginosis (BV) is caused by *Gardnerella vaginalis*.

Presenting Complaints

Female patients come with the common complaint of vaginal discharge in EDs while the men are mostly asymptomatic. Vaginal discharge can also be seen with infections such as *Chlamydia*, gonorrhea, *Trichomonas*, yeast, or BV. Trichomonas vaginitis is diagnosed in the ED generally.

Physical Examination

The pelvic examination reveals white copious, malodorous discharge, and irritated vaginal mucosa (strawberry cervix).

Diagnosis

Wet mount shows mobile trichomonads in TV while clue cells (vaginal epithelial cells with adherent coccobacillus) are seen in BV. Culture can be used to isolate the organism.

Patients with TV or BV, both will have a vaginal discharge of pH >4.5 and is a low cost and important test for the diagnosis.

Nucleic acid amplification tests are recommended over wet mount examination for definitive diagnosis of *Trichomonas*.

Treatment

Treatment of TV is metronidazole 2 g PO single dose or tinidazole 2 g PO single dose. Metronidazole 500 mg PO twice daily for 7 days can be given for BV.

Prevention and follow-up instructions are similar to other STIs. Patients with BV should be referred to primary care because of a high recurrence rate.

SYPHILIS

Syphilis is caused by the spirochete, *Treponema pallidum*. It is a complex disease with a course of clinical manifestation with a period of latency between primary and secondary stages. Since the symptoms are nonspecific, so it is also known as a great imitator and a high level of suspicion is required for the diagnosis.

Pathophysiology

It enters the body through the erosion in the skin or mucous membrane during sexual intercourse and spreads into the lymphatics and blood in few hours. Transplacental transmission is also seen in syphilis.

Clinical Presentation

Primary syphilis presents as a painless ulcer having indurated border called as a chancre which resolves in 3–6 weeks without treatment.

Secondary syphilis develops after 4–10 weeks after the chancre resolves. It presents as palmar/plantar rash, condyloma lata, arthralgia, and ocular syphilis in the form eye pain and blurry vision.

Tertiary syphilis follows 1–30 years after the infection.

Physical Examination

Ophthalmology evaluation may confirm uveitis or retinitis.

Diagnosis

It cannot be cultured in vitro. In primary syphilis, the sample is collected from chancre and direct fluorescent antibody (DFA) (darkfield microscopy) is done. Serological tests include nontreponemal test [e.g., rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL)]. They are sensitive in immunocompetent patients but nonspecific. So it should be followed by confirmatory treponemal-specific test [fluorescent treponemal antibody absorption (FTA-ABS), *T. pallidum* particle agglutination (TP-PA), *T. pallidum* particle agglutination assay, and enzyme immunoassay (EIA)]. All patient of syphilis should also undergo HIV testing.

Treatment

Treatment of primary, secondary, or early syphilis is benzathine penicillin G 2.4 million U IM single dose. Neurosyphilis or ocular syphilis is treated with aqueous crystalline penicillin G 18–24 million U/day for 10–14 days. Congenital syphilis is recently increasing. Thus pregnant women should be screened and referred to as obstetrics and gynecology.

HERPES SIMPLEX VIRUS

Epidemiology

Herpes simplex virus is the most important cause of painful ulceration. They are of two types; type 1 HSV (HSV-1) and type 2 HSV (HSV-2) which causes oral and genital lesions, respectively. Seroprevalence is high in old age and females.

Pathophysiology

Herpes simplex virus is a double-stranded deoxyribonucleic acid (DNA) virus and spread through by contact of abraded skins and mucus membranes. HSV-1 is transmitted through nonsexual contact, while HSV-2 spreads through sexual contact. The incubation period is 2–12 days after infection.

Once it enters the skin, it goes to peripheral nerves, sensory and autonomic ganglia, and remains in a latent stage for an indefinite period. It can also go to central nervous system (CNS). Reactivation of the latent virus can occur during stress and immunocompromised state.

Clinical Features

Primary HSV present with fever, bilateral lymphadenopathy, and painful lesions. Lesions are blister-like and coalesce to form a shallow ulcer after a few days. The lesion remains for 2–3 weeks.

The patient may also complain of symptoms of cervicitis, urethritis, and proctitis. Other less common features include encephalitis, myelitis, and ocular manifestations. There is also a risk of vertical transmission.

Diagnosis

Viral culture is the preferred method but only sensitive during the vesicular stage. The polymerase chain reaction (PCR) is more sensitive and practiced at many centers. Cerebrospinal fluid (CSF) PCR along with viral culture is the test of choice for CNS infection.

Treatment

Oral antivirals reduce the number of symptomatic days. If swelling or pain is severe, IV acyclovir may be given. Treatment does not eliminate the viral load.

The partner should be informed about HSV status and abstinence from sex when the lesion and use barrier method even when the lesions are absent.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease is an ascending infection of the upper reproductive tract and can lead to endometritis, salpingitis, tubal ovarian abscess, and pelvic peritonitis. It occurs due to complications of *Chlamydia* and gonorrhea infection. If untreated, it can lead to scarring and infertility.

Clinical Features

Clinical presentation varies from an asymptomatic state to a septic shock. The patient presents with abdominal pain, fever, and vaginal discharge.

Physical Examination

Mucopurulent cervical discharge, cervical motion tenderness, and adnexal tenderness are seen on examining the pelvis.

Diagnosis

All patients should be tested for *Chlamydia*, gonorrhea, and HIV. ESR and C-reactive protein (CRP) are supportive tests. Transvaginal ultrasonography (USG), laparoscopy, MRI, and endometrial biopsy are specific tests.

Treatment

Oral antibiotics are recommended for ambulatory patients. Ceftriaxone 250 mg IM once or 1 doxycycline 100 mg PO twice daily 14 days are considered. Metronidazole 500 mg orally twice daily for 14 days can also be prescribed. Management with hospitalization and IV antibiotics is indicated if patients are not tolerating oral antibiotics or have a complication like tubo-ovarian abscess (TOA) or are pregnant.

Cefoxitin 2 g IV every 6 hours + 1 doxycycline 100 mg PO twice daily for 14 days are given or metronidazole 500 mg PO twice daily for 14 days can also be used. Surgical consultation may need for management of TOA.

SPECIAL SCENARIO

Pediatrics

Sexual abuse should be suspected in case of STIs in pediatric patients. However, transmission from mother to child occurs in the neonates who present with conjunctivitis and pneumonia and can be life-threatening.

Sexually active adolescents are generally at higher risk of transmission due to several biological and behavioral features. Infections are often asymptomatic and follow-up is poor, so empiric treatment should be given.

Pregnant Women

Sexually transmitted infections can complicate the pregnancy in the form of preterm labor, premature rupture of membranes, low birth weight, stillbirth, and congenital infections in the newborn. These are mostly seen in gonorrhea and Chlamydia infections are unrecognized or untreated in the ED. Diagnosis and treatment is similar to nonpregnant patients. However, tetracyclines should be avoided in pregnancy. All pregnant females with STI should undergo regular prenatal care, PID workup, and empiric treatment and close follow-up.

Men having Sex with Men and Transgender

A high-risk group attending ED for STIs includes lesbian, gay, bisexual, and transgender (LGBT). There have to face discrimination in receiving proper healthcare. The National Transgender Health Survey has reported that 33% of transgender have faced discrimination in healthcare and 16% had experienced discrimination in an ED. Direct sexual history should be taken respectfully asking "What is the gender of your sex partner?" The Centers for Disease Control and Prevention (CDC) recommendations should be followed during the STI testing. All the sites of sexual contact must be tested. In MSM, apart from urine/urethral testing, samples from other sites such as pharynx and rectum for NAAT should be taken. For those who are not comfortable with testing, they should be allowed for self-collected NAATs.

Sexual Assault Victims

The ED healthcare provider should be familiar with local STIs prevalence. They should manage the case with professionals who are trained in assessing and counseling patients of sexual assault. As per the CDC STD guidelines, the following screening tests should be done in adult and adolescent victims of sexual assault:

- NAATs at sites of penetration or attempted penetration for GC and Ct
- NAATs from urine or vaginal specimen for trichomonad
- A wet mount with pH and KOH testing for BV and candidiasis
- Serum testing for HIV, hepatitis B, and syphilis

The CDC STD treatment guidelines recommend the following for treatment and prophylaxis:

- Due to low follow-up rate single-dose, empiric treatment is recommended whenever possible (i.e., for *Chlamydia*, gonorrhea, and *Trichomonas*)
- Emergency contraception
- Postexposure hepatitis B vaccination if the assailant is unknown or the victim has not been previously vaccinated
- If not received already, female victims aged 9–26 years, male victims aged 9–21 years (MSM up to 26 years), should receive the HPV vaccination
- *HIV postexposure prophylaxis (PEP)*: HIV PEP should be done in the following conditions:
  - For the patient presenting within 72 hours of the assault
  - Characteristics and HIV risk behavior of the assailant or assailants, if known (e.g., MSM or injection drug use)
  - The local epidemiology of HIV/acquired immunodeficiency syndrome (AIDS)
- *Exposure characteristics of the assault*:
  - Vaginal or anal penetration
  - Ejaculation on mucus membranes
  - Multiple assailants
  - Presence of mucosal lesions
- Any other characteristics that may increase the risk for HIV transmission
- For a specific regimen and to follow-up, infectious disease specialist should be consulted
- Dispense enough medications to last until the follow-up visit in 3–7 days
- Draw baseline complete blood count and complete metabolic panel

SUMMARY

Managing STI-related emergencies can be challenging. With increasing rates of STI, the role of EDs has proved invaluable in taking care of such patients. The healthcare providers must be aware of the incidence and prevalence of STIs in the local community and its treatment protocol. Proper follow-up, retesting, counseling, and treatment of the patient's partner should be done at an appropriate referral center or STIs clinic. Summary of treatment of STD are given in **Table 1**.

TABLE 1: Treatment summary: Sexually transmitted disease.

Genital ulcer disease	*Herpes simplex*	*First episode*	*Recurrent episodes*
		Acyclovir 400 mg orally thrice daily for 7–10 days or valacyclovir 1 g orally twice daily for 7–10 days	Acyclovir 400 mg orally thrice daily or 800 mg twice daily for 5 days or valacyclovir 1 g orally once daily for 5 days or 500 mg orally twice daily for 3 days
Syphilis	*Primary, secondary, or early syphilis*	*Late or unknown duration syphilis*	*Neuro/ocular syphilis*
	Benzathine penicillin G 2.4 million unit intramuscular (IM) single dose. Doxycycline 100 mg orally twice daily for 14 days	• Benzathine penicillin G 2.4 million unit IM once weekly three doses • Doxycycline 100 mg orally twice daily for 14 days	Aqueous crystalline penicillin G 18–24 million U/day for 10–14 days
Urethritis/cervicitis	*Gonorrhea*	*Disseminated gonococcal infection*	*Chlamydia*
	Ceftriaxone 250 mg once + azithromycin 1 g orally once (dual treatment is recommended)	Ceftriaxone 1 g IV daily or cefotaxime 1 g IV 8 hourly for 7 days	Azithromycin 1 g orally single dose or doxycycline 100 mg orally twice daily for 7 days
Pelvic inflammatory disease	*Outpatient*		*Inpatient*
	Ceftriaxone 250 mg IM once + doxycycline 100 mg orally twice daily for 14 days + metronidazole 500 mg orally twice daily for 14 days		Cefoxitin 2 g IV every 6 hourly + doxycycline 100 mg orally + metronidazole 500 mg orally twice daily for 14 days
Vaginitis/vaginosis	*Trichomonas*	*Trichomonas in pregnancy*	*Bacterial vaginosis*
	Metronidazole 500 mg orally twice daily for 7 days. Tinidazole 2 g orally single dose.	Metronidazole 2 g orally single dose	• Metronidazole 500 mg orally twice daily for 7 days • Clindamycin cream 2% intravaginally at bed time for 7 days • Metronidazole gel 0.75% intravaginally once daily once daily for 5 days

MULTIPLE CHOICE QUESTIONS

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CHAPTER

HIV Infections

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INDRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that attacks the body's CD4 subset of T cells making the body prone to infections and cancers. There are two major subtypes of HIV; HIV-1 and HIV-2 of which HIV-1 is the predominant subtype. HIV is a virus and acquired immune deficiency syndrome (AIDS) is a spectrum of conditions caused by infection with HIV. Ever since the breakthrough of antiretroviral drugs, there has been a major paradigm shift in the care of HIV-infected patients in the emergency department (ED) which includes better quality-of-life. With compliance and treatment success, there must be virtual elimination of AIDS-associated opportunistic infections (OIs). As a result, in United States, the emergency clinician is now more often confronted with adverse events related to these medications, but India differs in presentation. India, being a land of cultural bias and serious issues associated with the social stigma pertaining to acquiring the disease, diagnosis and continuation of antiretroviral therapy (ART) stands a matter of major concern. Thus, the emergency room (ER) doctor should have the following goals:

- High index of suspicion in the probable key cases
- Indigenous knowledge of rare OIs probable in HIV
- Identify patients with noncompliance and low CD4 counts
- Counsel each and every patient and his/her kinsmen who is newly diagnosed.

The HIV epidemic is concentrated globally, with 15 countries accounting for nearly 75% of all individuals living with HIV. An estimated 37.9 million people live with HIV out of which 36.2 million were adults and 1.7 million were children below 15 years. In India, the incidence of HIV is 0.1% and the prevalence of HIV is 0.2%.

ETIOLOGY

The HIV is a bloodborne pathogen acquired in nonoccupational settings, most readily either across mucous membranes or parenterally by the following modes of transmission:

- Unprotected sexual intercourse, especially receptive anal intercourse (eightfold higher risk of transmission)
- A large number of sexual partners
- *Prior or current sexually transmitted diseases (STDs)*: Gonorrhea and chlamydia infections increase the HIV transmission risk threefold, syphilis by sevenfold, and herpes genitals by 25-fold during an outbreak
- Sharing of intravenous drug paraphernalia
- Receipt of blood products (before 1985)
- Mucosal contact with infected blood or needlestick injuries
- *Maternal HIV infection (for newborns, infants, and children)*: Steps taken to reduce the risk of transmission at birth include cesarean delivery and prenatal ART in the mother and ART in the newborn immediately after birth.

PATHOPHYSIOLOGY

There are *five stages of HIV/AIDS infection*:

1. Primary or acute infection
2. The window period ending with seroconversion
3. The asymptomatic period
4. The symptomatic period
5. Full-blown AIDS

Human immunodeficiency virus, a ribonucleic acid (RNA) retrovirus targets hosts immune defense systems by infecting and eventually CD4 cells are the central player in both humoral and cell mediated immunity.

The life cycle of HIV-1 is complex and its outcome is largely determined by the target cell and cell activation. Initially, HIV-1 can gain access to cells without causing immediate lethal damages, but the entry process can stimulate further intracellular signal cascades and facilitation viral replication. During the entry process, the external glycoprotein, gp120 binds to the CD4+ receptor and attaches to the cell membrane surface. Subsequent interactions between virus and chemokine coreceptors (e.g., CCR5 and CXCR4) trigger irreversible conformational changes. The act of *fusion* and release of the viral core into the cell cytoplasm occurs within minutes. After the core disassembles, the viral genome is reverse transcribed into deoxyribonucleic acid (DNA) by the virus own reverse transcriptase enzyme. At the midpoint of infection, the viral protein *integrase* in conjunction with host *DNA repair enzymes* inserts the viral genome into the active domains of the host's chromosomal DNA. Integration is facilitated by an integrase binding host factor, lens epithelium-derived growth factor (LEDGF/p75), which irreversibly transforms the cell into a potential virus producer. This is the stage of *primary infection*. It is undetectable by any serological tests.

After HIV-1 breaches the mucosal barrier, a period in which viral propagation is not yet established and host defenses could potentially control viral expansion.

This *window period* could be between 2 and 12 weeks. The patient is infectious, high viral load, still picks up a negative anybody detection test. The initial replication takes place in the regional lymph organs (e.g., draining lymph nodes) and leads to primary amplification. With migration of infected T lymphocytes or virions into the bloodstream, secondary amplification occurs in the gastrointestinal tract, spleen, and bone marrow results in massive infection of susceptible cells. This is the stage of *clinical latency* and is an *asymptomatic stage.* With peaking viremia, clinical symptoms may manifest during primary HIV-1 infection. The level of viremia in a setting of chronic infection may be a magnitude lower than the primary infection. The reason is mainly attributed to reaching a viral set point because of development of CD8+ lymphocytes. This viral set point predicts the further disease progression. A gradual destruction of the naive and memory CD4+ T lymphocyte populations is the hallmark of HIV-1 infection, with *AIDS (full-blown disease) (CD4 <200)* being the last disease stage.

CLINICAL PRESENTATION

A variety of clinical features can make a patient present to the ED, but many patients present to the ED with complaints unrelated to the disease. Evaluation of HIV-infected patients should be carried out with the same priority-based logical approach used for all ED patients. AIDS manifests as recurrent, severe, and occasionally life-threatening infections and/or opportunistic malignancies. The patient may be asymptomatic leading to delay in diagnosis and treatment or may present with signs and symptoms at any of the stages of HIV infection. The asymptomatic phase is generally benign. Generalized lymphadenopathy is common and may be a presenting symptom.

In the acute stage of HIV infection (first 2–6 weeks after being infected), the symptoms may include fever, a blotchy red rash, diarrhea, headache, nausea/vomiting, fatigue, aching muscles, sore throat, and weight loss. The symptoms may last up to 2 weeks and then completely go away as the virus goes into a nonsymptomatic phase.

The second, chronic stage of HIV infection is usually asymptomatic. However, some HIV sufferers may present with conditions/symptoms such as the thrush, shingles, thrombocytopenia, anemia, seborrheic dermatitis, and weight loss. This period can last for over 10 years. It is during this period of time that HIV can be transmitted to others passed. During this, often asymptomatic phase, HIV is slowly destroying the lymphocytes and immune system. A healthy person has a CD4 T-cell count between 450 and 1,400 cells per mL. For an HIV-infected person, the number of CD4 T-cells steadily drops, putting them at a very high risk of developing other infections and AIDS which is the advanced stage of HIV infection. When the CD4 T-cell count drops to below 200, people are diagnosed with AIDS. Various OIs develop at this stage as described in **Table 1**. HIV infection itself does cause some sequelae, including AIDS-associated dementia/encephalopathy and HIV wasting syndrome (chronic diarrhea and weight loss with no identifiable cause).

Red Flags Features for Human Immunodeficiency Virus Infection

The red flags in HIV infection that warrant a patient to come to the ED and if not treated immediately can be life-threatening or causing permanent disability are persistent fever, headache, weight loss, diarrhea, dry cough, dyspnea on exertion, visual disturbance, neurological, and psychiatric manifestations. *Laboratory findings* include viral count >1,000 copies/mm and cell count 200–250 mL or less.

EVALUATION

History and Physical Examination

A detailed clinical history of the patient is absolutely important in making a provisional diagnosis of HIV-related infections. Physical examination findings may be related to the virus itself or secondary to the OIs of late disease:

- *General appearance of the patient*: The appearance of the patient depends on the stage of the disease. The patient may look very healthy or be ill-looking and cachectic
- *Vitals*: Temperature—fever may be present, pulse—tachycardia may be present, blood pressure—hypotension may be present, respiratory rate—tachypnea seen during fever and respiratory tract infections.
- *Skin*: Folliculitis, seborrheic dermatitis, or psoriasis can be present.
- *Eyes*: Retinal hemorrhage or retinal infiltrates.
- *Head*: Tenderness of sinuses may be elicited.
- *Nose*: Inflammation of the nasal turbinate may be present.
- *Ears*: Unilateral or bilateral deafness or discharge from the ears may be found.
- *Throat*: Periodontal disease or oral herpes simplex lesions or oral thrush may be found.
- *Lungs*: Crackles and rhonchi, dullness to percussion, and increased tactile fremitus can be present.
- *Cardiovascular system*: A heart murmur can be found.
- *Abdomen*: Abdominal tenderness, hepatomegaly, or splenomegaly may be detected.
- *Genitourinary*: Vaginal or urethral discharge can be present.
- *Extremities*: Muscle weakness or joint swelling may be present.
- *Central nervous system (CNS)*: Focal neurological deficits, behavioral changes or gait disturbances may be present.

Interpretation of the Finding

- *Visual field defects (loss or distortion)*: Screen for cytomegalovirus (CMV) retinitis
- *Persistent cough or shortness of breath*: Screen for *Pneumocystis carinii* pneumonia (PCP) and tuberculosis (TB)
- *Persistent headache, change in mental status, or focal neurological changes*: Cryptococcal meningitis (CM), toxoplasmosis, CNS lymphoma, and progressive multifocal leukoencephalopathy (PML)
- *Diarrhea*: Screen for isosporiasis, cryptosporidia, and microsporidia
- *Persistent fever, night sweats, or weight loss*: Screen for all OIs.

TABLE 1: List of opportunistic infections and their manifestations and management in emergency department.

Infection	*Symptoms in emergency*	*Treatment*
Candidiasis (bronchi, trachea, esophagus, and lungs)	Dysphagia, dyspnea, hoarseness, LRTI not responding to medical management directed towards bacterial organisms	Clotrimazole 10 mg troches five times a day or nystatin 500,000 units five times a day gargle
Cryptococcosis (*Cryptococcus neoformans*), pulmonary or CNS or disseminated	Pneumonia as it enters through inhalation, cerebral edema leading low GCS, also effects skin, bones, or urinary tract	Amphotericin B (0.7 mg/kg) IV once a day for 2 weeks alone or in combination with flucytosine (25 mg/kg) IV four times a day for 2 weeks and fluconazole 400 mg per day orally for 8–10 weeks
Cytomegalovirus (CMV) (mainly CMV retinitis) medical emergency	Pneumonia, gastroenteritis, encephalitis, and retinitis	• Ganciclovir 5 mg/kg IV twice a day for 2 weeks then 5 mg/kg/day or foscarnet 90 mg/kg every 12 h for 3 weeks then 90 mg/kg once a day • Ganciclovir implant and ganciclovir 1–1.5 g orally three times a day for ophthalmological manifestation
Herpes simplex virus (HSV)	Painful cold sores, severely lowered CD4 counts, infection of the bronchus, pneumonia, and esophagitis	Acyclovir 200 mg orally five times a day in mild disease and 5–10 mg/kg IV every 8 h for 7 days for severe disease
Kaposi's sarcoma	Flat or raised pink purple spots on skin, life-threatening when involves lung, lymph nodes, and intestine	Cryotherapy or radiation for localized disease or chemotherapy with vincristine, vinblastine, or doxorubicin for widespread disease
Mycobacterium tuberculosis	Cough with hemoptysis, night sweats, prolonged fevers, weight loss, and anorexia	Isoniazid 5 mg/kg orally once a day and rifampin 10 mg/kg orally once a day and pyrazinamide 15–30 mg/kg orally once a day and ethambutol 15–20 mg/kg orally once a day
Mycobacterium avium complex	Persistent fever, night sweats, weight loss, diarrhea, anorexia, and malaise	Clarithromycin 500 mg orally twice a day and ethambutol 15 mg/kg orally once a day and rifabutin 300 mg/kg orally once a day
Pneumocystis carinii	Dyspnea, high fever, and dry cough	Trimethoprim/sulfamethoxazole 15–20 mg of trimethoprim per day orally or IV in divided doses three times a day for 3 weeks
Progressive multifocal leukoencephalopathy	Loss of muscle control, paralysis, blindness, speech problems, and altered mental state	Often fatal
Salmonella	Diarrhea	Ciprofloxacin 500 mg orally twice a day for 2–4 weeks
Toxoplasmosis	Multiple organs	Pyrimethamine 200 mg loading and then 50–75 mg orally once a day for 6–8 weeks and sulfadiazine 1.5 g orally every 6 hours for 6 week and folinic acid 10 mg/day orally for 6–8 weeks

(CNS: central nervous system; GCS: Glasgow Coma Scale; IV: intravenous; LRTI: lower respiratory tract infection)

INVESTIGATIONS

Human immunodeficiency virus can be diagnosed through blood or saliva testing. Objectives of testing are transfusion and transplant safety, diagnosis of HIV infection in symptomatic and asymptomatic individuals, and prevention of parent to child transmission; for postexposure prophylaxis (PEP), epidemiological surveillance using unlinked anonymous HIV testing. *Research serological tests for the detection of HIV are classified as first- to fourth-generation tests based on the type of antigens used and principle of the assays* (**Table 2**). *The National AIDS Control Organisation* **(***NACO) recommends* the use of rapid test kits, which detect >99.5% of all HIV-infected individuals and have false-positive results in <2% of all those who are tested.

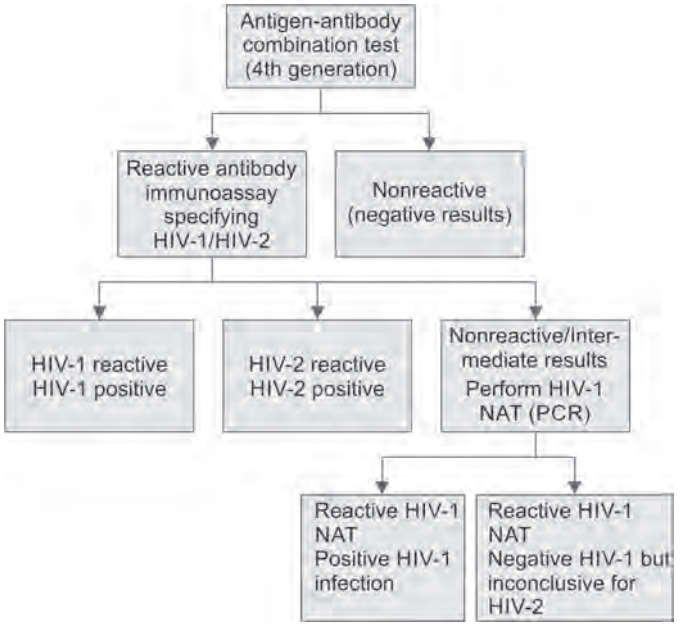
Nucleic Acid Tests

These tests look for the actual virus in your blood (viral load). They also involve blood drawn from a vein. If you might have been exposed to HIV within the past few weeks, your doctor may recommend nucleic acid test (NAT). *NAT will be the first test to become positive after exposure to HIV. Once diagnosis is established the following tests need to be done: Serial CD4 T-cell count monitoring and HIV viral RNA load is a must.* Lower the viral load, lower are the chances of complications and OIs.

More than 50% of new HIV infections are acquired from someone with acute HIV. For every 10-fold increase in viral load, the risk of transmission increases by a factor of 2, 5, 4, 6, and 9. Early diagnosis and treatment of acute HIV has become a public health goal, which translates to ED practice. With the

TABLE 2: Generation of anti-HIV antibody tests.		
First	Antigens from HIV lysates	Lack of sensitivity and specificity
Second	Recombinant proteins and/or synthetic peptides	Improved sensitivity
Third	Recombinant proteins and/or synthetic peptides in an antigen sandwich configuration	• Very high sensitivity. Detects HIV-1 and HIV-2 simultaneously • Reduces window period considerably. Detects IgM antibody in addition to IgG antibody
Fourth	Detection of both HIV antigen (p24) and both antibodies, IgG and IgM	Further reducing the window period

(HIV: human immunodeficiency virus; IgG: immunoglobulin G; IgM: immunoglobulin M)


Antigen-antibody combination test (4th generation)
Reactive antibody immunoassay specifying HIV-1/HIV-2
Nonreactive (negative results)
HIV-1 reactive HIV-1 positive
HIV-2 reactive HIV-2 positive
Nonreactive/Intermediate results Perform HIV-1 NAT (PCR)
Reactive HIV-1 NAT Positive HIV-1 infection
Reactive HIV-1 NAT Negative HIV-1 but inconclusive for HIV-2

(CDC: Centers for Disease Control and Prevention; HIV: human immunodeficiency virus; NAT: nucleic acid test; PCR: polymerase chain reaction)

FLOWCHART 1: CDC-recommended HIV testing algorithm.

Sources: (1) CDC. (2018). Quick reference guide: Recommended laboratory HIV testing algorithm for serum or plasma specimens. [online] Available from https://stacks.cdc.gov/view/cdc/50872. [Last accessed August, 2021]. (2) CDC. (2014). Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. [online] Available from https://doi.org/10.15620/cdc.23447. [Last accessed August, 2021].

advent of fourth-generation antigen-antibody serum tests, acute HIV can now be detected within 10–21 days after exposure. *Point-of-care tests are not as reliable;* therefore the US Centers for Disease Control and Prevention (CDC) recommends laboratory-based testing. A positive antigen-antibody test result, followed by a negative antibody-only test and a positive NAT is expected in cases of acute HIV (**Flowchart 1** shows the testing algorithm). Reverse transcription polymerase chain reaction (RT-PCR) results >1,000 copies/mL indicate likely true positives as the viral load in patients with acute HIV should be several orders of magnitude greater. RT-PCR can detect acute HIV 5 days sooner than the best performing fourth-generation test. However, there is still a window period of 1–2 weeks when patients with very early infection may test negative. In cases highly suspicious for acute HIV with negative testing, repeat testing in 1–2 weeks is recommended. The greatest benefits are experienced if treatment is started as early as possible.

TABLE 3: Antiretroviral drugs.	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz and rilpivirine
Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)	Abacavir, tenofovir, and emtricitabine
Protease inhibitors (PIs)	Atazanavir and darunavir
Integrase inhibitors	Bictegravir sodium/ emtricitabine/tenofovir
Entry or fusion inhibitors	Enfuvirtide and maraviroc

TREATMENT

The ART aim at controlling HIV and preventing its complications rather than curing the infection. So, any patient presenting to the ED should first undergo a thorough assessment of airway, breathing, and circulation to rule out life-threatening conditions followed by definitive therapy. Each class of drugs blocks the virus in different ways. Treatment involves combinations of drugs from different classes to account for individual drug resistance (viral genotype), avoid creating new drug-resistant strains of HIV, and maximize suppression of virus in the blood. *Two drugs from one class plus a third drug from a second class are typically used*. The classes of anti-HIV drugs are presented in **Table 3**. Initiation of antiretroviral treatment associated with numerous side effects such as hypersensitivity and lactic acidosis although starts with mild symptoms but can progress to severe life-threatening complications. Other group-specific complications are summarized in **Table 4**.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

In 2018, 23.3 million people with HIV (62%) were accessing ART globally, 78% of all people who knew their status were accessing ART and 86% of all people receiving ART had viral suppression. ART initiation leads to reduction in viral load in the plasma, temporary improvement in CD4+ T-cell counts, and partial restoration of immune function. However, a certain group of patients develop a dysregulated restoration of antigen-specific immune response and experience clinical deterioration. This was first noted by French et al. in 1992 where he observed a *Mycobacterium avium-intracellulare* infection after zidovudine monotherapy which he explained by a delayed type hypersensitivity (DTH) response to mycobacterial antigens. This phenomenon is known by multitude of names including "immune reconstitution inflammatory syndrome (IRIS)", "immune reconstitution or restoration disease (IRD)", and "immune reconstitution syndrome (IRS)".

TABLE 4: Side effects of antiretroviral therapy.

Group of drugs	*Drug name*	*Side effects*
NRTI	Tenofovir disoproxil fumarate (TDF)	Greater loss BMD than other NRTIs, osteomalacia with renal tubulopathy and urine phosphate wasting, increased serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, and nonanion gap metabolic acidosis
	Tenofovir alafenamide (TAF)	Associated with smaller declines in BMD than seen with TDF. Increase in TG, LDL, HDL, and renal effects but lesser than TDF
	Zidovudine (ZDV)	Anemia, neutropenia, diabetes mellitus, insulin resistance, increased TG and LDL, nausea, vomiting (more than other NRTIs), steatosis, myopathy, and lipoatrophy
	Abacavir (ABC)	Increased risk of MI, contraindicated if patient is HLA-B*5701 in view of HSR
	Lamivudine (3TC)	• Severe hepatic flares when withdrawn in patients with HBV and HCV coinfection • *ddI, ddC, and d4T*: Irreversible peripheral neuropathy
	Emtricitabine (FTC)	Hyperpigmentation
NNRTI	All	Decrease in BMD, neuropsychiatric events such as insomnia, abnormal dreams, dizziness, and depression psychosis (more than other drugs in this group)
	Efavirenz (EFV)	QTc prolongation, dyslipidemia (increased TG, LDL, and HDL), increased transaminases and fulminant hepatitis depression, psychosis, suicidal ideation, ataxia, and nervous system effects such as somnolence, insomnia, abnormal dreams, dizziness, and impaired concentration
	Nevirapine (NVP)	• Severe hepatotoxicity associated with HSR (greater risk with women on NVP with CD4 >250 cells/mm^3 and men with NVP with CD4 >400 cells/mm^3) • Never use NVP for postexposure prophylaxis • EFV and NVP are not recommended in patients with hepatic insufficiency (Child–Pugh B or C) • HSR in form of fever, conjunctivitis, facial edema, general malaise, fatigue, myalgia, arthralgias, blisters, oral lesions, granulocytopenia, and lymphadenopathy
	Rilpivirine (RPV)	QTc prolongation, depression, suicidality, and sleep disturbances
	Doravirine (DOR)	Sleep disorders and disturbances, dizziness and suicidality, and self-harm
PIs	All	Decrease in BMD, PR prolongation, dyslipidemia (LPV/r>DRV/r), lip hypertrophy, diarrhea, nausea, vomiting, drug-induced hepatitis, rash, and Stevens–Johnson syndrome (few reported cases)
	Atazanavir/ritonavir (ATV/r)	Cholelithiasis, kidney stones, jaundice due to indirect hyperbilirubinemia, and chronic kidney disease
	Lopinavir/ritonavir (LPV/r)	Diabetes mellitus and insulin resistance
INSTIs	All	Weight gain, insomnia, depression in patients with preexisting psychiatric conditions, rash, and decrease in bone mineral density

(BMD: bone mineral density; HBV: hepatitis B virus; HCV: hepatitis C virus; HDL: high-density lipoprotein; HLA: human leukocyte antigen; HSR: hypersensitivity syndrome reaction; INSTIs: integrase strand transfer inhibitors; LDL: low-density lipoprotein; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside or nucleotide reverse transcriptase inhibitor; PIs: protease inhibitors; TDF: tenofovir disoproxil fumarate; TG: triglyceride)

Definition

A paradoxical clinical worsening of a known condition or the development of a brand new condition after initiating ART in HIV-infected patients resulting from restored immunity to specific infectious or noninfectious antigens is defined as IRIS.

A certain minimum criterion should be fulfilled so as to diagnose IRIS. There must be a temporal association between initiation of ART and subsequent development of symptoms (usually within 3 months), with evidence of virologic and immunological response (decrease in plasma HIV RNA level by quite over 1 $\log_{10}$ copies/mL and a rise in CD4+ T-lymphocyte count from baseline) and must exhibit clinical symptoms and signs in keeping with an inflammatory process. A rise in CD4+ T cells (which is neither sensitive nor specific for immune restoration) is often seen in IRIS. But it is not a vital element for the diagnosis, a falling plasma viral load may be a more important indicator.

Criteria for Diagnosis of Immune Reconstitution Inflammatory Syndrome

French et al. have laid down criteria in order to aid the diagnosis. These are:

- *Major criteria*:
  - Atypical presentation of "OIs or tumors" in patients responding to ART
  - Decrease in plasma HIV RNA level by a minimum of 1 $\log_{10}$ copies/mL
- *Minor criteria*:
  - Increased blood CD4+ T-cell count after highly active antiretroviral therapy (HAART)
  - Increase in immune response specific to the relevant pathogen, e.g., DTH response to mycobacterial antigens
  - Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of ART.

Risk Factors

Out of the patients starting ART, 10–32% are reported to develop IRIS. Multiple studies investigating the risk factors for IRIS differ substantially because of difference of cohort groups depending on the study population. Risk factors identified for the developments of IRIS include lower CD4+ cell count at ART initiation, higher HIV RNA at ART initiation, lower CD4+ cell percentage at ART initiation, lower CD4+:CD8+ ratio at ART initiation, more rapid initial fall in HIV RNA on ART, antiretroviral naive at time of OI diagnosis, and shorter interval between OI therapy initiation and ART initiation.

There can also be a genetic predisposition and certain genes are related to an increased susceptibility to the event of IRIS within the presence of mycobacteria and herpes viruses. Young men are inconsistently related to IRIS.

Pathogenesis

The pathogenesis of IRIS remains largely speculative in spite of numerous studies and research. Current theories regarding the pathogenesis of the syndrome involve a combination of underlying burden of antigen, extent of immune restoration following ART, and genetic susceptibility of the host.

Infection and Immune Reconstitution Inflammatory Syndrome

A variety of mycobacterial, viral, fungal, and parasitic OIs are associated with IRIS. The inflammatory response may be to viable pathogens or to the nonviable pathogens or its residual antigen. The syndrome manifests as either of two patterns, "unmasking IRIS" or "paradoxical IRIS". "Unmasking IRIS" is an immune response against a pathogen that never caused any overt clinical disease before initiation of ART. This type of presentation is usually caused by viable organisms. In "paradoxical IRIS", OIs already present at initiation of ART and worsens after therapy. This may be a response to living pathogens or a response to the antigens of nonviable pathogens. *IRIS* should be termed only after ruling out a deterioration of symptoms due to noncompliance.

Tuberculosis

Mycobacterium tuberculosis is one of the most common pathogen known to cause IRIS with reported incidence varying from 8 to 43%.

Several risk factors for the development of paradoxical TB-IRIS have been identified including shorter delay between commencing TB treatment and ART, low baseline CD4+ cell count, higher baseline viral load, rapid reduction in viral load on ART, and disseminated TB.

Tuberculosis-IRIS generally presents as paradoxical disease within the first 2 months and commonly in the first 2–3 weeks of ART initiation. The patient often presents with worsening or appearance of new clinical or radiological features. Common manifestations include return of symptoms such as fever, lymph node enlargement or suppuration, and appearance of fresh infiltrates, mediastinal lymphadenopathy, or enlarging effusion on chest radiograph. TB-IRIS may also manifest as visceral or cutaneous abscesses, CNS disease, pericardial effusion, acute respiratory distress syndrome (ARDS), airway obstruction, and acute renal failure.

Nontuberculous Mycobacteria

The reported incidence of nontuberculous mycobacterial IRIS is 3.5% among patients with a baseline CD4+ count of <100 cells/μL. *Mycobacterium avium* complex (MAC)-associated IRIS typically develops in severely immunosuppressed individuals, who have an excellent response to ART. The syndrome manifests usually after 2–8 weeks of ART in patients with low CD4 counts. Most common manifestation of MAC-IRIS is fever with suppurative painful lymphadenitis (69%), followed by pulmonary disease (19%). It may also involve the joints, spine, skin, and soft tissue. In contrast to disseminated MAC disease of advanced AIDS, MAC-IRIS usually presents as localized disease.

Tuberculosis diagnosis in patients with HIV is challenging, particularly in resource-limited settings. These patients frequently have atypical clinical presentations, extrapulmonary disease, and normal chest radiographs, particularly in presence of advanced immunosuppression.

Blood cultures are effective in 4–56% in various studies.

Cryptococcosis

Manifestations of cryptococcal IRIS include meningitis, lymphadenitis, pneumonitis, and localized abscess. Overall incidence of neurological IRIS is 1.5% in individuals with CD4+ count of <200 cells/μL. Paradoxical CM-IRIS incidence has been reported as 10–42%, in ART-naive patients with CM. Approximately 60% of cases occur within the first month, although the symptoms may present as late as 10–12 months after treatment. Specific risk factors for the development of cryptococcal IRIS include shorter duration between cryptococcal diagnosis and ART initiation, low CD4 counts (<100 cells/μL), higher baseline plasma HIV RNA levels; and higher cerebrospinal fluid (CSF) cryptococcal antigen titers, opening pressures, white blood cell (WBC) counts, and glucose levels. CM iris carries a very high morbidity and mortality unlike other IRIS infections. It has been suggested to delay ART until CSF sterility is achieved with antifungal combinations such as amphotericin B and flucytosine. However, the exact timing of ART initiation and whether attaining CSF culture sterility is important in avoiding IRIS are unknown. Role of corticosteroids is still unknown.

Pneumocystis Jiroveci Pneumonia

Pneumonia caused by *Pneumocystis jiroveci* is one of the most common OIs in patients with advanced HIV disease. Worsening of treated infection may occur within the first 2–3 weeks after initiation of ART. Patients with PCP-IRIS present with recurrence of fever, worsening hypoxia, and fresh pulmonary infiltrates on chest radiograph. Risk factors for developing PCP-IRIS include severe disease (PaO_2<70 mm Hg), early initiation of ART, and recent completion of steroid therapy for PCP.

Viral Infections

Genital ulceration related to herpes simplex virus and genital warts related to human papillomavirus are among the most common presentations of IRIS. Herpes zoster IRIS usually manifests as uncomplicated disease limited to a single dermatome. Eye disease is the most common presentation of CMV IRIS. Three distinct ocular lesions associated with CMV-IRIS have been described: retinitis, vitritis, and uveitis.

IRIS provoked by hepatitis B and C viruses is characterized by hepatitis flare.

Noninfectious conditions associated with IRIS are lupus-like disease, thyroid disease, rheumatoid arthritis, sarcoidosis, and follicular lymphoma.

Prevention

Antiretroviral therapy should be initiated before the onset of severe immunodeficiency and after the treatment of OIs. A detailed evaluation is required for identification of OIs before ART initiation to prevent the unmasking form of IRIS and identification of high-risk features for development of IRIS. When an OI is present, the risk of delaying ART must be weighed in comparison of deferring the ART.

Treatment for Side Effects of Antiretroviral Therapy

Opportunistic infections should be optimally treated. In general, nonsteroidal anti-inflammatory drugs (NSAIDs) should be reserved for milder manifestations of IRIS and steroids for cases with severe inflammation.

Meintjes et al. demonstrated the reduced need for hospitalization and therapeutic procedures and hastened improvements in symptoms, performance, and quality-of-life in patients with TB-IRIS receiving prednisolone at a dose of 1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks.

Cryptococcal meningoencephalitis, the most severe form of cryptococcosis, is associated with high mortality rates. CM-IRIS requires prompt control of raised intracranial pressure or hydrocephalus. Corticosteroids are indicated for cerebral edema and raised intracranial pressure. Respiratory failure due to ARDS in pulmonary cryptococcosis should also be treated with corticosteroids.

The development of PCP-IRIS after discontinuation of steroid therapy suggests a role for the reintroduction of steroids in these patients.

Acyclovir is beneficial in IRIS-associated zoster. In cases of ocular CMV-IRIS, systemic or periocular steroid injections have been used, but a clear benefit has not been demonstrated. The role of corticosteroids in PML-IRIS is not clear.

POSTEXPOSURE PROPHYLAXIS

After proper history and documentation, PEP should be considered.

Recommended Regimen

Because PEP has its greatest effect if started within 2 hours of exposure it is essential to act immediately. Ideally, therapy should be started within 2 hours and definitely within 72 hours of exposure. *Fixed drug combination of tenofovir 300 mg plus lamivudine 300 mg plus efavirenz 600 mg once daily for 4 weeks* is the recommended regimen. If the source is already on ART, the exposed person must be started on the above-mentioned regimen at the earliest with proper counseling and then refer for an expert opinion. Also, if it is an unknown exposure or known patient of HIV then assessment of stage of infection is important (**Table 5**). Follow-up after exposure includes testing of HIV, anti-hepatitis C virus (HCV), hepatitis B surface antigen (HBsAg) should be done at baseline, month 3, and month 6.

TABLE 5: Assessing the postexposure risk of HIV.

HIV negative	Source is not HIV infected (but consider HBV and HCV)
Low risk	HIV positive and clinically asymptomatic
High risk	HIV positive and clinically symptomatic
Unknown	Status of the patient is unknown and neither the patient nor his/her blood is available for testing

(HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus)

DISPOSITION

An infectious disease specialist in coordination with others who are expert in HIV often plays a major role in disposition of an HIV-infected patient. Decisions regarding the disposition of all HIV-infected patients are taken based on whether the patient needs to be admitted as an inpatient or can be done away with as an outpatient, but that too only when patient is taking orally, self-ambulatory, and has availability of proper follow-up.

SUMMARY

Human immunodeficiency virus infects the body's CD4 subset of T cells and predisposes the body to acquire opportunistic or recurrent infections and cancers as the disease progresses. AIDS manifests as recurrent, severe, and occasionally life-threatening infections and/or opportunistic malignancies.

In the acute stage of HIV infection (first 2–6 weeks after being infected), the symptoms may include fever, a blotchy red rash, diarrhea, headache, nausea/vomiting, fatigue, aching muscles, sore throat, and weight loss. The second chronic stage of HIV infection is usually asymptomatic. However, some HIV sufferers may present with conditions/symptoms such as the thrush, shingles, thrombocytopenia, anemia, seborrheic dermatitis, and weight loss.

Human immunodeficiency virus infection itself does cause some sequelae, in which *AIDS-associated dementia/encephalopathy* and *HIV wasting syndrome* with some manifestations which have no identifiable cause as yet.

There are four generations of antibody tests of which the fourth generation used for the detection of both HIV antigen (p24) and both antibodies, immunoglobulin G (IgG) and immunoglobulin M (IgM) has the highest sensitivity and further reduces the window period significantly. Other tests include *NATs* and after diagnosis *serial CD4 monitoring and HIV viral RNA load*.

In ED, any case of HIV infection that is encountered should first include the assessment of airway, breathing, and circulation to save the patient from life-threatening emergencies. Following this, depending on the severity of the disease and the type of OIs, a multicentric approach is undertaken in coordination with the infectious disease specialist which involves the use of antibiotic, antifungal, or antiretroviral therapy of different classes.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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Care of Immunocompromised and Transplant Patient

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INTRODUCTION

With the ever-increasing number of immunocompromised patients presenting to the emergency department (ED), it is pertinent for the emergency physicians to possess the requisite knowledge and skills to recognize the infectious complications in this patient population. As compared to immunocompetent individuals, immunocompromised individuals have infections which are more severe and widespread but are deceptively benign. These patients may present with symptoms and signs that mimic noninfectious complications, only to deteriorate rapidly if they are not evaluated and treated urgently. Various immunocompromised conditions are described in this chapter.

Immune response is broadly categorized as:

- Innate (nonmicrobe specific) immunity:
  - Physical barriers
  - Initial inflammatory response
  - Reticuloendothelial system
- Acquired (microbe specific) immunity:
  - Humoral immunity:
    - Antibodies
    - Immunoglobulin
    - Complement
  - Cell-mediated immunity (CMI)
  - Granulocytic macrophages

NEUTROPENIA

Neutropenia is defined as a neutrophil count of <500 cells/mL (5×10^5 cells/L), including band forms, or <1,000 cells/mL (1×10^6 cells/L) and expected to fall to <500 cells/mL over next 48 hours.

Risk of infection in neutropenic individuals is inversely proportional to the absolute neutrophil count (ANC), being relatively less likely when ANC is >1,000 cells/mL and substantially increasing when ANC falls below 500 cells/mL.

Causes of Neutropenia

- Cytotoxic chemotherapy/radiotherapy (usually seen in first 2 weeks of starting treatment)
- Hematological malignant neoplasms

Common sites of infection in the neutropenic patient:

- Lung (25%)
- Mouth and pharynx (25%)
- Gastrointestinal tract (15%)
- Skin, soft tissue, and intravascular catheters (15%)
- Perineum and anorectal area (10%)
- Urinary tract (5%)
- Nose and sinuses (5%)

Fever in the neutropenic patient is defined as a single temperature of 38.3°C (101°F) or higher or a temperature of 38.0°C (100.4°F) or higher over 1 hour. In neutropenic patients, it is recommended to measure the oral temperature or the ear (tympanic) temperature. Rectal temperature measurements are not recommended as the thermometer can tear the thin rectal skin and introduce bacteria into the bloodstream leading to an infection. Fever may be suppressed by immunosuppressive agents such as corticosteroids or nonsteroidal anti-inflammatory drugs.

Neutrophils being an integral part of innate immunity, pose increased risk of bacterial and fungal infections in neutropenic patients. These infections may be manifested by unexplained tachypnea or tachycardia, mental status changes, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium concentration, or acute abdominal pain. Evaluation and management of febrile neutropenia patient is described in **Box 1**.

Risk Assessment and Disposition

Febrile neutropenic cancer patients can be classified into high-risk and low-risk groups by using the Multinational Association of Supportive Care in Cancer (MASCC) risk index score (**Table 1**) or Clinical Index of Stable Febrile Neutropenia

BOX 1: Evaluation and management of adult patient with febrile neutropenia in the ED.

History: Fever or history of fever may be present. The patient has signs and symptoms of acute infection

Physical examination (may give a clue for the offending pathogen):

- Ulcerative lesion in mouth: Viridans streptococci, herpes simplex, *Candida*, and anaerobes
- Necrotizing skin lesions: *Pseudomonas aeruginosa*, *Aeromonas hydrophila*, *Aspergillus*, and *Mucor*
- Nontender subcutaneous nodules: *Nocardia* and *Cryptococcus*
- Nontender pink skin papules: *Candida*
- Black eschar of nose/palate: *Aspergillus* and *Mucor*
- Generalized macular red rash: Viridians streptococci
- Right lower quadrant abdominal pain, tenderness, distention, bloody diarrhea: Typhlitis (neutropenic enterocolitis) caused by *Pseudomonas aeruginosa*, *Escherichia coli*, and *Clostridium septicum*
- Perineal pain and tenderness without inflammation or abscess: Gram-negative bacilli and anaerobes
- Redness or pain at vascular catheter sites: Coagulase-negative staphylococci, *Corynebacterium*, and *Bacillus* species

Investigation

- Complete blood count shows neutropenia (neutrophil count <500 cells/mL, including band forms, or <1,000 cells/mL and expected to fall to <500 cells/mL)
- Obtain blood for measurement of electrolytes, renal and hepatic function, and serum lactic acid
- Obtain blood cultures from each lumen of any existing central venous catheters and from at least one peripheral site, or two blood cultures from separate venepunctures of peripheral veins if no central venous catheter is present
- Chest radiograph if symptoms or signs of respiratory disease are present
- Urinalysis and urine culture if symptoms or signs of urinary tract infection are present
- Stool for culture for routine pathogens and PCR testing for *Clostridium difficile* if acute diarrhea or if acute abdominal pain without diarrhea is present
- Specimens for culture from any site of inflammation, including inflamed or draining catheter exit sites
- If severe mucositis, obtain herpes simplex culture (or PCR testing) if not receiving antiherpes prophylaxis, and obtain smear (Gram stain) for *Candida* pseudohyphae
- Lumbar puncture is not recommended as a routine procedure unless subtle symptoms or signs of meningitis are present
- Consider ultrasonography over a subcutaneous tunneled catheter track and its vein of insertion, which may reveal the presence of an abscess or infected thrombus
- Urgent CT scanning may be indicated: If the chest radiograph is normal or inconclusive in a patient with acute respiratory symptoms/signs, If facial pain or swelling is present, consider obtaining a CT scan of the sinuses without contrast enhancement. In patients with abdominal pain and tenderness, obtain a CT scan of the abdomen and pelvis with intravenous contrast

Treatment

- Assess the need for administration of intravenous fluids
- Febrile neutropenic patients should receive initial assessment within 15 min of triage and first dose of empiric antibiotic within 1 h of arrival at emergency room, as delay in treatment has been associated with poor outcomes and mortality
- Initiate empirical intravenous antimicrobial monotherapy with an antipseudomonal beta-lactam agent (cefepime, meropenem, imipenem-cilastatin, or piperacillin-tazobactam) as soon as possible after cultures are obtained. Other antimicrobials (such as, an aminoglycoside and/or vancomycin) may be added for hypotension or pneumonia (i.e., azithromycin) or if antimicrobial resistance is suspected. For suspected polymicrobial anaerobic infections (such as, intra-abdominal or perianal source), add an anaerobic drug metronidazole or clindamycin) if cefepime is used as the beta-lactam agent. For patients with history of severe penicillin allergy, consult an infectious diseases specialist
- Empirical use of vancomycin is not routinely indicated for all febrile neutropenic patients, but should be considered if there is suspicion for serious catheter-related infection; known colonization with MRSA or penicillin-resistant pneumococci; known isolation of a gram-positive organism before final identification and susceptibility is known; presence of shock; severe mucositis; prior fluoroquinolone prophylaxis; and institutions in which MRSA, vancomycin-susceptible enterococci, and *Streptococcus mitis* (viridans *Streptococcus* group) are frequent pathogens
- Empirical antifungal therapy is only rarely indicated in the ED and should not be initiated by the emergency clinician without consultation with an infectious diseases specialist
- *Aspergillus* and *Candida* species are the most common fungi producing infection in cancer patients with fever and neutropenia. Infection is most likely to develop in neutropenic patients treated with broad-spectrum antimicrobials and in those whose fever persists for > days
- Cell stimulation therapy: For prevention of chemotherapy-related neutropenia, some centers routinely use human recombinant hematopoietic or colony-stimulating growth factors. It may improve outcomes in high-risk patients. However current evidence does not recommend its use in all patients

(ED: emergency department; MRSA: methicillin-resistant *Staphylococcus aureus*; PCR: polymerase chain reaction)

TABLE 1: Multinational Association of Supportive Care in Cancer (MASCC) risk index score.

Characteristics	*Score*
Burden of febrile neutropenia with mild or no symptoms	5
No hypotension (systolic blood pressure >90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age younger than 60 years old	2
MASCC score ≥21 indicates low risk of complications	

TABLE 2: Clinical Index of Stable Febrile Neutropenia (CISNE) tool.

Characteristics	*Points*
Eastern Cooperative Oncology Group performance score	2
Stress induced hyperglycemia	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
Mucositis grade ≥2	1
Monocytes <200 cells/μL	1
CISNE score of <1 is considered low-risk group with risk of complications <1.5% in next 7 days. Outpatient therapy can be considered in low-risk patients	

(CISNE) (**Table 2**) tool in conjunction with clinical assessment. Both scores have been found to have fair discriminatory power. Both these tools used to dispose the patient.

The only recommended outpatient oral antimicrobial therapy for these patients is ciprofloxacin or levofloxacin plus amoxicillin/clavulanate (or plus clindamycin for those with penicillin allergy).

DIABETES

Diabetic patients have increased susceptibility to infection because of defects in immune function, excess substrate for fungal and bacterial growth, vascular insufficiency related to microangiopathy and atherosclerosis, and sensory neuropathy that lead to wound neglect.

Infections seen with increased frequency in diabetic patients include rhinocerebral zygomycosis (formerly mucormycosis) caused by *Rhizopus* and *Mucor* species; malignant (or necrotizing) otitis externa caused by *Pseudomonas aeruginosa*; pneumonia caused by *Staphylococcus aureus* and gram-negative bacilli; tuberculosis, emphysematous cholecystitis, and urinary tract infections including emphysematous cystitis and pyelonephritis; polymicrobial necrotizing fasciitis involving the perineum (Fournier's gangrene) and lower extremities; and psoas abscess, spinal epidural abscess, foot infections with osteomyelitis, and postoperative surgical site infection.

ALCOHOLISM AND CIRRHOSIS

Alcoholics exhibit an increased incidence of oropharyngeal colonization by gram-negative bacteria (35–59% of ambulatory alcoholic patients) compared with control subjects (14–18%). Alcoholics are also more likely to aspirate because of loss of reflex glottic closure associated with acute intoxication, withdrawal seizures, and encephalopathy.

RENAL FAILURE

Infections are a major cause of death in patients with chronic renal failure and are the second most common cause of mortality after coronary artery disease. These patients are often diabetic, which increases their risk for serious morbidity and mortality from infections.

FUNCTIONAL OR SURGICAL ASPLENIA

Functional or surgical asplenia predisposes to fulminant infection with pneumococci and other encapsulated organisms (*Haemophilus influenzae*, *Neisseria meningitidis*, and *Capnocytophaga canimorsus* after dog bites) and, when seen early, may be misdiagnosed as a viral illness, gastroenteritis, or food poisoning.

CORTICOSTEROID

High doses of corticosteroids cause profound dysfunction of neutrophils and mononuclear cells and impair CMI, resulting in an increase in infections caused by pyogenic bacteria, varicella-zoster and herpes simplex viruses, tuberculosis, and a wide variety of other bacteria, fungi, and parasites.

TRANSPLANT PATIENT CARE

Organ transplant patient population is growing rapidly, with the kidney being the most commonly transplanted organ (58%), followed by liver (21%), heart (8%), lung (5%), pancreas (5%), and, less commonly, combined organ transplants and intestine transplants.

Infections are the most common cause of death in transplant patients. Most common symptoms with which patients present to ED is fever.

Transplant patients can develop a number of acute to life-threatening emergencies:

- Transplant-related infection
- Medication side effects
- Rejection
- Graft-versus-host disease (GVHD)
- Postoperative complications or complications secondary to the transplanted organ

GENERAL APPROACH TO TRANSPLANT PATIENT

Transplant organs being devoid of their native innervations are dependent of surgical anastomosis to vessels and other viscera. They may hence present with nonspecific symptoms of pain and seemingly subtle signs and symptoms can be a harbinger of life-threatening complications. High suspicion for

drug toxicities and risk of infection due to immunosuppression needs to be considered in all transplant patients. General approach to post-transplant patient is summarized in **Box 2**. Also important for emergency physician to know various immunosuppressive medication used in post-transplant patient and their adverse effect (**Table 3**) which will be helpful in evaluating the patient.

BOX 2: General approach to transplant patient.

History:

- History of increase or decrease in body temperature
- Changes in baseline function
- Kidney transplant patients—reduced urine output
- Heart transplant patients—reduced exercise tolerance
- Date of transplant surgery
- History of rejection
- History of change in medication history

Physical examination:

- Vital signs
- Volume status assessment
- Head, ear, ear, nose, and throat—periorbital edema (glomerulonephritis), retina (opportunistic infections), sinuses (*Staphylococcus aureus*, mucormycosis, and invasive fungal disease), mouth (*Candida* and HSV), neck (meningismus and retropharyngeal abscess), lymphadenopathy (CMV, EBV, hepatitis, and post-transplant lymphoproliferative disorder)
- Lungs—sign of pneumonia which may be bacterial, viral, or parasitic
- Heart—new heart murmur suggestive of infection
- Pericardial friction rub suggests rejection
- Abdomen—pancreatitis and peritonitis
- Graft site examination
- Skin—graft-versus-host disease
- Extremities—signs of thrombophlebitis
- CNS—meningitis/encephalitis

Investigations:

- CBC, LFT/RFT, CRP, serum procalcitonin, lactate, NCCT head, serum cyclosporine, and tacrolimus levels. Cultures—blood, urine, stool, sputum, vascular access, wound sites, creatine kinase, and urinalysis
- Chest X-ray and chest CT biopsy

Empirical antimicrobial therapy:

- All patients—discuss with transplant team
- Neutropenia—third-generation cephalosporin such as ceftazidime or a carbapenem plus coverage for MRSA
- Suspected MRSA—vancomycin and linezolid
- Parasitic infections—trimethoprim-sulfamethoxazole
- Viral infections—ganciclovir or valganciclovir for CMV and acyclovir for herpes simplex and varicella zoster
- Fungal infections—agent depends on site and severity of illness

(CBC: complete blood count; CMV: cytomegalovirus; CNS: central nervous system; CRP: C-reactive protein; EBV: Epstein–Barr virus; HSV: herpes simplex virus; LFT: liver function test; MRSA: methicillin-resistant *Staphylococcus aureus*; NCCT: noncontrast computed tomography; RFT: renal function test)

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease is an important complication seen with allogenic stem cell transplant. GVHD has been classically divided into acute and chronic variants based on the time of onset using a cut off of 100 days.

Hyperacute GVHD is an unusual and severe form of acute GVHD. Onset occurs in the first week after hematopoietic stem cell transplantation and is characterized by fever, generalized erythroderma, severe hepatitis, fluid retention, widespread inflammation, and shock.

Acute GVHD is typically characterized by involvement of three different systems: skin (rash), gastrointestinal, and liver (jaundice and hepatitis). Consider GVHD in any patient with a rash.

Prophylaxis: Combination of a calcineurin inhibitor (e.g., cyclosporine and tacrolimus) with methotrexate.

Treatment: Treatment is directed by the transplant team, typically PO prednisone or intravenous (IV) methylprednisolone, at 1–2 mg/kg daily, and possibly adjustment of other immunosuppressant doses. Patients may require resuscitation with balanced crystalloids, blood product resuscitation (leukocyte-depleted and irradiated red blood cells), electrolyte replacement, and broad-spectrum antibiotics.

Chronic GVHD is a late complication characterized by immune dysregulation (>100 days after transplantation). It results in severe morbidity, with complications affecting skin (sclerodermatous contractures), muscles (myopathy), bone (osteoporosis), eyes (keratoconjunctivitis sicca), nerves (peripheral neuropathy), and the cardiopulmonary system (physical deconditioning), resembling autoimmune disorders. Risk factors include older age, cytomegalovirus (CMV) seropositivity, and a male who received a stem cell transplant from a multiparous woman. Management is similar to the acute form with prolonged immunosuppression.

TRANSPLANT-SPECIFIC PROBLEMS

Renal Transplantation

Renal transplantation is the treatment of choice for end-stage renal disease. Important complications of renal transplantation are given in **Table 4**.

Common presentations are hypertension, fever malaise, oliguria, graft pain, and tenderness over site worsening renal function with decreased urine output.

Diagnostic workup includes biochemical investigations, serum creatinine, urinalysis, cyclosporine/tacrolimus level, and radiological investigations. *Ultrasound* is done in cases of increased graft size, loss of corticomedullary junction, and prominent hypoechoic pyramids. Renal Doppler studies may demonstrate elevated vascular resistance indices. Biopsy may be required during admission.

Liver Transplantation

Pain abdomen and fever are the most common reasons for ED visits. Other complications and their approaches are discussed in **Box 3**.

TABLE 3: Transplant medication effects (immunosuppressants and relevant adverse effects).

Medication	*Adverse effects*
Cyclosporine	Acute/chronic nephrotoxicity, electrolyte derangements (hyperkalemia and hypomagnesemia), gout, hemolytic-uremic syndrome, gingival hyperplasia, hirsutism, hypertension, and hyperlipidemia
Tacrolimus	Neurotoxicity (headache, tremor, paresthesia, and seizures), hair loss instead of hirsutism, and less hypertension/hyperlipidemia
Azathioprine	Bone marrow suppression, macrocytosis, anemia, hepatotoxicity, and pancreatitis
Mycophenolate mofetil	Abdominal pain, decreased oral intake, nausea/vomiting, diarrhea, anemia, leukopenia, and thrombocytopenia
Corticosteroids	Weight gain, cataracts, acne, skin thinning, bruising, osteoporosis, GI bleeding, hyperglycemia, hyperlipidemia, psychological effects, and Cushingoid appearance
Sirolimus	Thrombocytopenia, leukopenia/anemia (less common), diarrhea, mucosal irritation, buccal ulceration, interstitial pneumonitis, and hyperlipidemia
Polyclonal antibodies	Fever, serum sickness, anaphylaxis, anemia, and thrombocytopenia
Monoclonal antibodies	• OKT3: Headache, aseptic meningitis, encephalopathy, seizures, nausea, vomiting, diarrhea, pulmonary edema, and nephrotoxicity • IL-2 receptor antibodies have rare adverse effects such as anaphylaxis

(GI: gastrointestinal; IL-2: interleukin-2)

TABLE 4: Postrenal transplant complications.

Vascular complications	*Nonvascular complications*
• Renal artery stenosis • Allograft infarction • Arteriovenous fistulas • Pseudoaneurysm • Graft hematoma • Renal artery or vein thrombosis	• Ureteral obstruction • Urine leak • Perigraft and allograft fluid collections (hematomas, lymphoceles, and abscesses) • Neoplasms • GI complications • Post-transplant lymphoproliferative disease

(GI: gastrointestinal)

BOX 3: Postliver transplant complications.

Biliary complications:

- Complication are bile leak, biliary stricture, and biloma
- Necessary investigations are liver enzymes, ultrasound, ERCP, CT, and MRI
- Treatment options are antibiotics, ERCP, and drainage of biloma

Hepatic artery complications:

- Hepatic artery thrombosis, hepatic vein thrombosis, portal vein complications, and pseudoaneurysm
- *Investigations*: Ultrasound (venous thrombus) and CT angiography (arterial thrombus)
- *Treatment*: Thrombolysis and transcatheter ablation

Neurological complications:

- Stroke, cerebral abscess, hypertensive encephalopathy, osmotic demyelination syndrome, and sinus thrombosis
- MRI is preferred in these situation
- Treatment as per complication

(ERCP: endoscopic retrograde cholangiopancreatography)

BOX 4: Approach to patient with lung transplant rejection.

History:

- Patients commonly present with fever, cough, and increasing dyspnea which may often be confused with a respiratory tract infection

Physical examination:

- Cyanosis, diaphoresis, use of accessory muscles of respiration, signs of congestive heart failure, and peripheral perfusion

Investigation:

- Chest radiography, arterial blood gas, and bronchoscopic biopsy (confirmatory diagnosis)

Treatment:

Beta-agonists and anticholinergics. Methylprednisolone 15 mg/kg intravenous (IV), common practice to cover both infections and rejection till definitive diagnosis with biopsy or cultures is confirmed

Lung Transplantation

Lung transplant involves three important anastomoses; airway, pulmonary arterial, and pulmonary vein. Lung transplant-related complications are summarized in **Box 4**.

Cardiac Transplantation

Cardiac transplantation is performed in patients with end-stage heart failure both in newborn and adults. Transplanted heart differs from a normal heart in terms of being denervated and therefore there is no response to centrally mediated tachycardia due to exercise and stress. The denervated heart however is catecholamine responsive. Thus, response to stress and exercise is blunted. However, with proper conditioning a normal response to stress may be ensured. The donor heart has two sinus nodes; one of the recipients and one of the donors.

The electrocardiogram (ECG) therefore has two distinct P waves often being mistaken as atrial fibrillation. Common complications postcardiac transplant are listed as **Table 5**.

TABLE 5: Postcardiac transplant complications.

- Altered physiology
- Dysrhythmia
- Sinus node dysfunction
- Cardiac ischemia
- Rejection
- Infection
- Congestive heart failure
- Stroke (ischemic/hemorrhagic)
- Complications related to ventricular assist devices
- Cardiac allograft vasculopathy
- Infection
- Pulmonary complications:
  - Pneumonia
  - Thromboembolic disease
  - Exercise-induced hypoxemia
  - Pneumothorax
  - Interstitial fibrosis

SUMMARY

While managing the patient in ED, emergency physician should be aware of immunocompromised state of any triaged patient as transplant patient are increasing day by day. So, emergency physician should be aware of various complications and evaluation of the conditions.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

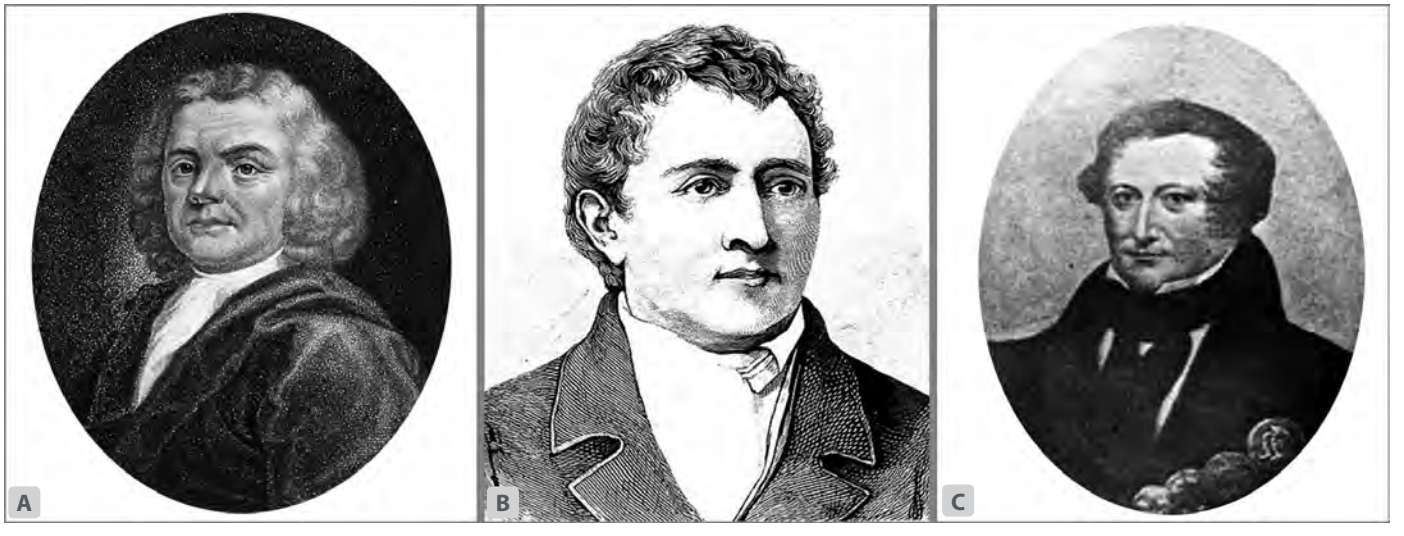
Analytical Toxicology

VV Pillay

INTRODUCTION

Scientific methods of analysis for poisons have only recently been developed. Until the 19th century, doctors and scientists harbored faulty notions about the effect of poisons on the human body. It was believed that if a dead body was black, blue, or spotted in places, or "smelled bad," the cause of death was a poison. Other fallacious ideas were that the heart of a poisoned person could not be destroyed by fire and that the body of a person dying from arsenic poisoning would not decay. The first person to suggest a method for detecting poisons in tissues was the Dutch physician *Hermann Boerhaave* (**Fig. 1A**) who theorized that various poisons in a hot vaporous condition yielded typical odors. He placed substances suspected of containing poisons on hot coals and tested their smells. Owing to the widespread use of arsenic as a homicidal poison in the middle ages, it is a small wonder that the first milestones in the chemical isolation and identification of a poison in body tissues and fluids centered around arsenic. In 1775, *Karl Wilhelm Scheele* (**Fig. 1B**) the famous Swedish chemist, discovered that white arsenic (arsenic trioxide) was converted to arsenious acid by chlorine water, and the addition of metallic zinc reduced the arsenious acid to arsine gas. Gently heating the ensuing gas led to the deposition of metallic arsenic on the surface of a cold vessel. In 1821, *Sevillas* utilized the decomposition of arsine for the detection of small quantities of arsenic in stomach contents and urine in poisoning cases. In 1836, *James Marsh* (**Fig. 1C**), a British chemist, developed the first reliable method to determine an absorbed poison (arsenic) in body tissues and fluids such as liver, kidney, and blood.

We have come a long way since then to the present era of sophisticated analytical techniques which can detect even micrograms of virtually any poison in almost any kind of biological specimen. Today, an analytical (toxicology) laboratory has become a vital adjunct to the proper management of poisoned patients. However, it is to be noted that the cornerstone of the management of such patients—*intensive supportive therapy*—is mostly independent of the kind of poison implicated, and hence routine employment of expensive analytical techniques should be avoided. The attending physician must be judicious in calling for necessary investigations and exercise discretion in the choice of tests to be done. At the time that the IV catheter is inserted, blood samples for glucose, electrolytes, blood urea nitrogen (BUN), a complete blood count (CBC), and any



FIGS. 1A TO C: (A) Herman Boerhaave (1668–1738); (B) Karl Wilhelm Scheele (1742–1786); (C) James Marsh (1794–1846).

indicated toxicologic analysis can be drawn. If the patient has an altered mental status, the attending physician may be tempted to send blood and urine specimens to identify any central nervous system (CNS) depressants or drugs of abuse, along with other medications, but the indiscriminate ordering of these tests rarely provides clinically useful information. For the potentially suicidal patient, a paracetamol concentration should be routinely requested, along with tests affecting the management of any specific xenobiotic such as carbon monoxide, lithium, theophylline, iron, salicylates, and digoxin (or other cardioactive steroids), as suggested by history, physical examination, or bedside diagnostic tests. In the vast majority of cases, the blood tests that are most useful in diagnosing toxicologic emergencies are not the toxicologic assays but the "nontoxicological" routine metabolic profile tests such as BUN, glucose, electrolytes, and arterial blood gases (ABGs) or venous blood gases (VBGs).

The potential indications for seeking the help of a toxicology laboratory are as follows:
All the seven indications mentioned can be remembered by the mnemonic *PROMISE*:

1. *P*rognosis: To assess the outcome of a case of poisoning
2. *R*esearch: Into toxicokinetics and mechanisms of toxicity
3. *O*rder: From court or law enforcement officer
4. *M*onitoring: Of treatment measures and their efficacy
5. *I*dentification: Of the nature of poison
6. *S*everity: To assess the seriousness of a given case
7. *E*xclusion: Or confirmation of toxic exposure

Mahoney and associates have categorized the treatment of a poisoning case into four groups with respect to toxicological evaluations:

1. *Toxicity correlates very well with serum levels and specific drug therapy can be instituted*, e.g., digoxin, ethylene glycol, lithium, methanol, paracetamol, salicylates, theophylline.
2. *Toxicity correlates closely with serum level, but only nonspecific care is required*, e.g., barbiturates, ethanol, phenytoin.
3. *Toxicologic testing only serves to confirm fairly clear-cut clinical parameters of poisoning*, e.g., cyanide, narcotics, organophosphates, tricyclics.
4. *Toxicity correlates poorly with serum level, and only nonspecific care is required*, e.g., amphetamines, benzodiazepines, cocaine, neuroleptics.

In fact, most poisoned patients can be treated successfully without any contribution from the laboratory other than routine clinical biochemistry and hematology. This is particularly true when there is no doubt about the poison involved and when the results of a quantitative analysis would not significantly affect therapy. In those cases where an analytical toxicological investigation is deemed beneficial, an orderly progression is desirable in the performance of necessary tests and their interpretation (**Table 1**).

TABLE 1: Phases of analytical toxicological investigation.

Preanalytical phase	*Analytical phase*
• Obtain details of current admission, including circumstantial evidence of poisoning, and results of biochemical and hematological investigations • Obtain the patient's medical history and decide the priorities for analysis	• Interpret the results and discuss them with the clinician looking after the patient • Perform additional analyses if indicated

TABLE 2: Toxic causes of hypo- and hyperglycemia.

Hypoglycemia	*Hyperglycemia*
Acetohexamide, Amprenavir, Chloramphenicol, Chlorpromazine, Chlorpropamide, Cibenzoline, Clove, Ethanol, Ethionamide, Fluorodeoxyglucose, Gatifloxacin, Ginseng, Glibenclamide, Gliclazide, Glimepiride, Glipizide, Gliquidone, Glisolamide, Glisoxepide, Insulin, Iron salts, Lanreotide, Levomepromazine, Mitiglinide, Nateglinide, Paracetamol, Pazopanib, Pentamidine, Perazine, Pipothiazine, Pramlintide, Quinine, Repaglinide, Ritonavir, Salicylates, Saquinavir, Somatostatin, Sulfamethoxazole, Temafloxacin, Tolazamide, Tolbutamide, Trimethoprim	Amphetamines (acute toxicity), Antipsychotic agents (some), Beta-blockers, Corticosteroids, Duloxetine, Epinephrine, L-asparaginase, Niacin, Octreotide, Olanzapine, Pentamidine, Protease inhibitors, Salbutamol, Salicylates, Theophylline, Thiazide diuretics

BIOCHEMICAL AND HEMATOLOGICAL TESTS USEFUL IN TOXICOLOGY

Biochemical Tests

- *Blood glucose*: Apart from insulin and other antidiabetic drugs, *hypoglycemia* is a common feature of poisoning with ethanol, iron salts, paracetamol, and salicylates (**Table 2**). *Hyperglycemia* may be seen less commonly in salicylates, while it is more common in salbutamol and theophylline overdose.
- *Electrolytes, blood gases, and pH*: The value of these parameters in various kinds of poisoning is discussed in the respective chapters dealing with specific poisons.
- *Plasma enzymes*: Shock, coma, and convulsions are often associated with nonspecific increase in plasma or serum activities of enzymes such as *lactate dehydrogenase, aspartate aminotransferase,* and *alanine aminotransferase*. In severe cases, there may be evidence of rhabdomyolysis and disseminated intravascular coagulation manifested by high serum aldolase or creatine kinase, together with myoglobinuria. High serum potassium, uric acid, and phosphate concentrations indicate the onset of acute renal failure. The plasma activities of hepatic enzymes are enhanced in poisoning due to carbon tetrachloride, copper salts, and paracetamol. Chronic alcoholism is often associated with increased *gamma-glutamyl transferase activity*.

Depressed plasma *cholinesterase* activity is a useful indicator of exposure to organophosphate or carbamate pesticide.

Hematological Tests

- *Blood clotting*: Prothrombin time and other blood clotting parameters are likely to be abnormal in acute poisoning with hepatotoxic agents, rodenticides containing anticoagulants, and in certain types of snake bite (especially viper).
- *Hematocrit*: Acute overdose involving iron salts, nonsteroidal anti-inflammatory drugs (NSAIDs), and salicylates can cause gastrointestinal bleeding leading to anemia. Anemia may also result from chronic exposure to heavy metals such as arsenic and lead. A less common (indirect) cause is *glucose-6-phosphate dehydrogenase* deficiency when any of the following drugs have been administered: chloramphenicol, chloroquine, nitrofurantoin, primaquine, etc.
- *Leukocyte count*: Leukocytosis is a recognized feature of acute metabolic acidosis resulting from the ingestion of poisons such as ethylene glycol and methanol. It is also seen as a secondary feature of hypostatic pneumonia following prolonged coma.

ANALYTICAL METHODS USED IN TOXICOLOGY

Toxicology laboratories use several methods to screen for poisons/drugs since there is no single, accurate, and inexpensive method for this purpose. Each method differs in cost, accuracy, complexity, speed, and specificity. The actual equipment required depends on the size of the laboratory and the kind of testing done. A basic, ideal laboratory should have the following facilities/resources:

- Calibrated laboratory balances
- Benchtop centrifuge
- Vortex mixer
- Water bath and heating block
- Butane gas burner
- Fume cupboard/fume hood
- Refrigerator and freezer
- pH meter
- Automatic/semiautomatic pipettes
- Low power polarizing microscope
- Thin-layer chromatography (TLC) plates
- Ultraviolet (UV) spectrophotometer
- UV lamp
- Conway microdiffusion apparatus
- Porcelain spotting tile
- Modified Gutzeit apparatus

In addition, it is desirable to have the following specialized equipment, although they are quite expensive:

- High-performance liquid chromatography (HPLC)[1*]
- Gas chromatography (GC)
- Mass spectrometry (MS)
- Facility for radioimmunoassay (RIA)
- Enzyme-mediated immunoassay technique (EMIT)[†]

There should also be access to sophisticated systems of analysis which are normally beyond the scope of a toxicology laboratory, such as atomic absorption spectrophotometry (AAS), and neutron activation analysis (NAA). In a given case of poisoning, it may be sufficient to know just the nature of poison (*qualitative analysis*) or there may be a need for identification as well as estimation of its concentration in the body (*quantitative analysis*).

QUALITATIVE ASSAYS

- *Trinder's test*: Add 100 mL of *Trinder's reagent* (40 g mercuric chloride in 850 mL water and 120 mL aqueous hydrochloric acid mixed with 40 g hydrated ferric nitrate diluted to 1 L with warm water) to 2 mL urine and mix for 5 seconds.
- A violet or purple color indicates the presence of salicylates (salicylic acid, salicylamide, and methyl salicylic acid). If the specimen merely darkens, the result is considered negative. If only stomach contents or scene residues are available, hydrolyze it by heating with 0.5 mol/L hydrochloric acid in a boiling water bath for 2 minutes and neutralize it with 0.5 mol/L sodium hydroxide before performing the test. The test has a sensitivity of 94% and a specificity of 74% for identifying patients whose salicylate concentrations are greater than 30 mg/dL (2.17 mmol/L). False-positive concentrations (2.8–14.3 mg/dL) have been reported to occur in neonates with hyperbilirubinemia, premature neonates, and children who are seriously ill (e.g., children who have extensive burns).
- *Ferric chloride test*: Add 1 mL of 5% ferric chloride solution to 2-mL urine. A persistent purple color indicates the presence of phenol, phenothiazines, phenylbutazone, oxyphenbutazone, or salicylates.
- *Network FPN test*: Add 1 mL of FPN reagent (a mixture of 5-mL aqueous ferric chloride, 45-mL aqueous perchloric acid, and 50-mL aqueous nitric acid) to 1 mL of urine or stomach contents and mix for 5 seconds. Colors ranging from pink, red, violet to blue may indicate the presence of phenothiazines. Tricyclics may give a green or blue color.
- *O-cresol test*: Add 0.5-mL concentrated hydrochloric acid to 0.5-mL urine or stomach contents, heat it in a boiling water bath for 10 minutes, and cool. Add 1 mL of aqueous O-cresol solution (10 g/L) to 0.2 mL of the hydrolysate, followed by 2-mL ammonium hydroxide, and mix for 5 seconds. A blue or blue-black color indicates the presence of paracetamol or phenacetin.
- *Dichromate test*: Add equal volumes of 10% sodium dichromate in 50% sulfuric acid to the urine sample. Development of a green color indicates the presence of ethanol.
- *Marquis test*: Add a mixture of 3-mL concentrated sulfuric acid and three drops of formalin to the gastric fluid. A purple color, which gradually turns blue, indicates the presence of opium or its derivatives.
- *Lee Jones test*: Add a few crystals of ferrous sulfate and four to five drops of 2% sodium hydroxide to 5-mL gastric fluid. Boil and cool. Add 8 to 10 drops of 10% hydrochloric acid. A greenish-blue color indicates cyanide, while a purple color indicates salicylates in the sample.
- *Reinsch test*: 20 mL of stomach contents or urine is placed in a conical flask along with 10-mL hydrochloric acid and a small strip of copper. This is gently heated for an hour in a boiling water bath inside a fume cupboard. The copper is then removed and examined. A silvery deposit indicates mercury poisoning, while a black deposit indicates

*Also referred to as high-pressure liquid chromatography.

[†]Also referred to as enzyme multiplied immunoassay technique.

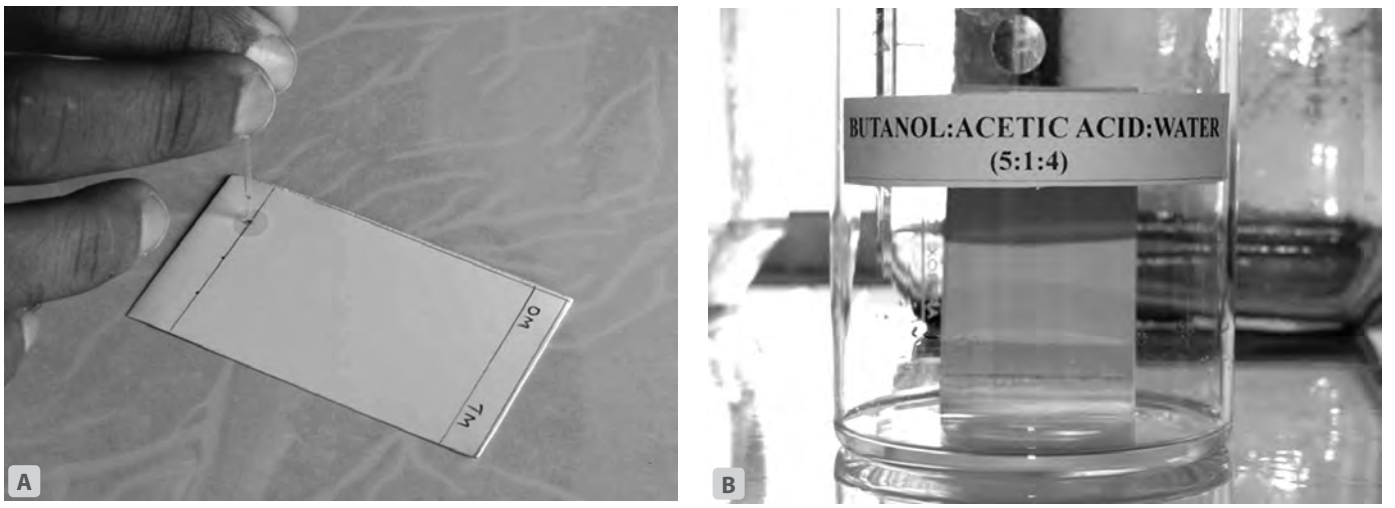
arsenic or bismuth, and a purplish-black deposit indicates antimony.

- *Qualitative desferrioxamine color test*: 2 mL of gastric fluid and two drops of 30% hydrogen peroxide are placed in two plastic tubes. 5 mL of desferrioxamine solution (500 mg in 4 mL of distilled water) is placed in one tube, and the resulting color change is compared with the other tube (control). If an orange or red color develops, it indicates the presence of toxic levels of iron. The test must be done within 2 hours of poisoning or else it is unreliable. A variation of this test is the *desferrioxamine challenge test (DCT)*, in which 25–50 mg/kg of desferrioxamine is administered to the patient by intramuscular injection. Iron poisoning is indicated if the urine, which is voided subsequently, is pinkish in color (*vin rosé urine).*
- *Meixner test*: This test can be done on either a stool or a gastric sample. Dilute the sample with methanol, centrifuge, and filter it. Add a drop or two to a piece of newspaper. Encircle the spot with a pencil and dry it. Add a few drops of concentrated hydrochloric acid to the spot. If a blue color forms within a few minutes, it is indicative of the presence of amatoxin (present in most toxic mushrooms).
- *Forrest test*: Add 1-mL Forrest reagent (a mixture of 25-mL aqueous potassium dichromate, 25-mL aqueous sulfuric acid, 25-mL aqueous perchloric acid, and 25-mL aqueous nitric acid) to 0.5 mL of the sample and mix for 5 seconds. A yellow-green color deepening to blue indicates the presence of imipramine or related compounds.
- *Fujiwara test*: To three 10-mL tubes, add 1-mL portions of (1) the sample, (2) purified water, and (3) aqueous trichloroacetic acid (10 mg/L), respectively. Add 1-mL sodium hydroxide solution (5 mol/L) and 1-mL pyridine to each tube, mix carefully, and heat in a boiling water bath for 2 minutes. An intense red/purple color in the top layer of tube 1 as in tube 3 indicates the presence of trichloro compounds such as chloral hydrate, chloroform, and trichloroethylene. Tube 2 should show no coloration.
- *Isonitrile test*: Mix a small amount of gastric contents with 10-mL water and add 1-mL purified aniline, followed by 2-mL 20% sodium hydroxide. Heat gently for a few minutes. A foul odor (*skunk odor)* will be perceived if one of the following poisons is present: carbon tetrachloride, chloral hydrate, chloroform, methyl bromide, or any other chlorinated hydrocarbon.
- *Tensilon test (edrophonium challenge test)*: When 10-mg edrophonium is given intravenously in a case of sudden paralysis, there will be dramatic recovery if it is due to myasthenia gravis, while a case of poisoning (e.g., botulism) will not show any improvement.
- *Melzer's test*: This is a test done to confirm whether a given mushroom is toxic (especially *Amanita phalloides*). The spores obtained from the mushroom are stained with 1 drop of Melzer's reagent (mixture of 20-mL water, 1.5-g potassium iodide, 0.5-g iodine, and 20-g chloral hydrate) and viewed under a microscope. Spores of *A. phalloides* and a few other deadly mushrooms will show a bluish-black color ("amyloid reaction"). However, a negative reaction does not mean that the mushroom is nontoxic.

Thin-layer Chromatography

Thin-layer chromatography is a *qualitative technique* which involves the movement by the capillary action of a liquid phase (usually an organic solvent) through a thin, uniform layer of the stationary phase (usually silica gel) held on a rigid support (usually a glass, aluminum, or plastic sheet). Compounds are separated by partition between the mobile and the stationary phases.

A very thin layer of silica gel or aluminum oxide is applied to a glass plate, 20 × 20 × 0.5 cm, and vertical lines are drawn 1.5 cm apart to allow individual runways for each sample. Purified tissue extracts dissolved in 0.5 mL of methanol are serially spotted with a micropipette and dried in a small circle in the lower center of a runway 1.5 cm from the bottom (**Fig. 2A**). Other samples are similarly spotted in other runways. A horizontal line (stop point) is drawn 10 or 15 cm above these starting points. A TLC tank is filled with suitable developing solvents to a depth of about 1 cm from the bottom. The plate properly spotted is then dipped into the solvent, the lid is firmly closed, and the atmosphere is allowed to saturate with vapor (**Fig. 2B**). When the solvent front just touches the 10-cm



(TLC: thin-layer chromatography)

FIGS. 2A AND B: (A) Spotting on a TLC plate; (B) Saturation of TLC plate inside TLC chamber.

Courtesy: Dr Ramakrishnan, UK.

horizontal mark, quickly remove the plate and examine it under UV light (at 254 and 366 nm) for characteristic fluorescence or absorbance. Calculate the Rf value. This can also be done after spraying the plate with appropriate reagents to bring out characteristic color spots.[2*] This widens the scope of the analysis and increases the confidence of identification.

$$\text{Rf is the ratio of } \frac{\text{Solute front}}{\text{Solvent front}} \times 100$$

Approximate quantitation can be done by comparison with standards, similarly prepared on the same plate, for the intensity of color and area size. The Rfs suggested in the literature can be used as a guide for identifying various poisons, though it is preferable that each analyst should prepare and establish his/her own Rf according to his/her own conditions and technique.

The recommended TLC visualization reagents are as follows:

- Mercurous nitrate reagent (acidic extract) which gives white spots with a gray center on a darker background with barbiturates and related compounds
- Acidified iodoplatinate reagent (basic extract) which gives mainly purple, blue, or brown spots with a range of basic and neutral drugs and metabolites
- Mandelin's reagent (basic extract) which gives colors ranging from blue and green to orange and red with a variety of basic compounds
- Sulfuric acid (500 mL/L) (basic extract) gives red, purple, or blue spots with many phenothiazines and their metabolites

Thin-layer chromatography is a simple and inexpensive technique which is widely used. It is to be noted that many additional mobile phase and spray reagent combinations could be used in place of those suggested here. It takes only about 2 hours from beginning to completion. It is also a very versatile method since the order of separation of compounds can be altered simply by changing the nature of the developing agent. However, the interpretation of the plates can prove difficult and calls for a trained eye with considerable experience in recognizing colors, spot shapes, and metabolite patterns. It is also well known that TLC can produce false-positive results because of interference between xenobiotics. It is always desirable to confirm results by more sophisticated methods, especially in forensic cases.

Troubleshooting

- *The compound runs as a streak rather than a spot*: It means that the sample was overloaded. Run the TLC again after diluting the sample. Or, the sample might just contain many components, creating many spots which run together and appear as a streak, i.e., the procedure did not go as well as expected. Repeat!
- *The sample runs as a smear or an upward crescent*: Compounds that possess strongly acidic or basic groups (amines or carboxylic acids) sometimes show up on a TLC plate with this behavior. Add a few drops of ammonium hydroxide (amines) or acetic acid (carboxylic acids) to the eluting solvent to obtain clearer plates.
- *The sample runs as a downward crescent*: Likely, the adsorbent was disturbed during the spotting, causing the crescent shape.
- *The plate solvent front runs crookedly*: Either the adsorbent has flaked off the sides of the plate or the sides of the plate are touching the sides of the container (or the paper used to saturate the container) as the plate develops. Crookedly run plates make it harder to measure Rf values accurately.
- *No spots are seen on the plate*: The operator may not have spotted enough compound, perhaps because the solution of the compound is too dilute. This can be resolved by concentrating the solution or spotting it several times in one place, allowing the solvent to dry between applications. Some compounds do not show up under UV light; try another method of visualizing the plate.
- If the solvent level in the developing jar is deeper than the origin (spotting line) of the TLC plate, the solvent will dissolve the compounds into the solvent reservoir instead of allowing them to move up the plate by capillary action. In such a case also, spots will not be seen after the plate is developed.

Note: All spray reagents used are very toxic. Spraying must be performed in a fume cupboard or under an efficient fume hood.

QUANTITATIVE ASSAYS

Ultraviolet Spectrophotometry

Ultraviolet spectrophotometry (UVS) is based on the principle that many drugs, when in solution, will absorb UV radiation. The degree of absorption depends on the chemical structure of the drug, its concentration in the solution, and the wavelength of the ultraviolet radiation (UVR). The functioning of this instrument is relatively straightforward. A beam of light from a visible and/or UV light source is separated into its component wavelengths by a prism or diffraction grating (**Fig. 3**). The monochromator can select from the light source an UV ray of any given wavelength from 200 to 340 nm. The sample extract in the aqueous medium is placed in a transparent quartz cuvette in the path of the radiation. Each monochromatic (single wavelength) beam in turn is split into two equal-intensity beams by a half-mirrored device. One beam, the sample beam, passes through a small transparent container

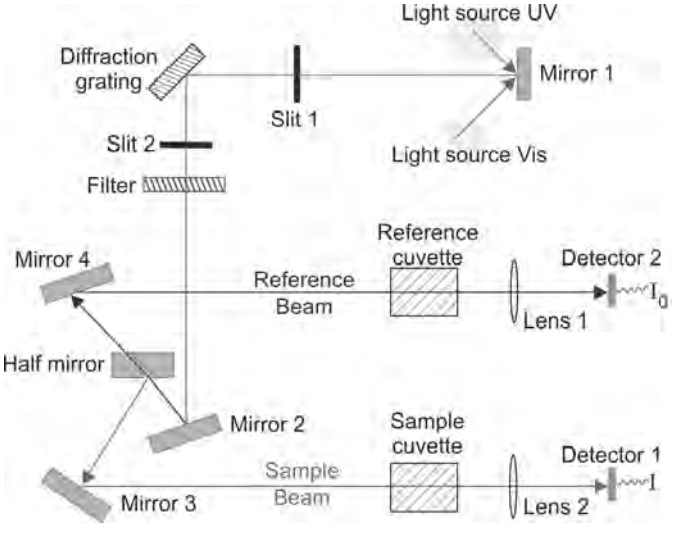


FIG. 3: Schematic diagram of a ultraviolet spectrophotometer.

(cuvette) containing a solution of the compound being studied in a transparent solvent. The other beam, the reference, passes through an identical cuvette containing only the solvent. The intensities of these light beams are then measured by electronic detectors and compared. The intensity of the reference beam, which should have suffered little or no light absorption, is defined as I_0. The intensity of the sample beam is defined as I. Over a short period of time, the spectrometer automatically scans all the component wavelengths in the manner described. The UV region scanned is normally from 200 to 400 nm, and the visible portion is from 400 to 800 nm.

If the sample compound does not absorb light of a given wavelength, $I = I_0$. However, if the sample compound absorbs light then I is less than I_0, and this difference may be plotted on a graph versus wavelength, as shown on the right. Absorption may be presented as *transmittance* ($T = I/I_0$) or *absorbance* ($A = \log I_0/I$). If no absorption has occurred, $T = 1.0$ and $A = 0$. Most spectrometers display absorbance on the vertical axis, and the commonly observed range is from 0 (100% transmittance) to 2 (1% transmittance). The wavelength of maximum absorbance is a characteristic value, designated as λ_{max}. Different compounds may have very different absorption maxima and absorbances. Intensely absorbing compounds must be examined in dilute solution, so that significant light energy is received by the detector, and this requires the use of completely transparent (nonabsorbing) solvents. The most commonly used solvents are water, ethanol, hexane, and cyclohexane. Solvents having double or triple bonds, or heavy atoms (e.g., S, Br, and I) are generally avoided. Because the absorbance of a sample will be proportional to its molar concentration in the sample cuvette, a corrected absorption value known as the *molar absorptivity* is used when comparing the spectra of different compounds. Molar absorptivities may be very large for strongly absorbing compounds ($\varepsilon > 10{,}000$) and very small if absorption is weak ($\varepsilon = 10$–100).

The amount of UV radiation that passes through the solution is measured by the photocell. By steady rotation of the monochromator, it is possible to pass sequentially UV rays of all wavelengths from 200 to 340 nm through the extract. The photocell monitors the amount of radiation absorbed at each wavelength and this is transcribed onto a recorder chart. The shape of the spectrum, the wavelength at which absorption is at a maximum, and any changes brought about by changing the pH of the extract are all used as an aid to characterize the agent present. This technique is ideal to quantitate blood levels of paracetamol and salicylates as well as urine levels of phenothiazines.

A major disadvantage of UVS is the possibility of interference in multiple drug overdose. In such a case, UV scanning can produce a composite spectrum of bewildering complexity from which neither qualitative nor quantitative information can be derived. Conventional spectrophotometric methods are known for producing false-positive results which can be disastrous in medicolegal cases.

Gas Chromatography

Gas chromatography is a more sophisticated system of quantitative analysis and has found great favor with analytical toxicologists since it offers a way of simultaneously separating, identifying, and measuring drugs and other organic poisons (**Fig. 4**). Gas chromatography—specifically gas-liquid chromatography—involves a sample being vaporized and injected onto the head of the chromatographic column. The sample is transported through the column by the flow of inert, gaseous mobile phase. The column itself contains a liquid stationary phase which is adsorbed onto the surface of an inert solid. The liquid or solid specimen dissolved in a solvent is injected into the chromatograph. The specimen is vaporized by heat and is carried through a column by an inert carrier gas (usually nitrogen). The choice of carrier gas is often

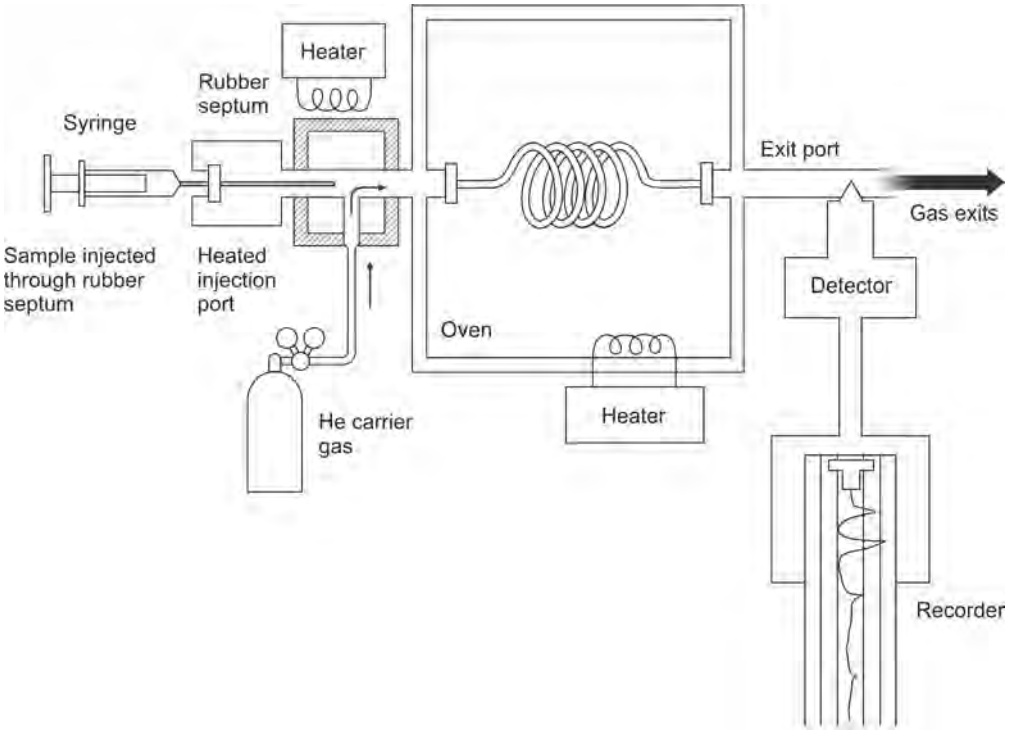


FIG. 4: Schematic diagram of a gas chromatograph.

dependent upon the type of detector which is used. The carrier gas system also contains a molecular sieve to remove water and other impurities. The column is packed with a substance like carbowax or adiponitrile, which is capable of changing the migration time of the specimen as it traverses the column.

For optimum column efficiency, the sample should not be too large and should be introduced onto the column as a "plug" of vapor—slow injection of large samples causes band broadening and loss of resolution. The most common injection method is where a microsyringe is used to inject a sample through a rubber septum into a flash vaporizer port at the head of the column. The temperature of the sample port is usually about 50°C higher than the boiling point of the least volatile component of the sample. For packed columns, the sample size ranges from tenths of a microliter up to 20 μL. Capillary columns, on the other hand, need much less sample, typically around 10^{-3} μL. For capillary GC, split/splitless injection is used.

The injector can be used in one of two modes: split or splitless. The injector contains a heated chamber containing a glass liner into which the sample is injected through the septum. The carrier gas enters the chamber and can leave by three routes (when the injector is in split mode). The sample vaporizes to form a mixture of carrier gas, vaporized solvent, and vaporized solutes. A proportion of this mixture passes onto the column, but most exits through the split outlet. The septum purge outlet prevents septum bleed components from entering the column.

A detector recognizes the presence of the chemical and graphically plots its emergence as a function of time. The retention time and peak area for a chemical compared to the known standard are used to identify and quantitate its presence. There are many detectors which can be used in gas chromatography. Different detectors will give different types of selectivity. A *nonselective* detector responds to all compounds except the carrier gas, a *selective detector* responds to a range of compounds with a common physical or chemical property, and a *specific detector* responds to a single chemical compound. Detectors can also be grouped into *concentration-dependent detectors* and *mass flow-dependent detectors*. The signal from a concentration-dependent detector is related to the concentration of solute in the detector and does not usually destroy the sample. Dilution of make-up gas will lower the detector's response. Mass flow-dependent detectors usually destroy the sample, and the signal is related to the rate at which solute molecules enter the detector. The response of a mass flow-dependent detector is unaffected by make-up gas.

The most common means of detecting the compounds is by flame ionization. On leaving the column, the inert gas is mixed with hydrogen and either air or oxygen, and the mixture is ignited to give a continuous jet of flame. It is decomposed into electrically charged fragments which are collected at an electrode. This results in an electrical signal which is amplified and transmitted to a pen recorder operating at a constant chart speed. This peak is transcribed each time a compound emerges from the column. Flame ionization detectors (FIDs) are mass sensitive rather than concentration sensitive; this gives the advantage that changes in mobile phase flow rate do not affect the detector's response. The FID is a useful general detector for the analysis of organic compounds; it has high sensitivity, a large linear response range, and low noise. It is also robust and easy to use, but unfortunately, it destroys the sample.

Gas chromatography is most commonly employed to quantitate blood levels of volatile liquids such as ethanol, ethylene glycol, and methanol. Other detectors have recently been developed which widen the scope of plasma screening, such as the *electron capture detector* and the *alkali flame detector (nitrogen detector)*.

High-performance Liquid Chromatography

High-performance liquid chromatography is similar to GC, except that it is not restricted to volatile compounds. A high-pressure (1,000–6,000 pound per square inch) pump facilitates the movement of the specimen through the columns packed with chromatographic adsorbents, e.g., silica gel and alumina. The effluent stream passes through a detector, usually an UV spectrophotometer, and the appearance of a drug in the solvent is signaled by a recorder peak in the same way as in GC (**Fig. 5**). Again, the size of the peak is proportional to the concentration of the drug in the sample. HPLC can be used to separate and analyze complex mixtures.

Applications of High-performance Liquid Chromatography

- *Preparative HPLC* refers to the process of isolation and purification of compounds. Important is the degree of solute purity and the throughput, which is the amount of compound produced per unit of time. This differs from *analytical HPLC*, where the focus is to obtain information about the sample compound. The information that can be obtained includes identification, quantification, and resolution of a compound.
- *Chemical separations* can be accomplished using HPLC by utilizing the fact that certain compounds have different migration rates given a particular column and mobile phase. Thus, the chromatographer can separate compounds from each other using HPLC; the extent or degree of separation is mostly determined by the choice of stationary phase and mobile phase.
- *Purification* refers to the process of separating or extracting the target compound from other (possibly

FIG. 5: High-performance liquid chromatography system.
Courtesy: Dr Ramakrishnan, UK.

structurally related) compounds or contaminants. Each compound should have a characteristic peak under certain chromatographic conditions. Depending on what needs to be separated and how closely the samples are related, the chromatographer may choose the conditions, such as the proper mobile phase, to allow adequate separation in order to collect or extract the desired compound as it elutes from the stationary phase. The migration of the compounds and contaminants through the column need to differ enough so that the pure desired compound can be collected or extracted without incurring any other undesired compound.

- *Identification* of compounds by HPLC is a crucial part of any HPLC assay. In order to identify any compound by HPLC, a detector must first be selected. Once the detector is selected and is set to optimal detection settings, a separation assay must be developed. The parameters of this assay should be such that a clean peak of the known sample is observed from the chromatograph. The identifying peak should have a reasonable retention time and should be well separated from extraneous peaks at the detection levels in which the assay will be performed. To alter the retention time of a compound, several parameters can be manipulated. The first is the choice of column, another is the choice of mobile phase, and the last is the choice in flow rate.
- Identifying a compound by HPLC is accomplished by researching the literature and by trial and error. A sample of a known compound must be utilized in order to assure identification of the unknown compound. Identification of compounds can be assured by combining two or more detection methods.
- *Quantification* of compounds by HPLC is the process of determining the unknown concentration of a compound in a known solution. It involves injecting a series of known concentrations of the standard compound solution onto the HPLC for detection. The chromatograph of these known concentrations will give a series of peaks that correlate with the concentration of the compound injected.

Mass Spectrometry

Mass spectrometry is usually combined with gas chromatography *(GC-MS)* (**Fig. 6**) and is considered to be the best technique for quantitative analysis of a wide variety of chemicals, but its expense (capital as well as operational costs) greatly restricts its use. In the simplest terms, the GC-MS instrument represents a device that separates chemical mixtures (the GC component) and a very sensitive detector (the MS component) with a data collector (the computer component). Once the sample solution is introduced into the GC inlet, it is vaporized immediately because of the high temperature (250°C) and swept onto the column by the carrier gas (usually helium). The sample flows through the column experiencing the normal separation processes. As the various sample components emerge from the column opening, they flow into the capillary column interface. This device is the connection between the GC column and the MS. Some interfaces are separators and concentrate the sample via removal of the helium carrier. The sample then enters the ionization chamber.

Two potential methods exist for ion production. The most frequently used method for toxicological purposes is electron impact (EI). The occasionally used alternative is chemical

FIG. 6: Gas chromatograph-mass spectrometer.

ionization (CI). For EI ionization, a collimated beam of electrons impacts the sample molecules causing the loss of an electron from the molecule. A molecule with one electron missing is represented by M+ and is called the molecular ion (or parent ion). When the resulting peak from this ion is seen in a mass spectrum, it gives the molecular weight of the compound. CI begins with the ionization of methane (or other gas), creating a radical which in turn will impact the sample molecule to produce M.H+ molecular ions. Some of the molecular ions fragment into smaller daughter ions and neutral fragments. Both positive and negative ions are formed, but only positively charged species will be detected.

Less fragmentation occurs with CI than with EI. Hence, CI yields less information about the detailed structure of a molecule, but it does yield the molecular ion; sometimes the molecular ion cannot be detected by the EI method. Hence, the two methods complement one another. Once ionized, a small positive potential is used to repel the positive ions out of the ionization chamber.

The next component is a mass analyzer (filter), which separates the positively charged particles according to their mass. Several types of separating techniques exist: quadrupole filters, ion traps, magnetic deflection, time-of-flight, radiofrequency, cyclotron resonance, and focusing, to name a few. The most common are quadrupoles and ion traps. After the ions are separated according to their masses, they enter a detector and then on to an amplifier to boost the signal. The detector sends information to the computer which acts as a "clearinghouse." It records all the data produced and converts the electrical impulses into visual displays and hard copy displays. The computer also drives the mass spectrometer.

Identification of a compound based on its mass spectrum relies on the fact that every compound has a unique fragmentation pattern. Even isomers can be differentiated by the experienced operator. Generally, more information is generated than could possibly be used. A library of known mass spectra, which may be several thousand compounds in size, is stored on the computer and may be searched using computer algorithms to assist the analyst in identifying the unknown. It is important to incorporate all other available structural information (chemical, spectral, and sample history) into the interpretation wherever appropriate.

A mass spectrometer can also be connected to a liquid chromatograph (LC-MS) (**Fig. 7**) for the detection of non-volatile compounds. Tandem MS consists of double mass spectrometers connected to gas chromatograph (GC-MS-MS) or liquid chromatograph (LC-MS-MS). These are very costly and sophisticated instruments that can refine the chemical analysis to an almost flawless degree.

Radioimmunoassay

Radioimmunoassay is a slow and expensive method of detecting drugs in the blood but is highly accurate. It involves mixing known quantities of a drug-specific antibody with a known amount of a radioactively labeled drug, which allows analysis of the precipitate with a gamma counter. The amount of emittance inversely correlates with the presence of assayed drug. This test is excellent for the detection of drugs in extremely low blood concentrations [cannabis, digoxin, lysergic acid diethylamide (LSD), paraquat, etc.].

Principle

In RIA, a fixed concentration of labeled tracer antigen is incubated with a constant amount of antiserum such that the concentration of the antigen-binding sites on the antibody is limiting; for example, only 50% of the total tracer concentration may be bound by antibody. If an unlabeled antigen is added to this system, there is a competition between the labeled tracer and the unlabeled antigen for the limited and constant number of binding sites on the antibody, and thus the amount of tracer bound to the antibody will decrease as the concentration of unlabeled antigen increases. This can be measured after separating antibody-bound from free tracer and counting either the bound fraction, the free fraction, or both. A calibration or standard curve is set up with increasing amounts of known antigen, and from this curve, the amount of antigen in the unknown samples can be calculated. Thus, the four basic necessities for a RIA system are an antiserum to the compound to be measured, the availability of a radioactively labeled form of the compound, a method whereby an antibody-bound tracer can be separated from the unbound tracer, and a standard unlabeled material.

Radioimmunoassay is widely used because of its great sensitivity. Using antibodies of high affinity ($K_0 = 10^8$–$10^{11}\ M^{-1}$), it is possible to detect a few picograms (10^{-12} g) of antigen in the tube.

FIG. 7: Liquid chromatograph-mass spectrometer.

Enzyme-mediated Immunoassay Technique

This is a fast, expensive method with good accuracy, which works on the principle that the amount of drug present is proportional to the inhibition of an enzyme-substrate reaction. A known quantity of a drug is labeled by chemical attachment to an enzyme. Drug-specific antibodies added to the specimen bind the drug–enzyme complex, thereby reducing enzyme activity. A free drug in the specimen competes with the enzyme-labeled drug and limits the antibody-induced enzyme inactivation. Enzyme activity correlates with drug concentration in the specimen as measured by absorbance change resulting from the enzyme catalytic action on a substrate.

Enzyme-mediated immunoassay technique is preferred over other RIA methods in the emergency situation because of its simplicity and speed in providing information on toxic drug concentrations (approximately one sample per minute). It eliminates the complex separation phase necessary in *RIA*. There are two types: (1) *EMIT-st* (*single test*), which consists of a compact spectrophotometer for small laboratories, and (2) *EMIT-dau (drugs of abuse*) for larger hospitals. The two main disadvantages are as follows:

1. A negative result does not exclude the ingestion of a drug that may be present in undetectable quantities.
2. Antibody cross-reactions can produce false-positive results.

Atomic Absorption Spectrophotometry

Atomic absorption spectrophotometry is the best method for detecting inorganic elements (arsenic, lead, mercury, thallium, etc.). However, it requires a large sample of blood for accurate analysis. The blood sample is introduced into a high-temperature oxyacetylene flame situated in the path of a beam of radiation. The organic matrix is combusted and the metal forms a cloud of atoms which absorbs a fraction of the radiation in proportion to the concentration of metal in the sample. Light of a suitable wavelength for a particular element is shone through the flame, and some of this light is absorbed by the atoms of the sample. The amount of light absorbed is proportional to the concentration of the element in the solution and hence in the original object. Measurements are made separately for each element of interest in turn to achieve a complete analysis of an object, and thus the technique is relatively slow to use. However, it is very sensitive and it can measure trace elements down to the part per million level as well as it is able to measure elements present in minor and major amounts.

The equipment is highly complex and can be operated only by trained personnel (**Fig. 8**). The capital cost is prohibitive. Flame AAS techniques are the oldest methods, and they can measure parts-per-million element concentrations with accuracies in the 1–3% range. Graphite furnace AAS, a more recent development, uses much smaller samples and can make parts-per-billion measurements with about 20% accuracy. The newest technique, diode laser AAS, can look at several elements in a sample simultaneously using an array of lasers that emit various wavelengths of light. A mathematical process is then used to separate the mixture of light wavelengths that reaches the detector.

FIG. 8: Atomic absorption spectrophotometer.

Inductively coupled plasma atomic emission spectroscopy (ICP-AES) is a new development that allows simultaneous multielement analysis. elements can be measured from a single sample: aluminum, barium, cadmium, chromium, copper, iron, lanthanum, lead, manganese, molybdenum, nickel, platinum, silver, strontium, tin, titanium, and zinc. **Table 3** gives the comparative status of efficiency of the commonly used laboratory techniques in toxicology.

TABLE 3: Comparison of analytical methods used in toxicology.

Method	*Specificity*	*Sensitivity*	*Speed*
Thin-layer chromatography	++	++	++
Gas-liquid chromatography	+++	+++	+
High-performance liquid chromatography	+++	+++	+
Spectrophotometry	+	++	+++
Gas chromatography-mass spectrometry	++++	++++	+
Immunology	+++	+++	++++

Neutron Activation Analysis

Neutron activation analysis was discovered in 1936 when Hevesy and Levi found that samples containing certain rare earth elements became highly radioactive after exposure to a source of neutrons. From this observation, they quickly recognized the potential of employing nuclear reactions on samples followed by measurement of the induced radioactivity to facilitate both qualitative and quantitative identification of the elements present in the samples.

This is a highly sophisticated and expensive method of detection of a variety of inorganic elements at levels well below the limits of conventional analytical techniques. The sensitivity attained is remarkable—sometimes 100 or even 1,000 times better than by any other method. It is based on the principle that many substances become radioactive when exposed to bombardment by neutrons. The induced radioactivity is highly specific of the elements contributing to it. Consequently, a study of this radioactivity permits the identification and quantitative estimation of many elements. Radioactivity is a spontaneous disintegration of the atomic nucleus. It occurs in a number of naturally occurring elements including radium, uranium, and thorium. Radioactive varieties (isotopes) of all other elements may be made artificially, as explained above, by exposing them to bombardment by neutrons. However, this requires the use of a nuclear reactor, although attack by charged particles, such as protons and deuterons, obtained from high-energy accelerators may also be serviceable. Assay of the induced radioactivity can be done by means of either a Geiger counter or a scintillation counter.

Neutron activation analysis is a sensitive analytical technique useful for performing both qualitative and quantitative multielement analyses of major, minor, and trace elements in samples from almost every conceivable field of scientific or technical interest. For many elements and applications, NAA offers sensitivities that are superior to those attainable by other methods, on the order of parts per billion or better. In addition, because of its accuracy and reliability, NAA is generally recognized as the "referee method" of choice when new procedures are being developed or when other methods yield results that do not agree. Worldwide application of NAA is so widespread that it is estimated that approximately 100,000 samples undergo analysis each year. NAA can be used for the estimation of any of the 90 naturally occurring elements including antimony, arsenic, cadmium, copper, iron, lead, mercury, phosphorus, selenium, thallium, and zinc.

SUMMARY

Analytical toxicology is helpful in the diagnosis, treatment, prognosis, and prevention of poisoning by detecting, identifying, and often also by measuring drugs and other foreign compounds (xenobiotics) in biological and related specimens. Analytical toxicology is important as it provides objective evidence (such objective evidence is needed in a court of law) of the nature and magnitude of exposure to a particular compound or group of compounds. Establishing analytical toxicology facilities in each and every country is the need of the hour as part of governmental forensic science laboratories.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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199 CHAPTER

General Management of Poisoning

VP Chandrasekaran, Balaji Muruga B

INTRODUCTION

What is poison? Anything taken in excess is a poison. As quoted by a famous Tamil proverb "ALAVUKKU MINJINAAL AMIRDHAMUM NANJU" carries the meaning of "Even Elixir when consumed beyond prescribed quantity, it will become poison." A material intended for treating, when taken in excess, is called an overdose and when some material is consumed, which is not prescribed to treat, resulting in toxicity, it is called poisoning. India is a unique country having citizens with multiple languages and a mix of cultures where the rural population is more than the urban population. The rural population is mainly based on agriculture as a profession and carries an unstable economy due to drought, poverty, and natural disasters. Similarly, in urban areas, there is joblessness, low wages, and work-related stress resulting in more cases of deliberate self-harm. Children are more prone to unintentional and accidental poisoning.

The scope of this chapter is to cover the general management of poisoning in an urban as well as a rural setup.

SETTING UP A POISONING CENTER

Location

A dedicated place for toxicology should be set up at the emergency room (ER) where the regular traffic of patients is relatively less than other areas in the ER.

Facilities

A decontamination area with an exhaust fan to maintain negative pressure, water facility to wash the patients, crash cart with all life-saving medications, defibrillator, monitors, ventilators, gastric lavage facilities, personal protective equipment to the staff, and good water draining facility should be available. Good illumination is a must. A good backup of a laboratory; intensive care unit; cardiac unit for intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), and pacing; nephrology unit for extracorporal removal of poisoning; and transplant unit for liver transplant should also be available. A counseling room with video and audio recording facilities is recommended. Textbooks and Internet connectivity for reference about poisoning should be available.

The Team

A team under the leadership of an emergency physician is preferred and when not possible, he/she shall be replaced by an intensivist, anesthetist, or general physician. The team should be supported by forensic experts, emergency medical technologists, nurses, trained ward assistants, and trained toxicology lab technicians. Some poisons may result in the immediate collapse of patients [cyanide, organophosphorus (OPC), aluminum phosphide, etc.] and some other poisons can result in delayed toxicity (*Cleistanthus collinus*, paraquat, 3% yellow phosphorous poisoning, etc.). Hence, many patients may need immediate resuscitation and some may need close monitoring until few days to months.

PRIMARY TOXICOLOGY SURVEY AND STABILIZATION

Airway and Breathing

All patients who have low Glasgow Coma Scale (GCS), altered sensorium with unprotected airway, impending rapid deterioration, increased work of breathing, severe refractory hypoxia, and anticipated airway compromise must be immediately intubated. A patient with hair dye poisoning may have severe laryngeal edema and it is better to intubate preemptively when the patient develops a husky voice than to wait and watch until stridor develops. Succinylcholine should not be used in OPC poisoning as both act by the same mechanism and the recovery may be delayed. Video-assisted laryngoscopes and bougies may help to aid the challenging intubations and the tracheostomy tray must be kept ready to protect the unanticipated failed airways. It is preferred to go for conscious intubation with midazolam and fentanyl in any case. Propofol is preferred when the patient is not in shock and has no cardiac comorbidity. Ketamine, atropine, and midazolam or ketofol are preferred when the patient is hemodynamically unstable. A "cannot-intubate-cannot-ventilate" situation is not uncommon in the ER, and in case of such a situation, it is

must to have a good backup of a team of doctors and resources. Unlike western countries, where ER has a strong backup from other specialties, Indian ERs, unless located in cities or big towns, do not have the same privilege. Although most of the studies have proven the efficacy of neuromuscular blocking agents in intubation, Dr Rajan et al. have proved acceptable intubating conditions without using any neuromuscular blockers in children posted for cleft lift surgeries. Keeping in mind the Indian rural emergency room scenario, muscle relaxant should be avoided.

It is better not to depend on noninvasive intubation in case of respiratory insufficiency secondary to poisoning as sudden deterioration is common in poisoning. Do not use heat and moisture exchange (HME) filters in poisonings like OPC as the poison may get filtered at HME and returned instead of completely getting exhaled. While setting the ventilator, do not just keep the routine ventilator settings at a fixed rate of 10–12/min and volume of 4–6 mL/kg. While deciding the ventilator settings, one needs to monitor the presence of metabolic acidosis, raised intracranial pressure (ICP), bronchospasm, etc. A patient with severe metabolic acidosis needs more respiratory rate and minute ventilation than normal and needs to maintain the pCO_2 less than the normal range to balance the pH. Similarly, a patient with a raised ICP needs hyperventilation to maintain pCO_2 between 30 and 35 mm Hg, whereas a patient with bronchospasm needs more expiratory time and less tidal volume to prevent air trapping and auto-positive end-expiratory pressure (auto-PEEP). Unexplained hypoxia with chocolate-colored arterial blood with saturation gap [low SpO_2 in monitor and normal saturation in arterial blood gas (ABG)] will respond to methylene blue or exchange transfusion only and may not respond to ventilation or oxygen.

Circulation

It is wise to have at least two intravenous (IV) access to counter any unforeseen events. One needs to go for central venous access, when there is a need for using irritant drugs such as potassium chloride, sodium bicarbonate, and vasopressors. Tachycardia should be managed by treating the reversible cause (correction of fluid and electrolyte imbalance, hypoxia). Tachycardia secondary to drug overdose such as tricyclic antidepressant (TCA) antipsychotics and drugs causing QT prolongation should be treated with sodium bicarbonate. Amiodarone can be harmful in treating the ventricular tachycardia secondary to these poisoning. Neostigmine can be used for atropine derivatives and use of beta-blockers is beneficial for thyroxine. Bradycardia which is refractory to atropine and drugs such as adrenaline needs pacing. In contrast to the bradycardia algorithm of advanced cardiac life support (ACLS), atropine should be given even beyond the vagolytic dose in case of OPC poisoning. If cath lab facility is not available, transcutaneous pacing (TCP) or transvenous pacing (TVP) with the help of bedside echocardography should be performed in cases of refractory bradycardia. ECMO shall be of valuable support in cardiovascular collapses secondary to poisoning like aluminum phosphide poisoning and not responding to vasopressors and IABP.

Calcium gluconate, insulin and dextrose (hyperinsulinemic euglycemic therapy), and glucagon were tried when the shock was secondary to beta-blocker and calcium channel blocker overdoses. Recently, lipid emulsion therapy has been found to be promising in refractory shock secondary to drug overdoses and poisoning. A dose of 1.5 mL/kg IV bolus repeatedly up to three doses and an infusion of 0.25 mL/kg/h has been used to treat refractory shock. Levosimendan and glucose–insulin–potassium infusion are promising in takotsubo cardiomyopathy.

Dysfunction

Any poisoned unconscoius patient brought to emergency room should be checked for blood glucose level and should be treated accordingly. Naloxone should be given in suspected opioid toxicity and it should be started with 0.4 mg IV. If the patient does not respond, 2 mg IV should be started later and up to 20 mg shall be given in highly suspicious conditions. Flumazenil should be given only in isolated benzodiazepine overdose and it should not be given in mixed overdoses. Altered sensorium is common in many poisonings, either because of the primary effect of the poison like benzodiazepine, TCA, and antipsychotics or secondary to hypoxia and hypotension. Seizures must be treated with benzodiazepine, phenobarbitone, or levetiracetam. Phenytoin sodium does not have any role in seizures secondary to poisoning. Seizures secondary to isoniazid (INH) should be treated with pyridoxin and those secondary to lignocaine overdose should be treated by lipid emulsion. A refractory seizure must be addressed with thiopentone or midazolam infusion. If seizures are refractory even to general anesthetic agents, it may be necessary to paralyze the patient to prevent rhabdomyolysis (secondary to repeated muscular contractions of seizures), severe metabolic acidosis, and death; and electroencephalogram (EEG) may help to monitor the seizure activities. Altered sensorium, irritability, tremor, rigidity, sweating, hyperthermia, and autonomous disturbances in a psychiatric patient receiving serotonin should raise the suspicion of serotonin syndrome. This can be treated with cyproheptadine, tepid sponging, and benzodiazepines. Similar clinical findings with a history of OPC poisoning and concomitant use of haloperidol should raise the suspicion of neuroleptic malignant syndrome and should be treated with bromocriptine, tepid sponging, and benzodiazepines.

Exposure

Clear all the dresses and wash the patient with water. Also, look for any trauma due to a fall or that happened while shifting the patient. The scalp should be palpated for hematoma as hair will cover the scalp.

G Vitals

Arterial blood gas , CBG, electrocardiogram (ECG), human chorionic gonadotropin (hCG), and ultrasonography (USG) are the G vitals, and these vitals will help us in immediate assessment and actions at ER. The role of G vitals in poisoning is given in the following text.

Arterial Blood Gas

It helps us to identify the type 1 and 2 respiratory failure, saturation gap, metabolic acidosis, and electrolyte abnormalities.

Severe hypoxia needs oxygenation and ventilation and CO_2 retention needs ventilation support. CO_2 retention, hyperventilation, and history of charcoal administration should raise the suspicion of charcoal aspiration, which is fatal.

Early bronchoscopy and aggressive bronchoalveolar lavage will save the patient.

Severe metabolic acidosis (aluminum phosphide poisoning, acid poisoning, salicylate poisoning, methyl alcohol poisoning, etc.) needs immediate hemodialysis. If the patient is unstable, plan for continuous renal replacement therapy (CRRT) or sustained low-efficiency dialysis (SLED). $NaHCO_3$ infusion shall be planned until the dialysis catheter is inserted.

The combination of hypokalemia and metabolic acidosis is the unique feature of *Cleistanthus collinus* poisoning and where only the hemodialysis should be done and $NaHCO_3$ should not be infused.

Hyperkalemia in digoxin/*oleander* seed poisoning denotes high mortality unless attended aggressively; mortality is inevitable even after pacing.

Capillary Blood Glucose

Hypoglycemia could be identified in seconds and replacement with dextrose solution will provide dramatic regaining of consciousness.

Electrocardiogram

Long QT, widened QRS, R/S ratio in aVR >0.7 ms, and VT should make the diagnosis of TCA and antipsychotics. Bradycardia with varying heart blocks is common in OPC and *oleander* seed poisoning, beta-blocker, calcium channel blocker, antihypertensives, and digoxin toxicity. Reverse tick sign is again a sign of digoxin toxicity. Acute coronary syndrome with exotic poisoning should raise the suspicion of cocaine and amphetamine toxicity.

Ultrasonography

The ultrasound may help us to identify the reason for shock and to decide the need for fluids or vasopressors. Poor left ventricular (LV) dysfunction takotsubo cardiomyopathy, is common in scorpion sting, aluminum phosphide poisoning, and many other poisonings. Presence of the above findings will mandate the need for vasopressor, IABP, or ECMO. Similarly, good cardiac contractility and collapsing inferior vena cava (IVC) shall help us to give more fluids. The presence of pneumothorax secondary to corrosive poisoning, paraquat, and airway accidents shall be identified at the earliest. Other complications such as pulmonary embolism and deep vein thrombosis (DVT), which arises in prolonged immobilization of poisoning cases, also shall be identified.

Human Chorionic Gonadotropin

Human chorionic gonadotropin will help us to identify the early pregnancy and take necessary precautions.

SECONDARY TOXICOLOGY SURVEY

A secondary survey for toxicology should be started once the patient is stabilized. Secondary survery for the poisoned patient should be performed under following headings.

History

Any unstable patient or patient with altered sensorium and unexplained by clinical assessment should arouse the suspicion of toxicity. It is also good to know the type of poison, time of exposure, time window between exposure and the presentation, and history of similar episodes in the past.

Clinical Assessment

Look for circumstantial evidence and toxidrome. OPC poison will have a typical smell and cyanide smells like bitter almond. IV drug abuser will have multiple needlestick marks. Repeated attempts of deliberate self-harm may have evidence such as hesitation marks.

Organophosphorus, opioids, phenothiazines, and clonidine toxicity will present with pinpoint pupils while sympathomimetics such as ephedrine and parasympatholytic such as *Atropa belladonna* seeds will have dilated pupils. Salivation is a common feature of OPC and dryness is the feature of antidepressants and antipsychotics. Coma with bullae is seen in barbiturate overdose. Tachycardia itself may not give us clear guidance to either identify or treat with antidotes as it is not only seen in sympathomimetics, thyroxin, and bronchodilators such as salbutamol, albuterol, and methylxanthine but also in hypoxia, shock, hypovolemia, and anxiety. Bradycardia is seen in beta-blocker and calcium blocker overdose, OPC poisoning, and *oleander* seed poisoning. Hence, toxidrome shall give us only little guidance and may not always be relied upon solely. Therefore, diagnosis should always be made after complete history, circumstantial evidence, toxidrome, laboratory investigations, clinical assessment, and judgment.

Unexplained hypoxia not responding to oxygenation in the ER should always arouse the suspicion of pulmonary thromboembolism, whereas in case of poisoning, one should think about methemoglobinemia. A clear chest, normal cardiac examination with good respiratory drive, and a fall in saturation with normal saturation in ABG (saturation gap) with chocolate color arterial blood is a typical case of methemoglobinemia, which is common in nitrobenzene, flowering agents, and dapsone toxicities. Some common toxidromes are described in **Table 1**. Various antidotes are described in **Table 2**.

REMOVAL OF POISONING

Gastric Lavage

The role of gastric lavage is highly controversial. While the Western literature is bluntly stating this as a harmful procedure, one needs to consider the regional variation in the poisoning scenario. Though India is still suffering from poisonings such as OPC, weedicides, and many plant poisons which are lethal with prolonged toxicity, Western countries have almost switched to tablet overdoses which are quickly absorbed into the circulation; the availability of antidotes and easy access to extracorporeal removal made their researchers conclude that gastric lavage is either harmful or contraindicated in patient who braught to ER after an hour of drug overdose or poison. But even westen literature favors gastric lavage in overdose of sustain release tablets or preparation. Most common agricultural poison organophosphorus compound (OPC) remain in enterohepatic circulation for longer duration, and prolonged toxicity can not be ruled out. Considering the variation in the poisoning scenario, unavailability of antidotes, and nature of poisons, we still feel that agricultural poisons deserve a good gastric lavage and late-presentation tablet overdoses do not require lavage. As we practice in a country

TABLE 1: Toxidrome: Common toxic syndrome.

Drugs	*Common syndromic features*
Cholinergic: Organophosphorus carbamates insecticides physostigmine edrophonium some mushroom	Confusion CNS depression weakness salivation lacrimation urinary/fecal incontinence GI cram vomiting muscle fasciculation pulmonary edema miosis bradycardia/tachycardia seizure
Anticholinergics: Antihistamine antiparkinsonians, atropine scopolamine amantadine antipsychotics antidepressants antispasmodics muscle relaxants	Delirium tachycardia dry flushed skin, dilated pupil myoclonus, temperature, urinary retention diminished bowel sound, seizure
Sympathomimetics: Cocaine amphetamines methamphetamines, decongestant in cough syrup (phenylpropanolamine, ephedrine, pseudoephedrine)	Delusion, paranoia tachycardia hypertension hyperpyrexia diaphoresis mydriasis hyperreflexia seizure hypotension arrhythmias
Opioid/sedative/ethanol: Narcotics, barbiturates benzodiazepines ethchlorvynol glutethimide, ethanol clonidine meprobamate	Respiratory depression, hypotension, miosis bradycardia hypothermic, pulmonary edema diminished bowel sound hyporeflexia seizure coma
Salicylates	Fever, metabolic acidosis, respiratory alkalosis, tinnitus, and altered sensorium
Serotonins: SSRI, TCA, and MAOI	Hyperreflexia, clonus, sweating, hyperreflexia, clonus, sweating, tremor, flushing, and hypertension tremor, flushing, and hypertension

(MAOI: monoamine oxidase inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants)

with a mixed culture, we should justify the role of lavage appropriately on an individual basis.

Multidose Charcoal

Charcoal adsorbs the poison directly from the gut as well as acts as a gut dialyzer across the membrane (i.e., between the gut wall and the arterial wall). The toxins are adsorbed from blood to charcoal in the gut as well as by breaking enterohepatic recirculation. Do not use charcoal when airway reflexes are not patent or impending respiratory failure of aspiration is possible. It is more useful in treating plant poisons.

Whole-bowel Lavage

Polyethylene glycol is used as a purgative, and appropriately added electrolytes prevent dyselectrolytemia. It is good to use whole-body lavage in all the cases and especially with sustained-release tablets and poisonous seeds. Whole-body wash is useful in poisons that are easily absorbed through skin and inhalation.

Forced Alkaline Diuresis

Forced alkaline diuresis is commonly used in TCA, phenobarbitone, and salicylate toxicities. Normal renal function is a must. It carries high risk including hypokalemia, hypernatremia, fluid overload, and pulmonary edema. Hence, it is better to avoid this.

Extracorporeal Removal of Drugs and Toxins

Hemodialysis

Hemodialysis removal is possible in toxins with physical characters of low molecular weight, water solubility, and less protein-bound (e.g., lithium, ethanol, methanol, ethylene glycol, valproate, salicylate and theophylline) **Flowchart 1**. Hemodialysis may not be effective for the removal of toxins that are lipid-soluble, protein-bound, or possess high molecular weight. However, the newer dialysis membranes have the capacity for removal of larger molecules and highly protein-bound poisons such as carbamazepine and phenytoin.

Continuous Renal Replacement Therapy

Slow-release toxins, poisons with large volume of distributions, and those who are with hemodynamic instability can be benefited from this therapy.

Plasmapheresis or Exchange Blood Transfusion

Blood is removed and centrifuged to remove the plasma. The remaining blood components are returned to circulation. The volume of plasma removed during a single procedure is between 30 and 60 mL/min over 3–4 hours. It is beneficial in toxins with a low volume of distribution and protein binding. It is useful in 3% yellow phosphorous poisoning and paracetamol overdoses when N-acetyl cysteine is considered to be ineffective or failed to give the desired benefit.

Charcoal Hemoperfusion

High molecular weight, low volume of distribution, protein-bound, and lipid-soluble toxins can be removed using this technique. Blood is passed through the charcoal filter or resin filter and the toxins are filtered. It has shown benefit in OPC, phenobarbitone, valproic acid, carbamazepine, theophylline, and plant poisonings. It is used widely to treat paraquat poisoning but the benefit is questionable. Treatment of drug overdose and poisoning are described in **Tables 3** and **4**, respectively.

TABLE 2: Antidotes and their indications.

Antidotes	*Indication*	*Dose*
Amyl nitrate	Cyanide poisoning	2–6 inhalations of vapor from crushed 0.3-mL capsules. It may be repeated after 5 min
Atropine	OPC	Until secretions are dried (tachycardia and dilatation of pupil are not the endpoints)
	Oleander seed, digoxin, beta-blocker toxicity with bradycardia	Maximum 3 mg IV
Calcium gluconate/ calcium chloride	Calcium channel blockers and beta-blocker toxicity	30 mL/kg of calcium gluconate or 10 mL/kg of calcium chloride. Maximum dose is 1 g. It should not be given in hyperkalemia secondary to digoxin/*oleander* seed poisoning
	Hydrofluoric acid poisoning	Injected locally as 2.5% solution and through a nebulizer in inhalation injury
Dantrolene	Malignant hyperthermia secondary to anesthetic agents	• 1 mg/kg with additional dose up to 10 mg/kg • 25–100 mg, four doses per day up to 7 days or as needed
D-penicillamine	Heavy metal poisoning	250–500 mg PO 8th hourly
Deferoxamine	Iron toxicity	Maximum initial dose of 1 g as 15 mg/kg/h shall be repeated; maximum 60 mg/kg until vin-rose color urination
Dextrose	Hypoglycemia secondary to OHAs, insulin, or any toxicity	40–100 mL of D25W solution or 20–50 mL of D50W solution IV; may require repeated boluses in severe cases
Dimercaprol	Arsenic/gold poisoning	• Day 1–2: 10–12 mg/kg/day divided q6h deep IM × 2 days • Day 3: 5–6 mg/kg/day divided q12h deep IM × 1 day • Day 4–14: 2.5–3 mg/kg deep IM every day × 11 days
	Mercury poisoning	• Day 1: 5 mg/kg deep IM × 1 day • Day 2–11: 2.5 mg/kg deep IM q12–24h × 10 days
	Lead poisoning	• Initial 4 mg/kg IM • Repeat dose at least 4 h later (but not until adequate urine flow established) and then • 4 mg/kg + EDTA 250 mg/m^2 IM q4h × 3–5 days
	Wilson disease	Rarely used because of deep IM injection of 2–3 mL that is painful 2.5–3 mg/kg IM BID/TID
Flumazenil	Symptomatic, isolated toxicity of benzodiazepine	• 0.2 mg IV over 15–30 s • If no response after 30 s, administer 0.3 mg over 30 s, 1 min later; if no response, repeat a dose of 0.5 mg IV over 30 s at 1-min intervals to a maximum cumulative dose of 3 mg/h
Glucagon	Beta-blocker and calcium channel blocker	• 50–150 µg/kg IV over 1 min initially and then • 3–5 mg/h or 50–100 µg /kg/h IV
Hydroxocobalamine	Cyanide poisoning	5 g IV
Lipid emulsion	Local anesthetics, OPC, TCA, and many lipid-soluble drugs	1.5 mg/kg IV stat and to be repeated every 5 min for a maximum of 3 times and then 0.5–1 mL/kg infusion
Naloxone	Opioid poisoning	0.4–2 mg IV/IM/SC; repeat every 2–3 min; not to exceed 10 mg (0.01 mg/kg)
N-acetyl cysteine	Acetaminophen toxicity, 3% yellow phosphorous poisoning	140 mg/kg in 500 mL 5D/NS over 2 h, 70 mg/kg in 250 mL IV over 45 min every 4th hourly for 72 h. It may be continued up to 7 days
	Glyphosate, hair dye poisoning, paraquat, *Cleistanthus collinus* (Oduvanthalai), and any poisons expected to cause renal or liver injuries	140 mg/kg in 500 mL 5D/NS over 2 h, 50 mg/kg in 250 mL IV over 4 h, and 150 mg/kg in 500 mL of D5/NS over 16 h
P2AM	OPC poisoning	25–40 mg per kg IV stat and 10 mg/kg/h infusion

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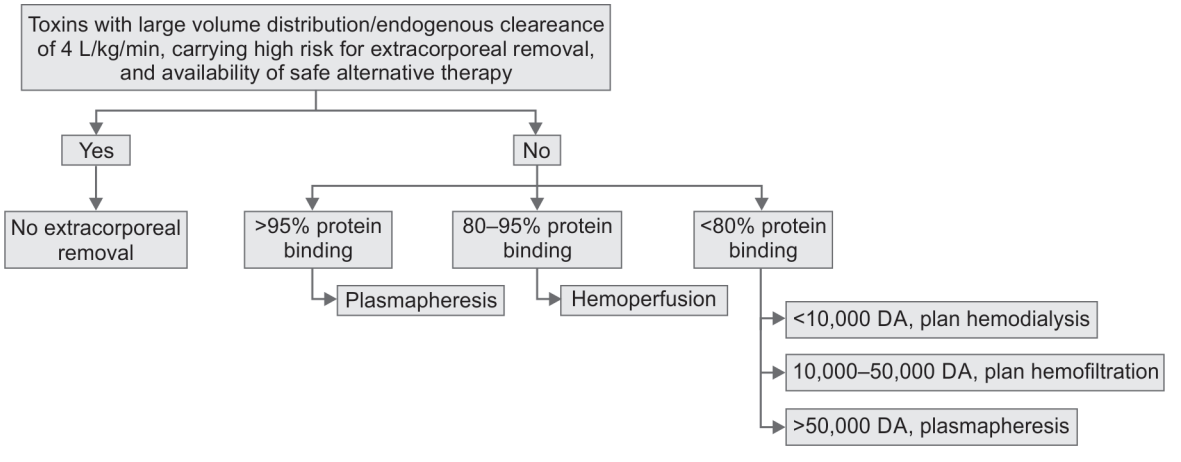
Antidotes	*Indication*	*Dose*
Physostigmine	*Datura*/*Atropa belladonna* poisoning	0.5–2 mg slow IV, not to exceed 1 mg/min; if no response, repeat every 20 min
Phytomenadione (vitamin K)	Warfarin	10 mg IV
Propranolol	β-adrenergics and thyroxin	• 10–30 mg PO q6–8h • 1–3 mg IV at 1 mg/min initially; repeat every 2–5 min to a total of 5 mg • Once response or maximum dose achieved, do not give additional dose for at least 4 h
Pyridoxine	INH overdose	100 mg/kg IV
Isoprenaline	Any drug overdose with AV block	5 µg/min IV infusion initially and then doses of 2–20 µg/min based on patient's response
4-methylpyrazole (Fomepizole)	Methanol and ethylene glycol	• Loading dose: 15 mg/kg IV infusion over 30 min, then • 10 mg/kg IV q12h for four doses, then increase to 15 mg/kg q12h
Naloxone	Opioid overdose	0.4–2 mg IV/IM/SC; repeat every 2–3 min; not to exceed 10 mg (0.01 mg/kg)
Neostigmine	Nondepolarizing neuromuscular blockade reversal	0.03–0.07 mg/kg slow IV, not to exceed 0.07 mg/kg or a cumulative total of 5 mg, whichever dose is less
	Neurotoxic snake envenomation	Neostigmine 1.5 mg IV stat (with atropine) and repeat dose of neostigmine 0.5 mg (with atropine) every 30 min for five doses
Oxygen	Carbon monoxide, cyanide, and hydrogen sulfide	Hyperbaric oxygen therapy
Sodium nitrite	Cyanide	300 mg (10 mL) IV infused at a rate of 2.5–5 mL/min
Sodium thiosulfate	Cyanide	• 12.5 g (50 mL of 25% solution) slow IV over 10 min immediately following sodium nitrite administration; adjust infusion rate according to blood pressure • If signs of poisoning reappear, repeat treatment using one half the original dose of both sodium nitrite and sodium thiosulfate
Charcoal	All poisons except heavy metals, hydrocarbons, and corrosives	1 g/kg in water initially and 0.5 g/kg per dose every 6–8th hourly
Antisnake venom	Cobra, krait, viper, and sea snake	• 10 vials initially if symptomatic and shall be repeated within 6 h • If no response, plan plasmapheresis
Egg white	Corrosives	6–10 raw egg whites shall be given to patients who consumed corrosives
Fuller's earth	Paraquat	A handful of fuller's earth in water

(AV: atrioventricular; EDTA: ethylenediaminetetraacetic acid; IM: intramuscular; INH: isoniazid; IV: intravenous; NS: normal saline; P2AM: pyridine-2-aldoxime methiodide; SC: subcutaneous; TCA: tricyclic antidepressants)



FLOWCHART 1: Extracorporeal removal of drugs and toxins.

TABLE 3: Intervention in drug overdose.

Drug or toxin	*Potential intervention*
Acetaminophen overdose and 3% yellow phosphorous poisoning	• N-acetyl cysteine 140 mg/kg in 500 mL normal saline over 1–2 h, then 70 mg/kg in 250 mL over an hour every 4 h for 72 h and can be extended up to 7 days • Plasmapheresis shall be planned in patients with delayed presentation/patients who consumed more/patients with low body weight
Carbamazepine	Repeat-dose charcoal, hemoperfusion
Digoxin and *oleander* seed poisoning	Digoxin-specific antibodies/pacing
Methanol or ethylene glycol	Ethanol or fomepizole therapy, hemodialysis
Iron	Deferoxamine chelation
Lithium	Hemodialysis
Methanol	Ethanol or fomepizole therapy, hemodialysis
Methemoglobinemia	Methylene blue 2 mg/kg repeated maximum up to 7 mg/kg and exchange transfusion
Salicylic acid	Alkalinization, hemodialysis
Theophylline	Repeat-dose charcoal, hemoperfusion
Valproic acid	Hemodialysis, repeat-dose charcoal

TABLE 4: Management of poisoning.

Drug or Toxin	*Management*
OPC poisoning	• *A, B, C* stabilization to be done and elective ventilation if *secretions* and *poor neck holding* • *Low serum cholinesterase:* ○ High diagnostic value ○ No prognostic value • *Gastric lavage:* ○ *MDAC* (charcoal) 1 g/kg stat followed by 0.5 mg/kg every q6h for 48 h ○ *Intralipid* 100 mL stat followed by 25 mL/h infusion ○ Injection atropine to be administerd until secretions are dry—*drug of choice* ○ 1–3 mg IV and doubling doses followed by 10% cumulative dose infusion (tachycardia or dilatation of pupils are not the endpoints) ○ *PAM can be given in moderate-to-severe poisoning cases as early as possible* ○ *2 g stat followed by 500 mg/h for 48–72 h* ○ As aging occurs very early, *no role of PAM in dimethyl* group of OPC poisonings *Early tracheostomy* may help to wean early
Oduvanthalai (*Cleistanthus collinus*) poisoning	• *MDAC* (charcoal) 1 g/kg stat followed by 0.5 mg/kg every q6h for 48 h • *NAC*: *NAC* dosage 150 mg/kg stat over 45 min followed by 75 mg/kg q4H for 72 h • *Correction of electrolyte abnormalities*: ○ *If metabolic acidosis*, sodium bicarbonate to be given ○ *If refractory*, plan renal replacement therapy • *If hypotension and shock*: ○ *ECHO* can identify poor cardiac contractions ○ *Noradrenaline and dobutamine* to be started • IABP, if inotropes fail

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Drug or Toxin	Management
Oleander seed poisoning	• Attach to transmembrane Na-K ATPase that *increases* intracellular *calcium* • Gastric lavage and whole-bowel irrigation • *Bradycardia and heart blocks*: ○ Initially, *atropine* to be given ○ *If ineffective:* – Transcutaneous pacing Or – Dopamine infusion Or – Epinephrine infusion *Consider transvenous pacing* • *Hyperkalemia*: ○ *Gastrointestinal* (25% dextrose 100 mL with 10 units of regular insulin) ○ Salbutamol nebulization ○ Soda bicarbonate ○ Resins ○ Lasix ○ *Renal replacement therapy* ○ *No calcium gluconate* • *Tachyarrhythmia*: ○ *Membrane-stabilizing agents* ○ Lignocaine ○ Magnesium sulfate may be beneficial • *DigiFab*: 5–12 vials if available
Glyphosate poisoning	• *Toxicity is due to surfactant in glyphosate* • *MDAC* (charcoal) 1 g/kg stat followed by 0.5 mg/kg q6h for 48 h • *NAC*: ○ NAC dosage 150 mg/kg stat over 45 min followed by 75 mg/kg ○ q4h for 72 h • *ABG*: ○ *Metabolic acidosis*, due to cardiac compromise ○ Inotropes ○ Soda bicarbonate ○ Hemodialysis *No metabolic acidosis*, observation
Sani powder (yellow auramine-O)	• *Gastric lavage*: *MDAC* (charcoal) 1 g/kg stat followed by 0.5 mg/kg q6h for 48 h • *If seizures present*: ○ *Injection lorazepam* 4 mg IV stat followed by 4 mg thrice daily ○ *Injection phenobarbitone* 20 mg/kg IV stat and 10 mg IV TDS for 3 days ○ If refractory seizures or persistent low GCS, *intubate and ventilate* • *Watch for*: ○ *Electrolyte* abnormality ○ Respiratory distress
Paraquat poisoning	• *MOA—oxygen radical damage* • *Prehospital care: Immediate* advice → Ask them to take a handful of fuller's earth (*multani mitti*) and charcoal/soil • *Serum and urine dithionite* to detect the poison • Initial stabilization of *ABCs* in ER • *Avoid oxygen* • (*MDAC*) 1 g/kg stat followed by 0.5 g/kg body weight q6h for 48 h • *PEGLEC* • *NAC* 150 mg/kg stat followed by 75 mg/kg q4h • Vitamins *C and E*

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Drug or Toxin	Management
	• *Glutathione* 600 mg BD • *Pirfenidone* 200 mg OD • *Charcoal—hemoperfusion and dialysis*—when initiated as early as possible, it will help in adsorbing the toxin • *Initiation of immunosuppressive therapy*: ○ Injection *methylprednisolone* 300 mg/h infusion ○ Injection *cyclophosphamide* 15 mg/kg IV for 3 days • *Maintain immunosuppressive therapy*: Injection hydrocortisone/tablet prednisolone for at least 1 month or until symptom-free
Aluminum phosphide poisoning	• A, B, C stabilization and elective intubation • Gastric lavage with *coconut oil and MDAC* (charcoal) • *NAC* dosage 150 mg/kg stat over 45 min followed by 75 mg/kg q4h up for 72 h • *ABG* and *lactate* levels to be checked • If *metabolic acidosis*: ○ $NaHCO_3$ infusion 100 cc stat followed by 50 cc/h ○ *CRRT* for 72 h • If *lactate* levels are high or *poor cardiac contractility:* ○ Start *GIK* (100 mL of 25% dextrose + 10 mEq/L potassium chloride + 8 units of regular insulin) at the rate of 50 cc/h ○ Noradrenaline/Dobutamine/Dopamine ○ Vasopressin ○ IABP
Ratol poisoning (yellow phosphorous)	• *Cellular toxin* • Gastric lavage with *coconut oil and MDAC* (Charcoal) • *NAC* dosage 150 mg/kg stat over 45 min followed by 75 mg/kg q4h for 72 h • *Glutathione* 600 mg BD • *Plasmapheresis* to be initiated if consumption is more than half tube: >90% survival rate, if *initiated within* 12 h of poisoning • *Repeat LFT*; if prolonged PT, initiate *plasmapheresis:* ○ If normal, *Tablet NAC* 1.2 g PO BD ○ If increased, continue *NAC* dosage • *Repeat LFT/coagulation profile*: ○ *Liver function deranged* ○ *Decreased sensorium* ○ *Coagulation abnormality* ○ FFP/Vitamin K ○ Plan for *liver transplantation*
Methemoglobinemia secondary to poisoning	• *Suspect, if* ○ *Unexplained hypoxemia* (refractory to oxygenation treatment), secondary to poisoning in the absence of cardiorespiratory cause and having saturation gap *(pulse oximetry shows hypoxia but ABG shows normal PaO_2)* ○ When history reveals exposure to *Hb oxidizing chemicals, flowering agents and drugs* such as nitrites and benzene compounds (*amyl nitrite, aniline, isobutyl nitrite, nitrobenzene, nitroglycerine, sodium nitrite*) • *Clinical features*: ○ *Chocolate brown*-colored blood ○ Central and peripheral cyanosis *(>1.5 g/dL* of *methemoglobin)* • *Bedside echocardiography to rule out* cardiac and pulmonary etiology of cyanosis • *Treatment*: ○ ABCs ○ Decontamination with MDAC ○ *Antidote* ○ *Methylene blue 1–2 mg/kg* IV over 5 min up to 7 mg/kg If refractory to methylene blue, therapeutic *exchange transfusion* is the Rx modality ○ Adjuncts: Vitamin C (ascorbic acid)

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Drug or toxin	Management
Bee and wasp sting	• ABCs stabilization • *Watch for urticaria*: Parenteral *antihistamines and steroids* • *Watch for anaphylaxis*: ○ *Injection adrenaline 0.3–0.5 mL SC* of 1:1,000 dilution ○ If severe, intravenous adrenaline 2–5 mL of a 1:10,000 dilution ○ Parenteral *antihistamines, H1 and H2 blockers* ○ Steroids • *Sting removal*: Scrap using *scale* and do not squeeze and take it out • *Pain*: ○ Only one sting—local anesthetic ○ Multiple stings—systemic opioid analgesics
Beta-blocker overdose	• Block inotropic, chronotropic, dromotropic effects • *Cardiovascular symptoms*: ○ *Bradycardia—most common* ○ Hypotension—2nd most common ○ Conduction delays and blocks ○ Ventricular dysrhythmias • *CNS symptoms*: ○ Depressed mental status ○ Coma—3rd most common ○ Psychosis ○ Seizures • *Treatment*: ○ *ABCs* ○ Decontamination with MDAC • *Hypotension*: ○ Intravenous fluids *bolus* 20–40 mL/kg (avoid in CAD) ○ Refractory—*calcium gluconate*—10 cc IV ○ Refractory—*glucagon*—5-mg bolus ○ Still refractory—*High-dose insulin* 1 µ/kg *stat followed by increasing up to* 10 µ/h ○ Still not responding—Pressors—*Norad* ○ Still not responding—*lipid emulsion* • *Bradycardia*: ○ *Atropine* (0.5–1 mg q3–5 min) if *HR <50* ○ Dopamine and epinephrine infusion ○ Pacing (transcutaneous/transvenous) • *Glucagon*: ○ If bradycardia and hypotension *not responsive* to bolus, calcium and atropine ○ *5–10 mg IV stat*; if there is a response, repeat dose with infusion over an hour • *Hypoglycemia*: Intravenous dextrose • *Seizures*: Benzodiazepines • *Glucagon*: ○ 0.05–0.15 mg/kg stat ○ If beneficial, infusion (1–10 mg/h) to be initiated ○ *Adrenergic receptor agonists*: ○ Noradrenaline, dopamine, epinephrine, and isoproterenol • *Hyperinsulinemia euglycemia therapy (HIET)*: ○ 1 U/kg IV stat followed by 0.5 U/kg/h infusion ○ Glucose 0.5 g/kg bolus, if blood glucose < 400 mg/dL ○ Potassium supplementation if needed

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Drug or toxin	Management
	• *Calcium*: ○ Recommended (not routinely) in refractory shock ○ Intravenous calcium supplementation ○ Calcium gluconate (10%) 0.6 mL/kg stat followed by 0.6–1.5 mL/kg/h ○ Calcium chloride (10%) 0.2 mL/kg stat followed by 0.2–0.5 mL/kg/h • *Phosphodiesterase inhibitors*: ○ Inamrinone, milrinone, enoximone ○ *Lipid emulsion* • *Sodium bicarbonate*: ○ Recommended in wide QRS interval dysrhythmias and severe acidosis ○ *IABP*
CCB overdose	• *Symptoms* ○ *Early symptoms:* – Hypotension – Bradyarrhythmias – Conduction blocks – Cardiogenic pulmonary edema – Seizures, delirium, coma secondary to cerebral hypoperfusion • *Treatment*: *ABCs—Early* airway management is recommended • *Decontamination*: ○ MDAC ○ Whole-bowel irrigation in overdose of sustained release CCB overdose • *Hypotension*: *IVC* diameter guided fluids (avoid overaggressive fluids) (20–40 mL/kg) • *Bradycardia*: ○ *Atropine* (0.5–1 mg q3–5 min), ineffective if given alone ○ Intravenous calcium salts ○ Calcium gluconate (10%) 0.6 mL/kg stat followed by 0.6–1.5 mL/kg/h ○ Calcium chloride (10%) 0.2 mL/kg stat followed by 0.2–0.5 mL/kg/h ○ Dopamine and epinephrine infusion ○ Pacing (transcutaneous/transvenous) • *Hypoglycemia*: Intravenous D25 • *Intralipid*: 100 mL stat followed by 25 mL/h for 3–5 days • *Adrenergic receptor agonists*: Noradrenaline, dopamine, epinephrine, and, isoproterenol • *Glucagon*: ○ 0.05–0.15 mg/kg stat ○ If beneficial, infusion (1–10 mg/h) to be initiated • *HIET*: ○ 1 U/kg IV stat followed by 0.5 U/kg/h infusion ○ Glucose 0.5 g/kg bolus, if blood glucose <400 mg/dL ○ Potassium supplementation if needed • *Methylene blue* in amlodipine toxicity: • *IABP* Extracorporeal life support
Cypermethrin poisoning	• MDAC (charcoal) 1 g/kg stat followed by 0.5 mg/kg followed by q6h for 48 h • If seizures administer—injection lorazepam and phenobarbitone • If ARDS (due to hypersensitive pneumonitis) ○ Ventilator management (poor prognosis) ○ Antihistamine and epinephrine (questionable value) Cholestyramine may have a role

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Drug or toxin	*Management*
Snakebite	• 10–20 vials of ASV IV if signs and symptoms of envenomation appear • If coagulopathy persists even after 20 vials of ASV, plan for emergency plasmapheresis (remove 40 mL/kg plasma and replace with fresh plasma)
Scorpion sting	• Bupivacaine + lignocaine 50%; 50% locally to alleviate the pain (only lignocaine will last for less than an hour) • Autonomic disturbances—prazosin 30 microgram/kg/dose PO every 4th hourly until autonomic disturbances settle • Levosimendan is beneficial in takotsubo cardiomyopathy secondary to toxicity and cardiogenic shock • Antidote—if available • Supportive care

(ABG: arterial blood gas; ASV: antisnake venom; ARDS: acute respiratory distress syndrome; CCB: calcium channel blocker; CNS: central nervous system; CRRT: continuous renal replacement therapy; ECHO: echocardiogram; FFP: fresh frozen plasma; GIK: glucose–insulin–potassium; GCS: Glasgow Coma Scale; IABP: intra-aortic balloon pump; IV: intravenous; IVC: inferior vena cava; LFT: liver function test; MDAC: multiple-dose activated charcoal; NAC: N-acetyl cysteine; PAM: pralidoxime; PT: prothrombin time)

SUMMARY

Poisoning is a global problem of both developing and developed countries in which large number of healthcare resources are consumed and responsible for premature death. Individuals exposed to poison by ingestion, inhalation, injection, insufflation, and through cutaneous and mucous membrane route. Poisoning presents in different ways, in children as accidental poisoning due to lack of childproof medicine containers, in adult as either suicidal or as drug abuse by various route smoking, intravenous. Patient may also present as acute as well as chronic poisoning from environmental, industrial agriculture toxins exposure. Drug's reaction, drug interactions and envenomation are also common presentation as emergency patient who need immediate resuscitation. Management of poisoned patient consists of general management and specific action for toxins by antidotes. Expert advice from medical toxicologist and regional poison centre are helpful in management of poisoned patient.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Common Pesticides Poisoning in India

VV Pillay

INTRODUCTION

Poisoning due to pesticides are the major problems in India. Pesticides are compounds that are used to kill or repel pests which may be insects, rodents, fungi, nematodes, mites, ticks, mollusks, and unwanted weeds or herbs. They include substances which prevent, destroy, repel, or mitigate any pest or are used as a plant regulator, defoliant, or desiccant. Classification of pesticides discussed below. In this chapter, only organophosphorus (OP) compound (organophosphate), carbamate insecticide, and aluminum phosphide poisoning will be discussed. Pesticides can be classified as shown in **Table 1**.

ORGANOPHOSPHORUS POISONING

Organophosphorus insecticides (henceforth referred to as organophosphates, for the sake of convenience) are among the most popular and most widely used insecticides in India. **Table 2** lists common varieties along with respective brand

TABLE 1: Classification of pesticides.

Group	*Compounds*
Insecticides	Compounds which kill or repel insects and related species *Examples*: Organophosphates, carbamates, organochlorines, diethyltoluamide (DEET), and pyrethrum and its derivatives (pyrethroids)
Rodenticides	Compounds which kill rats, mice, moles, and other rodents *Examples*: Anticoagulants (bromadiolone), thallium, vacor, phosphorus, alpha-naphthyl-thiourea, cholecalciferol, arsenic, barium carbonate, bromethalin, fluoroacetamide, sodium monofluoroacetamide, red squill, strychnine, and zinc phosphide
Herbicides	Compounds which kill weeds *Examples*: Acrolein, dalaphon, glyphosate, paraquat, diquat, atrazine, propazine, simazine, nitrofen, trichloroacetic acid, and chlorophenoxy compounds
Fungicides	Compounds which kill fungi and moulds *Examples*: Thiocarbamates, captan, captafol, bavistin, vitavax, hexachlorobenzene, and sodium azide
Nematicides	Compounds which kill nematodes (i.e., worms) *Examples*: ethylene dibromide
Acaricides	Compounds which kill mites, ticks, and spiders *Examples*: Azobenzene, chlorobenzilate, tedion, and kelthane
Molluscicides	Compounds which kill molluscs such as snails and slugs *Examples*: metaldehyde
Fumigants	Methyl bromide, phosphine, aluminium phosphide, naphthalene, paradichlorobenzene, dichloropropene, hydrogen cyanide
Miscellaneous pesticides	Neonicotinoid compounds, phthalic acid diamides (flubendiamide), compounds of lead, copper, and mercury, nicotine, rotenone, sabadilla, tetrachloroethylene, trichloroethane, dinitrophenol, dinitrocresol, dinitrobutylphenol, pentachlorophenol, chlorfenson, chloralose and fipronil. Dioxins which are present as contaminants of some herbicides also can produce toxicity

TABLE 2: Common organophosphate compounds.

Generic name	*Brand name*
Acephate	Acemil, Acet, Acetaf, Agrophate, Asataf, Dhanraj, Hilfate, Hythane, Orthene, Ortran, Sicothene, Starthene, Torpedo
Anilofos	Aniloguard, Arozin, Dhanudan
Chlorfenvinphos	Birlane, Chlorfenvinphos
Chlorpyriphos	Agrofas 20, Calban, Chlorofos 20, Classic, Coroban, Cyfos, Daspan, Dermite, Dermot, Dhanuchlor, Dhanvan, Dursban, Force, Gilphos, Hildan, Hyban 20, Lasso, Lethal, Nuchlor, Phors 20, Primaban, Radar, Roban, Ruban 20, Sicobon, Strike, Suchlor, Tafaban, Tefaban, Tricel
Cyclopyriphos	Duramet
Demeton-methyl	Metasystox
Diazinon	Agroziron, Basudin, Bazanon, Ditaf, Suzinon, Tik 20, Zincoseal 50
Dichlorvos	Agrovan 76, Agro 76 EC, Bangvas, Cockroach killer, Dash, DDVP, Divap, Divisol, Madhuvun, Nuvan, Nuvasul 76, Paradeep, Savious, Vapona, Vapox, Vegfru
Dimethoate	Agrodimet 30, Agromet 30EC, Bangor 30EC, Corothate, Cropgor 30, Cycothate, Cygon, Devigor, Dimethoate, Dimex, Entogor, Hexagor, Hygro 30, Klex Dimethoate, Krogar, Methovip, Milgor, NB Dimethoate, Paragor, Parrydimate, Primogor, Ramgor, Rogor, Tagor, Tara 909, Tara Dimex Sulgor, Tka 30, Unigor, Vijaygor, Vikagor
Ediphenphos	Hinosan, Nukil
Ethion	Challenge, Demite, Dhanumit, Dhan-unit, Ethion, Ethione, Ethiosul 50, Fosmit, Mit 505, Mitex, Miticil, Mitvip, Phostech, RP-thion, Tafethion, VegFru Fosmite, Volathin
Fenitrothion	Accothion, Agrothion, Danathion, Fenicol, Fenitrosul, Folithion, Sicothoin, Sumithion, Vikathion
Fenthion	Agrocidin, Baytex, Fenthiosul, Labaycid, Lebaycid, Lebazate
Formothion	Anthio
Iprobenfos	Tagkite
Malathion	Agromal, Bharat, Celthion, Cythion, Dhuthione, Finit, Himalaya, Kathion, Licel, Madhuthione, Maladan, Maladol, Malafil, Malathione, Malazene, Primothion, Sulmathion, VegFru Malatox
Methyl parathion	Ant repellant,* Agropara, Agrotex, Ekatox, Folidol, Folidol-M, Harvest Kempar, Kilex-M, Metacid, Metapar, Metpar, Milphor, Paracrop, Paradol, Parahit, Parataf, VegFru Paratox
Monocrotophos	Atom, Azodrin, Balwan, Corophos, Entophos, Hilcrone, Luphos, Macrophos, Microphos, Monocil, Monochrovin, Monocrome, Monocron, Monocrown, Monocyl, Monodhan, Monokem, Monostar, Monovip, Nuvacron, Phoskill, Sicocil, Sufos, Unicron
Oxydemeton-methyl	Dhanuciytax, Hexasystox, Hymox, Knock Out, Metaciyta, Metasystox
Phenthoate	Agrofen, Delsan, Elsan, Guard, Phentox
Phorate	Anuphorate, Croton, Dhan, Dhang, Dragnet, Fortan, Glorat, Luphate, Phorachem, Phoratox, Phrotax, Thimate 10G, Thimet, VegFru Foratox, Vijayphor, Volphor
Phosalone	Zolone
Phosmet	Phosmite
Phosphamidon	Agromidon 85, Bangdon 85, Bilcran 85, Cildon, Delphamidon, Demacron, Demecron, Dimecron, Directon, Eagle, Entecron 85, Hildon, JK Midon, Midon, Phamidon, Phosul, Rilon, Sudon, Sumidon, Vimidon
Phoxim	Phoxin
Pirimiphos-methyl	Acetellic
Profenfos	Carina, Curacrone, Polytrine, Profex
Quinalphos	Agroquin, Agroquinol, Bayrusil, Chemlox, Coroqueen, Dhanulux, Dyalux, Ekalux, Fact, Flash, Kilex, Quenguard, Quick, Quinal, Quinaltof, Quinseed 25, Silofos, Solux, Vazara, Vikalux
Temephos	Abate 50EC, Farmico's
Thiometon (morphothion)	Agrothimeton, Ekatin
Triazophos	Hostathion, Sutathion, Triphos, Truso
Trichlorphon	Dipterex

**Caution*: *The same brand name may refer to lindane.*

names. These compounds are available as dusts, granules, or liquids. Some products need to be diluted with water before use and some are burnt to make smoke that kills insects.

Usual Fatal Dose

The following compounds are *extremely toxic* (*LD50*: *1–50 mg/kg*) or highly toxic (*LD50*: *51–500 mg/kg*): Chlorfenvinphos, Chlorpyriphos, Demeton, Diazinon, Dichlorvos, Dimethoate, Disulfoton, Ediphenphos, Ethion, Fenitrothion, Fensulfothion, Fenthion, Fonophos, Formothion, Methyl Parathion, Mevinphos, Monocrotophos, Oxydemeton Methyl, Phenthoate, Phorate, Phosphamidon, Quinalphos, Tetraethyl pyrophosphate (TEPP), and Thiometon.

The following compounds are *moderately toxic* (*LD50*: *501–5,000 mg/kg*) or slightly toxic (*LD50*: *>5,000 mg/kg*): Abate, Acephate, Coumaphos, Crufomate, Famphur, Malathion, Phenthoate, Primiphos Methyl, Ronnel, Temephos, Triazophos, and Trichlorphon. Even in cases where treatment was begun early with atropine and oximes, mortality in organophosphate poisoning is generally to the extent of 7–12%.

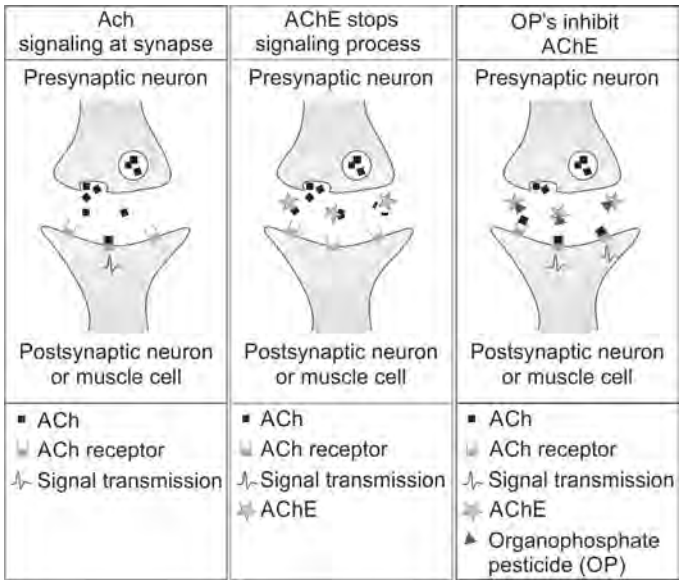
Toxicokinetics

Organophosphorus compounds are very well absorbed from the lungs, gastrointestinal (GI) tract, skin, mucous membranes, and conjunctiva following inhalation, ingestion, or topical contact. Even percutaneous exposure can cause severe toxicity. The difficulty in removing these compounds from the skin and clothing may explain some chronic poisonings, and inadequate skin and respiratory protection during pesticide application is responsible for most of the remainder. Most OP insecticides are lipophilic. Adipose tissue gradually accumulates the highest levels. Cholinergic crisis may recur in patients when unmetabolized OP agents are mobilized from fat stores. More lipophilic compounds, such as fenthion and chlorfenthion, are more likely cause of this phenomenon.

The peak levels of most OP insecticides are measured around 6 hours after oral ingestion in man. Although the serum half-lives of these compounds range from minutes to hours, prolonged absorption or redistribution from fat stores may allow for measurement of circulating insecticide concentrations for up to 48 days.

Organophosphorus insecticides are metabolized by various mixed-function oxidases in the liver and intestinal mucosa, although the exact pathways are not yet clearly understood. The phosphorylating ability of these substances is lost when any of the side chains are hydrolyzed. Certain indirect-acting compounds are activated to a more toxic compound by this initial metabolism. Particularly lipophilic OP compounds may be protected from metabolism by fat storage, markedly prolonging their eliminated half-life. Inactive metabolites of these compounds are excreted in the urine.

Recent studies have suggested a possible relationship between human serum paraoxonase (PON) activity and susceptibility to acute and chronic effects of OP poisoning. PON is an A-esterase that can hydrolyze the active (oxon) metabolites of some OP compounds. Some animal models of OP poisoning demonstrate protection from toxicity when exogenous PON is administered and greater susceptibility to poisoning when enzyme-deficient animals are exposed. Some authors have postulated that genetic polymorphisms in human PON activity may lead to variations in interindividual susceptibility to some OP insecticides.



(AChE: acetylcholinesterase)

FIG. 1: Mode of action-organophosphate pesticides.

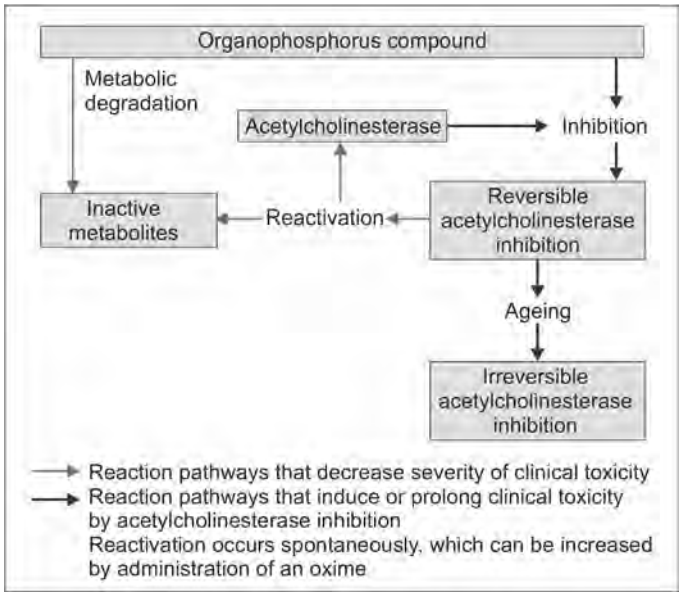
Mode of Action

Organophosphates are powerful inhibitors of acetylcholinesterase (AChE) which is responsible for hydrolyzing acetylcholine to choline and acetic acid after its release and completion of function (i.e., propagation of action potential). As a result, there is accumulation of acetylcholine with continued stimulation of local receptors and eventual paralysis of nerve or muscle* (**Fig. 1**). Although organophosphates differ structurally from acetylcholine, they can bind to the AChE molecule at the active site and phosphorylate the serine moiety. When this occurs, the resultant conjugate is infinitely more stable than the acetylcholine-AChE conjugate, although endogenous hydrolysis does occur. Depending on the amount of stability and charge distribution, the time to hydrolysis is increased. Phosphorylated enzymes degrade very slowly over days to weeks, making the AChE essentially inactive (**Flowchart 1**).

Figure 2 represents the basic formula for OP compounds. The "X" or "leaving group" determines the main characteristics of the compound and is useful in classifying organophosphates into four main groups:

1. Group 1 compounds contain quaternary nitrogen at the X position and are called phosphorylcholines. These chemicals, originally developed as chemical warfare agents, are powerful cholinesterase inhibitors and can also directly stimulate cholinergic receptors because of their structural resemblance to ACh. Example: Echothiophate iodide.
2. Group 2 compounds are called fluorophosphates because they possess a fluorine molecule as the leaving group. Like group 1 compounds, these compounds are volatile and highly toxic, making them also well suited for chemical warfare. Examples: Dimefox, sarin, and mipafox.

*Acetylcholine is the neurotransmitter at pre- and postganglionic parasympathetic synapses, sympathetic preganglionic synapses, and the neuromuscular junction.



FLOWCHART 1: Organophosphates: Reaction pathways.

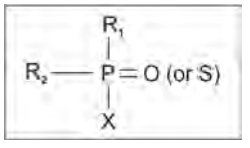


FIG. 2: Formula for organophosphorus compounds.

3. The leaving group of group 3 compounds is a cyanide molecule or a halogen other than fluorine. Examples: Cyanophosphates such as tabun.
4. The fourth group is the broadest and comprises various subgroups based on the configuration of the R_1 and R_2 groups, with the majority falling into the category of either a dimethoxy or diethoxy compound. Most of the insecticides that are in use today fall into this last class.
   i. Leaving group
      (a) *Dimethoxy*: Azinphos-methyl, bromophos, chlorothion, crotoxyphos, dicapthon, dichlorvos, dicrotophos, dimethoate, fenthion, malathion, mevinphos, parathion-methyl, phosphamidon, temephos, trichlorfon
      (b) *Diethoxy*: Carbophenothion, chlorfenvinphos, chlorpyriphos, coumaphos, demeton, diazinon, dioxathion, disulfoton, ethion, methoxsalen, parathion, phorate, phosfolan, TEPP
      (c) *Other dialkoxy*: Isopropyl paraoxon, isopropyl parathion
      (d) *Diamino*: Schradan
      (e) *Chlorinated and other substituted dialkoxy*: Haloxon
      (f) *Trithioalkyl*: Merphos
      (g) *Triphenyl and substituted triphenyl*: Triorthocresyl phosphate (TOCP)
      (h) *Mixed substituent*: Crufomate, cyanofenphos

"Direct"-acting OP insecticides can inhibit AChE without being structurally altered by the body. However, many OPs, such as parathion and malathion, are "indirect" inhibitors or prodrugs requiring partial metabolism (to paraoxon and malaoxon, respectively) within the body to become active. Most of the indirect inhibitors undergo desulfuration in the intestinal mucosa and liver following absorption to form the more active phosphate or "oxon" metabolites. The active form is a more potent cholinesterase inhibitor. The covalent bond is completed as the leaving group of the OP insecticide is split off by AChE, resulting in a stable but reversible bond between the remaining substituted phosphate of the OP compound and AChE, effectively inactivating the enzyme. Although the splitting of the choline-enzyme bond in normal ACh metabolism is completed within microseconds, the severing of the OP compound-enzyme bond can be prolonged. In OP poisoning, the complex becomes irreversibly bound during the next 24–72 hours when one of the R groups leaves the phosphate molecule. This step is termed "aging." As this occurs, the enzyme can no longer spontaneously hydrolyze and becomes permanently inactivated. De novo synthesis of AChE is required to replenish its supply once aging has occurred.

Apart from AChE, organophosphates exert powerful inhibitory action over other carboxylic ester hydrolases such as chymotrypsin, plasma cholinesterase (pseudocholinesterase), hepatic carboxylesterase, PONs, and other nonspecific proteases. It has been proposed that delayed peripheral neuropathy caused by organophosphates is due to phosphorylation of some esterase(s) other than AChE, such as neurotoxic esterase, also known as neuropathy target esterase (NTE). Neuropathy caused by inhibition of NTE may develop 2–5 weeks after an acute poisoning.

Clinical Features

Acute Organophosphates Poisoning

Patients with massive ingestions can become symptomatic very quickly, sometimes within 5 minutes following ingestion, and deaths have occurred within 15 minutes of ingestion. Most victims, however, become symptomatic in about 8 hours of exposure and virtually all within 24 hours. Delays usually occur with compounds requiring metabolic activation, such as malathion, or highly lipid-soluble agents, such as fenthion. Symptoms may last for variable periods of time, again based on the exact compound and the nature of the exposure. For example, lipophilic compounds such as dichlofenthion can cause cholinergic excess for several days following ingestion.

- *Muscarinic effects (hollow organ parasympathetic manifestations)*: Common manifestations include bronchoconstriction with wheezing and dyspnea, cough, pulmonary edema, vomiting, diarrhea, abdominal cramps, increased salivation, lacrimation, sweating, bradycardia, hypotension, miosis, and urinary incontinence. Excessive salivation, nausea, vomiting, abdominal cramps, and diarrhea are common muscarinic effects and have been reported even following the cutaneous absorption of organophosphate. Bradycardia and hypotension occur following moderate-to-severe poisoning. Bronchorrhea can be so profuse that it mimics pulmonary edema even when the lungs are not edematous.
- *Nicotinic effects (autonomic ganglionic and somatic motor effects due to stimulation of nicotinic adrenal receptors and postganglionic sympathetic fibers)*: Nicotinic effects include fasciculations, weakness, hypertension, tachycardia, and paralysis. Mydriasis has been reported in as many as 13% of cases, presumably from nicotinic stimulation of

sympathetic receptors.Muscle weakness, fatiguability, and fasciculations are very common.

Hypertension can occur in up to 20% of patients. Tachycardia is also common. Cardiac arrhythmias and conduction defects have been reported in severely poisoned patients. Electrocardiogram (ECG) abnormalities may include sinus bradycardia or tachycardia, atrioventricular and/or intraventricular conduction delays, idioventricular rhythm, multiform premature ventricular extrasystoles, ventricular tachycardia or fibrillation, torsades de pointes, prolongation of the PR, QRS and/or QT intervals, ST-T wave changes, and atrial fibrillation.

Bronchodilation and urinary retention can occur as a result of sympathetic activity on smooth muscle.

Rarely, patients may present only with paralysis from nicotinic effects without any other initial signs and symptoms suggestive of OP toxicity. This is more common with chemical warfare OP compounds (sarin, tabun, soman, etc.).

Central nervous system effects: Restlessness, headache, tremor, drowsiness, delirium, slurred speech, ataxia, and convulsions are the central nervous system (CNS) effects. Coma supervenes in the later stages. In a review of 16 cases of pediatric organophosphate poisoning, all 16 children developed stupor and/or coma.

Death usually results from respiratory failure due to weakness of respiratory muscles as well as depression of central respiratory drive. Acute lung injury (noncardiogenic pulmonary edema) is a common manifestation of severe poisoning. Acute respiratory insufficiency, due to any combination of CNS depression, respiratory paralysis, bronchospasm, acute respiratory distress syndrome (ARDS), or increased bronchial secretions, is the main cause of death in acute organophosphate poisonings. Metabolic acidosis has occurred in severe poisonings.

A characteristic kerosene-like odor is often perceptible in the vicinity of the patient since the solvent used in many organophosphate insecticides is some petroleum derivative such as aromax.

The Peradeniya Organophosphorus Poisoning (POP) scale is predictive of death, a necessity for mechanical ventilation, and the required total atropine dose over the first 24 hours. This scale rates five clinical variables, each on a 0–2 scale: (1) Miosis; (2) Muscle fasciculations; (3) respiration; (4) Bradycardia; and (5) Level of consciousness.

It is important to note that:

- In a given case, there may be either tachy- or bradycardia and hypo- or hypertension.
- Miosis, while being a characteristic feature, may not be apparent in the early stages. In fact, mydriasis is very often present, and hence treatment should not be delayed if there is absence of pupillary constriction.Blurred vision may persist for several months.
- Ocular exposure can result in systemic toxicity. It can cause persistent miosis despite appropriate systemic therapy and may necessitate topical atropine (or scopolamine) instillation.
- Exposure to organophosphate vapors rapidly produces symptoms of mucous membrane and upper airway irritation and bronchospasm, followed by systemic symptoms if patients are exposed to significant concentrations.
- Although respiratory failure is the most common cause of death, other causes may contribute including hypoxia due to seizures, hyperthermia, renal failure, and hepatic failure. Nephrotoxicity has been postulated to be a matter of concern in some cases of organophosphate poisoning which is often not paid due attention by the attending physician.
- Unequal sympathetic stimulation of myocardial cells and interactions with potassium channels and the Na^+/Ca^{++} exchanger in the myocardial cell membrane are probably responsible for the occasional prolonged QTc interval. This prolongation in QTc interval can be associated with polymorphic ventricular tachycardia (torsades de pointes). Finally, hypotension may occur because of stimulation of vascular receptors by excessive circulating ACh. Patients with OP poisoning and QTc prolongation are more likely to develop respiratory failure and have a worse prognosis than patients with normal QTc intervals. Patients with OP poisoning who develop premature ventricular contractions (PVCs) are more likely to develop respiratory failure and have a higher mortality rate than patients without PVCs.
- Because liquid preparations are usually dissolved in a hydrocarbon, aspiration frequently results following ingestion in severe poisoning and can lead to hydrocarbon pneumonitis.
- Excessive adrenergic influences on metabolism cause glycogenolysis with hyperglycemia and ketosis that may be mistaken for diabetic ketoacidosis. Hypoglycemia can also occur, although the mechanism is unclear. Increased sympathetic activity usually precipitates white blood cell demargination, resulting in leukocytosis.
- Elevations of hepatic enzymes can occur following OP pesticide exposures.

Intermediate Syndrome

- An intermediate syndrome sometimes occurs 1–4 days after poisoning due to long-lasting cholinesterase inhibition and muscle necrosis. This phenomenon was first described in 1987 and is termed the "intermediate syndrome" because it occurs in between the periods of acute and delayed toxicity. It is more common with chlorpyriphos, dimethoate, monocrotophos, parathion, sumithion, fenthion, fenitrothion, ethyl parathion, methyl parathion, diazinon, malathion, trichlorfon, and methamidophos. Redistribution of these lipophilic pesticides and their metabolites from adipose tissue may be responsible, and the syndrome may resolve when the body burden of these metabolites diminishes and cholinesterase levels normalize. The main features include muscle weakness and paralysis. The most commonly affected muscles are the facial, extraocular, palatal, respiratory, and proximal limb muscles. Paralytic signs include inability to lift the neck or sit up, ophthalmoparesis, slow eye movements, facial weakness, difficulty swallowing, limb weakness (primarily proximal), areflexia, respiratory paralysis, and death. There is growing speculation that intermediate syndrome may result from inadequate oxime therapy, although more recent case reports question this theory. One recent study suggests that the occurrence of intermediate syndrome strongly correlates with the initial degree of cholinergic crisis and appears to be a continuum with the neuromuscular paralysis resulting from the early stages of

poisoning. The study suggests that muscle injury during early cholinergic crisis may progress to intermediate syndrome. Electromyograms will often show tetanic fade in these patients and suggest both pre- and postsynaptic involvement. However, repetitive nerve stimulation may not always accurately predict the occurrence or severity of intermediate syndrome but may be beneficial in determining the need for mechanical ventilation. Once it sets in, the intermediate syndrome will have to be managed by supportive measures, since it does not respond to oximes or atropine. However, because some reports correlating pralidoxime dose and intermediate syndrome suggest that insufficient dosing may play a part, it is recommended that pralidoxime infusion be reinstituted at 500 mg/h when intermediate syndrome is suspected. The weakness and paralysis commonly resolve in 5–18 days. In one study from India, up to one third of admissions of organophosphate poisoning in a major hospital developed intermediate syndrome.

- A delayed syndrome (now called delayed encephalopathy and neuropathy syndrome) sometimes occurs 1–4 weeks after poisoning due to nerve demyelination and is characterized by flaccid weakness and atrophy of distal limb muscles or spasticity and ataxia. A mixed sensory-motor neuropathy usually begins in the legs, causing burning or tingling, then weakness. Severe cases progress to complete paralysis, impaired respiration, and death. The nerve damage of organophosphate-induced delayed neuropathy is frequently permanent. This disorder seems to result from inhibition of an enzyme within nervous tissue named neurotoxic esterase or NTE. Symptoms seem to be initiated by the phosphorylation of this enzyme, or perhaps of some related compound, followed by the aging of the complex. Such neuropathies may even result from exposure to OP compounds that do not inhibit red blood cell (RBC) cholinesterase or produce clinical cholinergic toxicity. Pathologic findings demonstrate effects primarily on large distal neurons, with axonal degeneration preceding demyelination. Organophosphates that have been associated with delayed neuropathy in humans include chlorophos, chlorpyriphos, dichlorvos, dipterex, ethyl parathion, fenthion, isofenphos, leptophos, malathion, mecarbam, mephosfolan, merphos, methamidophos, mipafox, trichlorfon, trichloronate, and TOCP. Electromyograms and nerve conduction studies may be helpful in diagnosing the delayed syndrome by identifying the type of neuropathy (such as axonopathy, myelinopathy, or transmission neuropathy) and differentiating it from similar presentations such as Guillain–Barré syndrome. Recovery of these patients is variable and occurs over months to years, with residual deficits common.
- Hyperamylasemia is occasionally reported in cases of severe OP pesticide poisoning, and although pancreatitis may result from spasm of the sphincter of Oddi, hyperamylasemia is most often the result of salivary gland stimulation and not the result of pancreatic dysfunction. Parathion ingestion has resulted in fatal hemorrhagic pancreatitis. Diazinon has also been implicated. Hemoperfusion is said to be beneficial if this occurs.
- Patients poisoned with highly lipid-soluble Ops, such as fenthion, have rarely developed extrapyramidal effects including dystonia, resting tremor, cog-wheel rigidity, and choreoathetosis. These effects began 4–40 days after acute OP poisoning and spontaneously resolved over 1–4 weeks in survivors.
- It is important to note that children may have different predominant signs of organophosphate poisoning than adults. In some studies of children poisoned by organophosphate or carbamate compounds, the major signs and symptoms were CNS depression, stupor, flaccidity, dyspnea, and coma. Other classical signs of organophosphate poisoning such as miosis, fasciculations, bradycardia, excessive salivation and lacrimation, and GI symptoms were infrequent.

Chronic Organophosphates Poisoning

It usually occurs as an occupational hazard in agriculturists, especially those who are engaged in pesticide spraying of crops. The route of exposure is usually inhalation or contamination of the skin. Following are the main features:

- *Polyneuropathy*: Paresthesias, muscle cramps, weakness, gait disorders
- *CNS effects*: Drowsiness, confusion, irritability, anxiety
- *Sheep farmer's disease*: Psychiatric manifestations encountered in sheep farmers involved in long-term sheep-dip operations.
- A study of 24 agricultural workers revealed significantly lower cancellous bone area and bone formation at cellular and tissue levels in workers with long-term exposure to organophosphates compared with healthy age-matched controls.
- Organophosphate poisoning has been associated with a variety of subacute or delayed onset chronic neurological, neurobehavioral, or psychiatric syndromes. One author has termed these "chronic organophosphate induced neuropsychiatric disorder (COPIND)" and noted that the standard hen neurotoxic esterase test is not sufficient to detect which OPs can cause this condition. Signs and symptoms include confusion, psychosis, anxiety, drowsiness, depression, fatigue, and irritability. Electroencephalographic changes may be noted and can last for weeks. Single-photon emission computed tomography (SPECT) scanning may reveal morphologic changes in the basal ganglia. Although no specific treatment is effective, most psychological abnormalities resolve within a year.
- A cluster of congenital anomalies has been reported in a Hungarian village where pregnant women were believed to have consumed trichlorfon-contaminated fish during pregnancy. Of 15 live births, 11 (73%) had congenital abnormalities and 6 were twins. Other likely causes (known teratogenic factors, familial inheritance, consanguinity) were excluded. Abnormalities included Down syndrome (4 births), ventricular septal defect and pulmonary atresia, congenital inguinal hernia, stenosis of the left bronchus, anal atresia, choanal atresia, cleft lip, and Robin sequence.
- In a pesticide exposure study in children, a significant association was found between the risk of non-Hodgkin lymphoma and increased frequency of reported pesticide use in the home, professional exterminations within the home, and postnatal exposure. Higher risks were found in both young (younger than 6 years of age) and older children, for T-cell and B-cell lymphomas and for lymphoblastic large cell Burkitt's lymphoma. In addition,

there was a higher risk for non-Hodgkin lymphoma with occupational exposure to pesticides.

- Some studies indicate a link between Parkinson disease and chronic exposure to OP insecticides. The structures of some of these compounds are similar to those of known neurotoxins like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Some individuals may have a possible genetic susceptibility. In some cases of acute exposure to OP compounds, there have been reports of self-limited movement disorders resembling Parkinson that resolve over weeks to months. Although statistics derived from some epidemiologic studies suggest the connection, other studies have failed to find an association between OP compounds and Parkinsonism.

There are some organophosphates that are extremely potent but do not find a place as insecticides; instead, they have been used in chemical warfare. These include sarin, tabun, soman, etc.

Diagnosis

Depression of Cholinesterase Activity

Plasma cholinesterase (butyrylcholinesterase) metabolizes various xenobiotics, including succinylcholine and cocaine. Erythrocytes contain a form of AChE (RBC cholinesterase) that is structurally similar to the enzyme found in neuronal tissue. Inhibition of either RBC cholinesterase or plasma cholinesterase serves as marker for cholinesterase inhibitor poisoning, but the extent of inhibition of these enzymes does not correlate well with the severity of poisoning. There is also tremendous interindividual and interchemical variability in the degree and duration with which OP insecticides affect various cholinesterases.

After significant exposure, plasma cholinesterase activity usually falls first, followed rapidly by RBC cholinesterase. By the time patients present with acute symptoms, the levels of both cholinesterase activities have usually fallen well below baseline values and often have fallen below detectable limits. Plasma cholinesterase activity usually recovers before RBC cholinesterase activity, often returning to normal within a few days. However, plasma cholinesterase activity is less specific for exposure than is RBC cholinesterase activity. The former can be lowered significantly in patients with a number of disorders, including hereditary deficiency of the enzyme, malnutrition, hepatic parenchymal disease, chronic debilitating illnesses, and iron deficiency anemia. In fact, day-to-day variation in the activity of this enzyme in healthy individuals may be as high as 20%.

Red blood cell cholinesterase activity is more reliable because the AChE in RBCs is true AChE. It is generally suggested that clinical OP pesticide poisoning can be said to have occurred when RBC cholinesterase activity falls to below 50% of baseline values.

However, there are several pitfalls in interpreting cholinesterase laboratory values. First, it is AChE inhibition in nervous tissue that causes toxicity, and RBC and plasma cholinesterase activity may not always reflect neuronal enzyme activity. OP insecticides vary in their ability to inhibit both enzymes. Because these tests are only markers of neuronal enzyme inhibition, this variation may lead to some patients presenting highly symptomatic after minimal reductions in RBC or plasma cholinesterase, although others can be asymptomatic after losing 50% activity. It is also well known that there is a wide normal range of RBC and plasma cholinesterase activity, which allows for patients with high normal values to suffer significant falls in cholinesterase activity, yet still register near-normal levels of cholinesterase activity on laboratory assay.

Red blood cell cholinesterase regenerates more slowly than AChE found in neurons. To completely replenish the RBC AChE supply, the RBCs in circulation at the time of the OP insecticide exposure must be replaced or pralidoxime administered. An average of 66 days may be necessary for RBC cholinesterase activity to recover following severe inhibition, and activity may take up to 120 days to return to normal. The patient may have completely recovered neuronal activity of AChE and resolved all cholinergic symptoms, yet still has low RBC cholinesterase laboratory values. For this reason, in subacute poisoning with OP compounds, it is difficult to accurately predict the actual time of onset or duration of exposure when only the RBC cholinesterase activity is known. In fact, the ability of RBC cholinesterase activity to serve as a historical marker for excessive exposure to OP insecticides provides the basis for monitoring the activity of this enzyme in pesticide workers.

It is important to note that depressed RBC cholinesterase activity may be the result of exposures or conditions other than insecticide poisoning, such as in therapy with antimalarial agents such as chloroquine and pernicious anemia. Genetic and circadian variations are also common, with daily fluctuations within the same individual as high as 10%. Additionally, levels are normally slightly lower in children younger than 4 months of age, probably increasing as hepatic function matures. Oral contraceptives raise RBC cholinesterase activity.

Blood samples for cholinesterase activity must be obtained in the appropriate blood tubes. Tubes containing fluoride will permanently inactivate the enzyme, yielding falsely low activity levels, and should not be used. Specimens for RBC cholinesterase must be drawn into tubes containing a chelating anticoagulant such as ethylenediaminetetraacetic acid (EDTA) to prevent clot formation. Plasma cholinesterase does not require an anticoagulant and can be drawn into a tube without chelators or anticoagulants.

Table 3 gives an overview of the benefits and disadvantages of estimating RBC and plasma cholinesterase levels in suspected OP or carbamate pesticide poisoning.

Plasma cholinesterase usually recovers in a few days or weeks; RBC cholinesterase recovers in several days to 4 months depending on the severity of depression. Some studies have found plasma cholinesterase either to have no significant association with the mortality or as a means to assess the need for patients requiring ventilator support.

P-nitrophenol Test

P-nitrophenol is a metabolite of some organophosphates (e.g., parathion, ethion) and is excreted in the urine.

Procedure of the test: Steam distills 10 mL of urine and collect the distillate. Add sodium hydroxide (2 pellets) and heat on a water bath for 10 minutes. Production of yellow color indicates the presence of p-nitrophenol. The test can also be done on vomitus or stomach contents.

Levels of alkyl phosphates, such as diethylphosphate (DEP) and dimethylphosphate (DMP), may be more sensitive markers of exposure.

TABLE 3: Comparison of RBC and plasma cholinesterase assays in OP/carbamate poisoning.		
	RBC cholinesterase	***Plasma cholinesterase***
Advantage	More reliable	Easier to measure, declines faster
Site	RBC (reflects CNS grey matter, motor endplate)	CNS white matter, plasma, liver, pancreas, heart
Regeneration (untreated)	1%/day	25–30% in first 7–10 days
Normalization (untreated)	35–49 days	28–42 days
Use	Unsuspected prior exposure with normal plasma cholinesterase	Acute exposure
False depression	Pernicious anemia, hemoglobinopathies, antimalarial treatment, oxalate blood tubes	Liver dysfunction, malnutrition, hypersensitivity reactions, drugs (succinylcholine, codeine, morphine), pregnancy, genetic deficiency

(CNS: central nervous system; RBC: red blood cell)

Atropine Challenge Test

An atropine sulfate challenge may be helpful in diagnosing cholinergic poisoning in a patient who presents with findings suggestive of this disorder, but in whom no history is available to suggest excessive exposure to an OP or carbamate insecticide. In an individual not exposed to significant amounts of insecticide, a test dose of 1–5 mg of atropine (adult), or 0.05 mg/kg (children), should produce classic antimuscarinic findings such as mydriasis, tachycardia, and dry mucous membranes. Conversely, the persistence of cholinergic signs and symptoms after an atropine challenge strongly suggests the presence of OP compound or carbamate poisoning. However, some patients suffering from mild-to-moderate anticholinesterase poisoning may respond to these doses of atropine. Therefore, the reversal of cholinergic findings does not exclude poisoning by one of these compounds.

Electromyogram

Repetitive nerve stimulation testing is an accurate method of quantifying AChE inhibition at the neuromuscular junction. Spontaneous repetitive potentials or fasciculations following single-nerve stimulation resulting from persistent ACh at nerve terminals can be a sensitive indicator of AChE inhibition at the motor endplate and may be useful in the early diagnosis of OP or carbamate poisoning. This kind of evaluation may also be of benefit in early detection of rebound cholinergic crisis caused by continued insecticide absorption or redistribution from adipose tissue, or onset of an intermediate syndrome.

Thin Layer Chromatography

The presence of an organophosphate in a lavage, or vomit, or gastric aspirate sample can also be determined by thin layer chromatography (TLC). The sample is extracted twice with 5 mL of petroleum ether, and the extract is washed with distilled water. It is then dried in steam-compressed air, reconstituted in methanol, and spotted on silica gel-coated TLC plate along with the standard and run in a mixture of petroleum ether and methanol (25:1). After the solvent has traveled a considerable distance, the plate is dried and exposed to iodine vapor. The RF is compared with that of the standard.

Ancillary Investigations

There may be evidence of:

- Leukocytosis (with relatively normal differential count)
- High hematocrit
- Anion gap acidosis
- Hyper- or hypoglycemia. Hypoglycemia can be recalcitrant to treatment.
- Elevation of serum creatine kinase

In every case, monitor electrolytes, ECG, and serum pancreatic isoamylase levels in patients with significant poisoning. Patients who have increased serum amylase levels and those who develop a prolonged QTc interval or PVCs are more likely to develop respiratory insufficiency and have a worse prognosis. If pancreatitis is suspected, an abdominal CT-scan can be performed to evaluate diffuse pancreatic swelling. If respiratory tract irritation is present, monitor chest X-ray. Many organophosphate compounds are found in solution with a variety of hydrocarbon-based solvents. Aspiration pneumonitis may occur if these products are aspirated into the lungs. Bronchopneumonia may develop as a complication of organophosphate-induced pulmonary edema. High-performance thin layer chromatography (HPLC) technique can be used to identify several organophosphate compounds in human serum.

Treatment

Determine plasma or RBC cholinesterase activities. Depression in excess of 50% of the baseline is generally associated with severe symptoms (*vide supra*). The initial treatment for a patient exposed to OP compounds must be directed at ensuring an adequate airway and ventilation and at reversing excessive muscarinic effects. Seizures must be treated with standard anticonvulsants such as benzodiazepines or barbiturates.

Decontamination

- If skin spillage has occurred, it is imperative that the patient be stripped and washed thoroughly with soap and water.
  Procedure:
  - Shower is preferable. Make the patient stand (if he/she is able to) under the shower or seated in a chair.
  - Wash with cold water for 5 minutes from head to toe using nongermicidal soap. Rinse hair well.
  - Repeat the wash and rinse procedure with warm water.
  - Repeat the wash and rinse procedure with hot water.

  Treating personnel should protect themselves with water-impermeable gowns, masks with eye shields, and shoe covers. Neoprene or nitrile gloves must be used, if available. Double-gloving with standard vinyl gloves may be protective for short intervals. Although alcohol-based soaps are sometimes

recommended to dissolve hydrocarbons, these products can be difficult to find, and immediate skin cleansing should be the primary goal. It must be noted that skin absorption can also result from contact with OP compounds in vomitus and diarrhea. Oily insecticides may be difficult to remove from thick or long hair, even with repeated shampooing, and shaving scalp hair may be necessary. Exposed leather clothing or products should be discarded because decontamination is very difficult once impregnation has occurred.

- If ocular exposure has occurred, copious eye irrigation should be done with normal saline or Ringer's solution. If these are not immediately available, tap water can be used.
- In the case of ingestion, stomach wash can be done, though this is often unnecessary because the patient would have usually vomited by the time he is brought to the hospital. Activated charcoal can be administered in the usual way even though the evidence is lacking as to its efficacy in OP poisoning. One dose (1 g/kg) may be sufficient.

Decontamination of Spills

A variety of methods have been described for organophosphate spill decontamination, most of which depend on changing the pH to promote hydrolysis to inactive phosphate diester compounds. The rate of hydrolysis depends on both the specific organophosphate compound involved and the increase in pH caused by the detoxicant used.

- Caution! Do not use a mixture of bleach and alkali for decontaminating acephate organophosphates. This can cause release of toxic acetyl chloride, acetylene, and phosgene gas. Spills of acephate organophosphates should be decontaminated by absorption and scrubbing with concentrated detergent.
- Treatment of the spilled material with alkaline substances such as sodium carbonate (washing soda), sodium bicarbonate (baking soda), calcium hydroxide (slaked or hydrated lime, or lime water), and calcium carbonate (limestone) may be used for detoxification.
- Chlorine-active compounds such as sodium hypochlorite (household bleach) or calcium hypochlorite (bleaching powder, chlorinated lime) may also be used to detoxify organophosphate spills.
- Disposal of large quantities or contamination of large areas may be regulated by various governmental agencies and reporting may be required.

Antidotes

- *Atropine*: Atropine, a competitive antagonist of acetylcholine at the muscarinic postsynaptic membrane and in the CNS, will block the muscarinic manifestations of organophosphate poisoning.
- *Pralidoxime*: This is a nucleophilic oxime which helps to regenerate AChE at muscarinic, nicotinic, and CNS sites. Actually, human studies have not substantiated the benefit of oxime therapy in acute organophosphate poisoning, but they are widely used. Most authors advocate the continued use of pralidoxime in the clinical setting of severe organophosphate poisoning. The antidotes for organophosphates have been discussed in details further in this chapter.

Supportive Measures

Maintain airway patency and oxygenation. Suction secretions. Endotracheal intubation and mechanical ventilation may be necessary. Monitor pulse oximetry or arterial blood gases to determine the need for supplemental oxygen.

- Administer intravenous (IV) fluids to replace losses.
- Oxygenation/intubation/positive pressure ventilation. To minimize barotrauma and other complications, use the lowest amount of positive end-expiratory pressure (PEEP) possible while maintaining adequate oxygenation. Use of smaller tidal volumes (6 mL/kg) and lower plateau pressures (30-cm water or less) has been associated with decreased mortality and more rapid weaning from mechanical ventilation in patients with ARDS.
- The following drugs are contraindicated: Parasympathomimetics, phenothiazines, antihistamines, and opiates. Do not administer succinylcholine (suxamethonium) or other cholinergic medications. Prolonged neuromuscular blockade may result when succinylcholine is administered after organophosphate exposure.
- Treat convulsions with benzodiazepines or barbiturates.
- Antibiotics are indicated only when there is evidence of infection.
- Hemoperfusion, hemodialysis, and exchange transfusion have not been shown to affect the outcome or duration of toxicity in controlled trials of organophosphate poisoning.

Prevention of Further Exposure

After the patient has recovered, he/she should not be re-exposed to organophosphates for at least a few weeks since he/she is likely to suffer serious harm from a dose that normally would be harmless, owing to the alteration of body chemistry.

Following acute poisoning, patients should be precluded from further organophosphate exposure until sequential RBC cholinesterase (AChE) levels have been obtained and confirm that AChE activity has reached a plateau. Plateau has been obtained when sequential determinations differ by number >10%. This may take 3–4 months following severe poisoning.

Treatment of a Pregnant Victim

Therapeutic choices during pregnancy depend upon specific circumstances such as stage of gestation, severity of poisoning, and clinical signs of mother and fetus. The mother must be treated adequately to treat the fetus. A severely poisoned patient with a late gestation viable fetus may be a candidate for an emergency cesarean section. The fetus may require intensive care after birth. Pralidoxime chloride is recommended for use in the pregnant patient to counteract muscle weakness. Both atropine and pralidoxime are pregnancy class C drugs and therefore not contraindicated outright.

Glycopyrrolate: Unlike atropine, glycopyrrolate usually does not readily cross the placenta and would not directly affect fetal poisoning. However, the fetus may be best served by treating the mother to retain good respiratory function and fetal oxygenation.

Autopsy Features

External:

- Characteristic odor (garlicky or kerosene-like)
- Frothing at mouth and nose. Some compounds may impart a characteristic discoloration, e.g., greenish in dichlorvos poisoning (**Fig. 3**).
- Cyanosis of extremities
- Constricted pupils

FIG. 3: Greenish frothy fluid oozing out of mouth and nose—dichlorvos poisoning. ***(For color version, see plate 37)***

Courtesy: Dr Swapnil Agarwal.

Internal:

- Congestion of GI tract; garlicky or kerosene-like odor of contents
- Pulmonary and cerebral edema
- Generalized visceral congestion

A useful sign in mortuaries infested with flies is that some of these flies after settling on an opened body (dead of organophosphate poisoning) may themselves subsequently die and land on the autopsy table. It is also pertinent to remember that organophosphates resist autolysis and can be easily detected even in putrefied bodies.

Antidotes for Organophosphates

Atropine

Mode of action: It blocks the muscarinic manifestations of organophosphates. However, since atropine affects only the postsynaptic muscarinic receptors, it has no effect on muscle weakness or paralysis.

Diagnostic dose: Organophosphate-poisoned patients are generally tolerant to the toxic effects of atropine (dry mouth, rapid pulse, dilated pupils, etc.). If these findings occur following a diagnostic atropine dose, the patient is probably not seriously poisoned.

Diagnostic dose: Adult: 1 mg intravenously or intramuscularly; Child: 0.25 mg (about 0.01 mg/kg) intravenously or intramuscularly

Therapeutic dose: 1–2 mg IV or IM (*adult*); 0.05 mg/kg IV (*child*); every 15 minutes until the endpoint is reached, i.e., drying up of tracheobronchial secretions. Pupillary dilatation and tachycardia are not reliable indicators of the endpoint. Atropine can also be administered as an IV infusion after the initial bolus dose, at a rate of 0.02–0.08 mg/kg/h. Once the endpoint has been reached, the dose should be adjusted to maintain the effect for at least 24 hours. Atropinization must be maintained until all of the absorbed organophosphate has been metabolized. This may require administration of 2–2,000 mg of atropine over several hours to weeks. Large doses of atropine are often needed to reverse the bronchospasm, bronchorrhea, bradycardia, and heart block associated with severe OP pesticide toxicity. Some patients with mild symptoms need only 1 or 2 mg of atropine to reverse cholinergic toxicity, but the moderately poisoned adult commonly requires total doses as large as 40 mg or more. Severe poisonings may necessitate even higher doses. Some adults have received over 1,000 mg of atropine in 24 hours (with adequate pralidoxime dosing) without demonstrating antimuscarinic effects, and total doses as high as 11,000 mg during the course of treatment have been reported. Children have been managed with continuous infusions of atropine starting at 0.025 mg/kg/h, and adult infusions of atropine can begin at 0.5–1 mg/h and titrated as needed. Continuous infusions have been used for as long as 32 days in severely poisoned patients.

Atropine therapy must be withdrawn slowly to prevent recurrence or rebounding of symptoms, often in the form of pulmonary edema. This is especially true of poisonings from lipophilic organophosphates such as fenthion.

Precautions:

- Many parenteral atropine preparations contain benzyl alcohol or chlorobutanol as preservatives. High-dose therapy with these preparations may result in benzyl alcohol or chlorobutanol toxicity. Preservative-free atropine preparations are available and should be used if large doses are required.
- The half-life of atropine is significantly longer in children under 2 years and adults over 60 years; the rate of administration in these patients should be adjusted accordingly.
- Effects of overdosing with atropine include fever, warm dry skin, inspiratory stridor, irritability, and dilated and unresponsive pupils.
- A urinary catheter should be inserted in all atropinized patients to prevent urinary retention.
- If atropine supplies are exhausted during therapy, other antimuscarinic agents like diphenhydramine may be used.

Endpoint: "Atropinization" is said to have occurred when the patient exhibits dry skin and mucous membranes, decreased or absent bowel sounds, tachycardia, reduced secretions, no bronchospasm, and mydriasis. Reduction or disappearance of pulmonary secretions is the most important target in atropine therapy and can be guided by following lung sounds and oxygenation. Tachycardia is not a contraindication to atropine therapy. Although the pupils are often helpful in gauging the need for atropine, the miosis encountered in severe ingestions and by direct ocular exposure to OP insecticides may respond only to topical ophthalmic atropine. Conversely, a positive pupillary response alone should not be used to discontinue further therapy.

Adverse effects: Atrial arrhythmias, A-V dissociation, multiple ventricular ectopics, photophobia, raised intraocular pressure, hyperpyrexia, hallucinations, and delirium

Glycopyrrolate

When antimuscarinic CNS toxicity becomes evident, yet peripheral cholinergic findings necessitate the administration of more atropine (e.g., bradycardia, bronchorrhea, vomiting), glycopyrrolate bromide can be substituted for atropine because its quaternary ammonium structure limits CNS penetration.

The initial IV dose of glycopyrrolate for adults is 1–2 mg, repeated as needed, and in children 0.025 mg/kg up to adult doses. As with atropine, much higher doses of glycopyrrolate may be required to stabilize patients with severe poisoning.

Pralidoxime: PAM (Pyridine-2-aldoxime Methiodide)

Structurally, pralidoxime is 2-hydroxyiminomethyl-1-methylpyridinium chloride.

Mode of action: It is usually given along with atropine. Although phosphorylated AChE undergoes hydrolytic regeneration at a very slow rate, this process can be markedly enhanced by using an oxime such as pralidoxime hydrochloride (2-PAM). In addition to rejuvenating AChE, pralidoxime may also reverse toxicity by directly inactivating free OP molecules and by exhibiting an apparent antimuscarinic effect on nervous tissue. Regeneration of AChE lowers ACh concentrations to normal levels, reversing both muscarinic and nicotinic effects. An immediate rise in RBC cholinesterase activity is often noted after the administration of pralidoxime.

Pralidoxime competes for the phosphate moiety of the OP compound and releases it from the AChE enzyme, thereby liberating the latter and reactivating it. Most phosphorylated AChE will usually be "aged" within 24–48 hours of exposure. Pralidoxime is unable to rejuvenate active enzyme from the OP compound-AChE complex that has undergone aging. Therefore, pralidoxime therapy is most effective if started early in the course of toxicity. The actual rate of aging, however, varies significantly among OP compounds. Although it is advisable to begin pralidoxime therapy within 48 hours of poisoning, it can be administered even much later with beneficial effects. Circulating OP pesticide concentrations have been measured for as long as 48 days after exposure, either because of prolonged absorption from the GI tract or because of redistribution from fat stores. Therefore, some AChE may still be undergoing new inhibition for days or weeks after exposure in symptomatic patients, and such inhibition may be reversible by pralidoxime. Some reports support this theory by recording dramatic effects in reversing paralysis, weakness, and cholinergic symptoms even after late administration of pralidoxime.

Pralidoxime is not equally effective in reversing cholinergic symptoms in all types of OP compound poisonings. It is particularly effective in reversing toxicity from parathion, diazinon, methyl parathion, TEPP, dimethoate, and dichlorvos but dimethoxy compounds, such as malathion and methyl demeton, may be more resistant to reversal.

Till recently, pralidoxime was said to be contraindicated in carbamate poisoning because experiments with carbaryl (*Sevin*) suggested a worsening of symptoms when it was administered. However, studies have pointed out that while pralidoxime is not a necessary adjunct to atropine in carbamate overdose, it may be beneficial in some cases.

Dose: *For adults*: 1–2 g in 100–150 mL of 0.9% sodium chloride, given IV over 30 minutes. This can be repeated after 1 hour, and subsequently every 6–12 hours, for 24–48 hours. Alternatively, a 2.5% concentration of pralidoxime can be given as a loading dose followed by a maintenance dose. Serious intoxication may require continuous infusion of 500 mg/h in adults. Many workers feel that this high-dose therapy minimizes the incidence of complications such as the intermediate syndrome. Maximum dose should not exceed 12 g in a 24-hour period. Infusion over a period of several days may be necessary and is generally well tolerated. Although minimal serum concentrations of 4 μg/mL are estimated to be necessary for the maintenance of enzyme reactivation, the degree of reactivation may be dependent on the specific identity and concentrations of both oxime and OP compound. Bolus dosing of pralidoxime every 4–8 hours is ineffective in maintaining these levels, and therefore a constant infusion appears to be more appropriate. Present recommendations for adults are to begin the maintenance infusion at 250–500 mg/h, titrating to symptoms. Alternative dosing by weight reported in other studies suggests using 4–5 mg/kg as a loading dose over 15–30 minutes, followed by a continuous infusion of 2–4 mg/kg/h to maintain serum concentrations.

The World Health Organization (WHO) currently recommends an initial bolus of at least 30 mg/kg, followed by an infusion of >8 mg/kg/h.

For children: About 20–40 mg/kg to a maximum of 1 g/dose given IV and repeated every 6–12 hours for 24–48 hours. Alternatively, IV infusion can be resorted at a rate of 9–19 mg/kg/h.

Adverse effects: Side effects of pralidoxime are usually minimal at normal doses. Severely poisoned patients have received 500 mg/h for weeks without adverse effects. Rapid infusion can cause mild cholinergic effects because of transient blockade of AChE and has resulted in neuromuscular blockade and central respiratory depression. Occasional visual complaints are also reported in patients receiving pralidoxime. Rapid administration can cause tachycardia, laryngospasm, and even cardiac or respiratory arrest. Other adverse effects include drowsiness, vertigo, headache, and muscle weakness.

It is generally not advised for the treatment of carbamate overdose, especially carbaryl.

In cases where IV administration is not possible, pralidoxime can be given intramuscularly as an initial dose of 1 g or up to 2 g in cases of very severe poisoning. Recent research in animals suggests that oral dosing of pralidoxime and atropine may also improve survival.

In some countries, obidoxime is used instead of pralidoxime, although it does not appear to be superior to the latter. It is apparently favored over pralidoxime in clinical practice in Belgium, Israel, The Netherlands, Scandinavia, and Germany and is the only oxime available in Portugal.

Several investigators have started suggesting that oximes have only a limited role in organophosphate poisoning, and successful management is possible without employing them at all, though this view is not shared by some other workers in the field.

Diazepam

Several studies demonstrate that administering diazepam along with oximes in the treatment of OP nerve agents (sarin, soman, tabun, VX) or OP pesticides can increase survival and decrease the incidence of seizures and neuropathy. Diazepam can also decrease cerebral morphologic damage resulting from OP compound-induced seizures. Some investigators suggest that diazepam may also help attenuate OP-induced respiratory depression by minimizing the overstimulation of central respiratory centers caused by OP insecticides.

Dose: *For adults*: 5–10 mg IV slowly, every 15 minutes, up to a maximum of 30 mg.

For children: 0.25–0.4 mg/kg IV slowly, every 5–10 minutes, up to a maximum of 10 mg.

If diazepam is ineffective, phenytoin or phenobarbitone can be used instead.

CARBAMATES

Carbamates are as popular as organophosphates in their role as insecticides (and fungicides) and share a number of similarities. Only the differentiating features will be discussed. Indian brands are listed in **Table 4**.

Usual Fatal Dose

The following are *extremely toxic* (*LD50*: *1–50 mg/kg*) or highly toxic (*LD50*: *51–500 mg/kg*): Aminocarb, Bendiocarb, Benfuracarb, Carbaryl, Carbofuran, Dimetan, Dimetilan, Dioxacarb, Formetanate, Methiocarb, Methomyl, Oxamyl, Propoxur.

The following are *moderately toxic* (*LD50*: *501–5,000 mg/kg*) or slightly toxic (*LD50*: *>5,000 mg/kg*): Aldicarb, Bufencarb, Isoprocarb, MPMC, MTMC, Pirimicarb.

Mode of Action and Clinical Features

Carbamates were discovered in the 19th century when it was observed that the calabar bean (*Physostigma venenosum Balfour*) (**Fig. 4**) was being used in tribal rituals in West Africa. These beans were imported to Great Britain in 1840, wherein 1864, Jobst and Hesse isolated an active alkaloid they named "physostigmine." This alkaloid was first medicinally used to treat glaucoma in 1877. In the 1930s, the synthesis of aliphatic esters of carbamic acid led to the development and introduction of carbamate pesticides, marketed initially as fungicides. In 1953, the Union Carbide Corporation developed and first marketed carbaryl, the very same insecticide that was being manufactured at the notorious plant in Bhopal, during the methyl isocyanate tragedy in 1984.

TABLE 4: Common carbamates.

Generic name	*Brand name*
Aldicarb	Aldrin, Temik
Carbaryl	Agrovin, Agroyl, Bangvin 50, Caravet, Corovin, Hexavin, Kevin 50, Kilex Carbaryl, Sevidal, Sevin 50, Sujacarb, Sulfarl 50
Carbaryl + Gamma BHC	Sevidol
Carbofuran	Agrofuron 3G, Carbocil 3, Carburan, Crane, Furadan 3G, Hexafuran, VegFru Diafuran
Carbosulfan	Marshal
Fenobucarb	Merlino
Methomyl	Astra, Dunet, Lannate, Lannet, Mathoyl
MPMC (Xylylcarb)	Bipuin
MTMC (Metolcarb)	Emisan
Propoxur	Baygon, Isocarb, Protox Bait
Thiodicarb	Larvin

As described in the previous chapter, those cholinesterase-inhibiting (anticholinesterase) insecticides that contain phosphorus are collectively termed OP compounds, while those that contain the OC=ON linkage are termed carbamates. Most carbamate insecticides are N-methyl carbamates derived from carbamic acid. Medicinal carbamate compounds include physostigmine, pyridostigmine, and neostigmine. Drugs such as meprobamate and various urethanes are also carbamate derivatives, but they do not inhibit cholinesterase. Thiocarbamate fungicides and herbicides (e.g., maneb, zineb, nabam, mancozeb) also do not inhibit AChE and do not produce cholinergic excess.

Carbamates (like organophosphates) are inhibitors of AChE, but carbamylate the serine moiety at the active site instead of phosphorylation. This is a reversible type of binding and hence symptoms are less severe and of shorter duration. Aging cannot occur since the carbamate-AChE bond hydrolyzes spontaneously, reactivating the enzyme. As such, the duration of symptoms in carbamate poisoning is generally <24 hours. As a result, both morbidity and mortality are limited when compared to organophosphate poisoning. Also, since carbamates do not penetrate the CNS to the same extent as organophosphates, CNS toxicity is likewise much less. With respect to all other clinical manifestations, there is a general similarity between carbamates and organophosphates.

Carbamates are well absorbed across skin and mucous membranes, and by inhalation and ingestion. Peak serum levels of some compounds are generally achieved in 30–40 minutes following ingestion. Most carbamates undergo hydrolysis, hydroxylation, and conjugation in the liver and intestinal wall, with 90% excreted in the urine within 3 days. There are two main pharmacokinetic differences between carbamates and OP compounds. First, carbamates do not easily cross into the CNS. CNS effects are thus limited, although CNS dysfunction may still occur in massive ingestion (especially aldicarb), or from hypoxia secondary to pulmonary toxicity and paralysis. Second, the carbamate-cholinesterase bond does not "age" as in OP compound poisoning; thus it is reversible, with spontaneous hydrolysis occurring usually within several hours. Carbamates are rapidly metabolized. Most of them are rapidly hydrolyzed by liver enzymes to methyl carbamic acid and a

FIG. 4: *Physostigma venenosum*—calabar bean. ***(For color version, see plate 37)***

variety of low toxicity phenolic substances. These metabolites may sometimes be measured in urine as long as 2–3 days after significant pesticide absorption.

Miosis, a muscarinic effect, is characteristic of severe and moderately severe poisonings, but may appear late.Miosis was the most common symptom seen (57%) in a retrospective observational study of 54 children admitted to a pediatric intensive care unit following anticholinesterase (carbamate and organophosphate) poisoning. Pupil dilation may occur as a nicotinic effect and may be present in up to 10% of patients.

Sinus tachycardia with ST segment depression may occur early in the course of poisoning. Repolarization abnormalities may occur and are generally transient. Complete heart block has been reported.

Dyspnea is a common manifestation of carbamate exposure. Chest tightness, bronchospasm, increased pulmonary secretions, and rales may develop secondary to muscarinic effects. Acute lung injury (pulmonary edema) is a potential clinical manifestation of severe carbamate poisoning and is attributed to the muscarinic action of the insecticide. Contributing factors to the development of pulmonary edema include bradycardia and weakened cardiac contraction from an accumulation of acetylcholine on the cardiovascular system. Hypoxia may develop due to increased capillary permeability.

Headache, dizziness, blurred vision, tremor, paresis, mental depression, coma, delayed neuropathies, various dystonias, weakness, muscle twitching, and convulsions have all been reported with carbamate poisoning. In an outbreak of gastroenteritis reported in patrons of a Thai restaurant, it was discovered that the food had been seasoned with methomyl-contaminated salt. Patients reported dizziness (72%), headache (52%), and chills (48%). Dizziness, lightheadedness, or a feeling of disequilibrium were reported as the initial symptom in 51 cases (48%). Children may be more likely to develop CNS depression, convulsions, and hypotonia than the typical cholinergic syndrome. The absence of classic muscarinic effects has been reported in several children intoxicated with carbamate insecticides. The presence of either a cardiac arrhythmia or respiratory failure is associated with a higher incidence of fatal poisoning.

Delayed neuropathies are not usually associated with carbamate insecticides. One reason for this difference is presumed to be that "aging" of the NTE pesticide complex is a requirement for neuronal degeneration. Paradoxically, studies suggest that subgroups of carbamates may actually bind NTE and exert a protective effect against more toxic OP compounds. However, cases of possible delayed neuropathy associated with carbamates have been reported. These cases involve ingestion of carbaryl, m-tolyl methyl carbamate, and carbofuran; include both sensory and motor tracts; and tend to resolve over 3–9 months. EMG findings in these subjects are variable. The symptoms are similar to those seen with organophosphates. Behavioral toxicity following carbamate exposure is extremely rare.

Acute pancreatitis has been reported with propoxur.

Combined toxicity of organophosphate and carbamate compounds can cause multiple complications, e.g., Parkinsonism, thrombocytopenia, intermediate syndrome, and neuropsychiatric manifestations (COPIND) during acute phase, and treatment can be complicated.

Diagnosis

Carbamates inhibit neuronal and RBC AChE, and plasma cholinesterase. However, the relative rapidity with which spontaneous decarbamylation of cholinesterase takes place may result in the measurement of relatively normal RBC cholinesterase activity despite severe cholinergic symptoms if the assay is not performed within several hours of sampling. In vitro decarbamylation has been found to be promoted by dilution of the sample. The carbamylated sample should be stored undiluted and refrigerated or frozen. As in the case with OP pesticide poisoning, the wide "normal" range of cholinesterase values may make interpretation of cholinesterase activity difficult at times when the patient's baseline values are unknown. Unlike OP pesticides, carbamates generally do not cause persistent depressed RBC and plasma cholinesterase activities.

Rotenberg et al. proposed an assay technique to distinguish between carbamate and organophosphate poisoning. Carbamylated cholinesterase activity follows a nonlinear kinetic pattern over time, whereas phosphorylated enzyme activity is linear. At an inhibition of greater than 40%, the nonlinear pattern characteristic of carbamates is easily mapped.

The atropine challenge test, as described for diagnosis of OP pesticide poisoning (in the previous section), can be done in carbamate poisoning also.

One technique for assessing absorption of the principal N-methyl carbamate compounds is measurement of specific phenolic metabolites in urine, e.g., carbaryl (alpha-naphthol), carbofuran (carbofuran phenol) propoxur (isopropoxyphenol).

Chest X-ray should be obtained in all symptomatic patients. The major cause of morbidity and mortality in carbamate insecticide poisonings is respiratory failure and associated pulmonary edema.

Treatment

An important differentiating point from organophosphates is that oximes are generally not recommended, while atropine can be given.

Especially in carbaryl poisoning, oxime therapy can lead to the production of a carbamylated oxime which may be a more potent AChE inhibitor than carbaryl itself. With other carbamate insecticides (particularly aldicarb), oximes may be a useful adjunct to atropine therapy. The current consensus is that pralidoxime can be used in conjunction with atropine for specific indications as follows:

- Life-threatening symptoms such as severe muscle weakness, fasciculations, paralysis, or decreased respiratory effort
- Continued excessive requirements of atropine
- Concomitant organophosphate and carbamate exposure

Fortunately, because of the rapid hydrolysis of the carbamate-AChE complex, symptoms, including weakness and paralysis, usually resolve within 24–48 hours without pralidoxime therapy. However, administering pralidoxime to a poisoned patient in a cholinergic crisis is appropriate when it is not known whether the patient is suffering from OP or carbamate pesticide poisoning. If the poisoning is from a carbamate pesticide, pralidoxime therapy may not be

necessary, but if used, should not prove detrimental. Second, significant inhibition of RBC cholinesterase and plasma cholinesterase by carbamates generally does not last for >1–2 days, assuming absorption is complete. Patients exposed to carbamates usually have normal values by the time of discharge. There are no reported cases of recurrent or delayed poisonings following carbamate insecticide poisoning. Therefore, repeating cholinesterase tests after patients are asymptomatic is usually unnecessary.

In all cases, administer atropine in repeated doses intravenously until atropinization is achieved (indicated by drying of pulmonary secretions). *Adult dose:* 2–4 mg IV every 10–15 minutes. *Pediatric dose:* 0.05 mg/kg IV every 10–15 minutes. Convulsions can be controlled with a benzodiazepine (diazepam or lorazepam). If they persist or recur, administer phenobarbitone.

ALUMINUM PHOSPHIDE POISONING

Aluminum phosphide—solid fumigant, $AlPO_4$ tablets most commonly used as insecticides and rodenticides—is also referred to as "rice tablets," "wheat pill," celphos, and alphos as shown in **Figure 5**. Peculiar features of aluminum phosphide (**Table 5**) poisoning are as follows:

- It is kept as tablets which are used in grain storage after harvesting.
- It is found to be the most common cause of acute poisoning in India. It was also found to be the most common cause of suicidal death in North India.
- It shows a distinct male preponderance in the lower socioeconomic strata and in rural areas, probably due to the heavy social stress burden in this group.
- A positive history of ingestion is the basis of diagnosis in most cases.
- The presence of typical clinical features, garlicky odor from the mouth, and highly variable arrhythmias in a young patient with shock and no previous history of cardiac disease points toward $AlPO_4$.
- Unfortunately, its widespread use has been associated with a galloping rise in the incidence of $AlPO_4$ poisoning. Recent studies have indicated that the number of deaths so far has exceeded the number of fatalities in the Bhopal gas tragedy. The mechanism of aluminum phosphide toxicity, shown in **Flowchart 2**, consists of the release of phosphene gas, inhibition of cytochrome failure of cellular respiration, formation of highly reactive radicles, and cellular injury due to lipid peroxidation.

Clinical Features

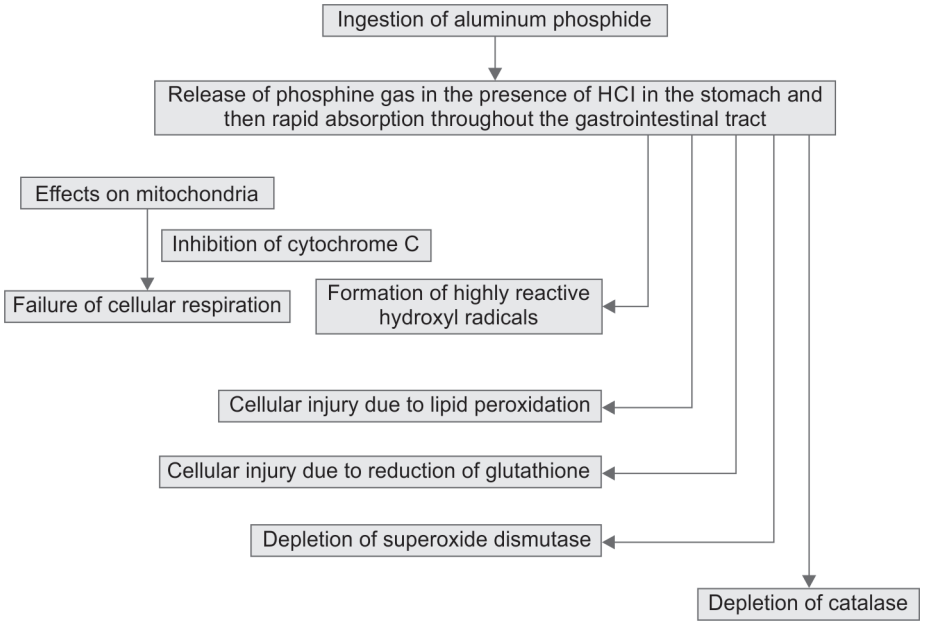
- The presenting symptoms depend on the route of administration.

FIG. 5: Tablet form of aluminum phosphide.

TABLE 5: Comparison of aluminum phosphide and organophosphorus compound.

	Aluminum phosphide	***Organophosphorus compound***
Compound	Metallic salt of phosphorus	Organic compound of phosphorus
Available	Tablets/Powder	Liquid form dissolved in kerosine
Pesticides	Fumigant in closed grain storage	Spray on open crops
Fatal	Cardiotoxic and cellulotoxic	Neurotoxic and respiratory failure
Life-saving treatment	IABP and supportive	Intubation and mechanical ventilation
Antidote	NIL	Atropine and pralidoxime
Fatal period	Within hours	Within hours
Fatal dose	1 tablet (3 g)	10–15 mL
Smell	Mousy odor	Kerosine like noxious smell

(IABP: intra-aortic balloon pump)


Ingestion of aluminum phosphide
Release of phosphine gas in the presence of HCl in the stomach and then rapid absorption throughout the gastrointestinal tract
Effects on mitochondria
Inhibition of cytochrome C
Failure of cellular respiration
Formation of highly reactive hydroxyl radicals
Cellular injury due to lipid peroxidation
Cellular injury due to reduction of glutathione
Depletion of superoxide dismutase
Depletion of catalase

FLOWCHART 2: Mechanism of aluminum phosphide toxicity.

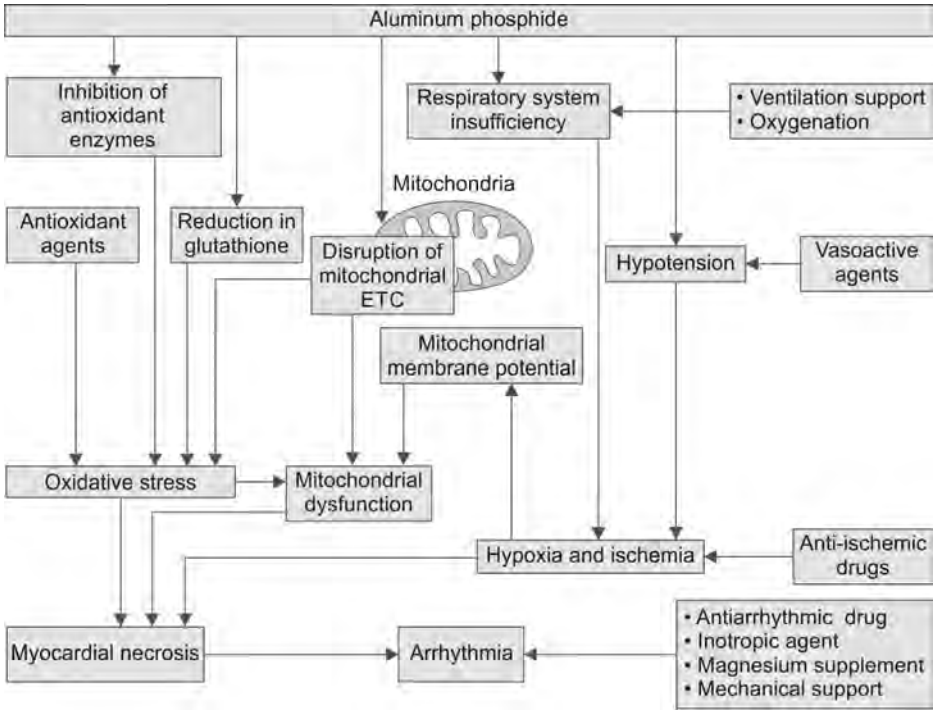
- Poisoning by inhalation produces irritation of mucous membrane, dizziness, easy fatigability, nausea, vomiting, headache, and diarrhea in mild exposure.
- Ataxia, numbness, paresthesia, muscle weakness, paralysis, diplopia, and jaundice result from a moderate degree of exposure.
- In severe cases of inhalational poisoning, the patient presents with ARDS, congestive cardiac failure, convulsion, and coma.
- Nausea, vomiting, and abdominal pain are the earliest symptoms that appear after ingestion.
- GI symptoms present in moderate-to-severe poisoning are excessive thirst, abdominal pain, and epigastric tenderness while cardiovascular abnormalities seen are profound hypotension, dry pericarditis, myocarditis, acute congestive heart failure, and arrhythmias.
- Involvement of the respiratory system may lead to dyspnea, which may progress to type I or II respiratory failure.
- Nervous system manifestations include headache, dizziness, altered mental status, convulsion, acute hypoxic encephalopathy, and coma.
- Cardiac arrhythmias, respiratory failure, metabolic acidosis. *ECG abnormalities*: Most probably due to hypomagnesemia caused by cardiotoxic effect of phosphine (**Flowchart 3**).

Diagnosis

- A positive history of ingestion is the basis of diagnosis in most cases. The presence of typical clinical features, garlicky odor from the mouth, and highly variable arrhythmias in a young patient with shock and no previous history of cardiac disease points toward $AlPO_4$ poisoning.
- Confirmation can be done by the silver nitrate test. In this test, 5 mL of gastric aspirate and 15 mL of water are put in a flask and the mouth of the flask is covered by filter paper impregnated with 0.1 N silver nitrate. The flask is heated at 50°C for 15–20 minutes. If phosphine is present, the filter paper turns black. For performing the test on exhaled air, the silver nitrate impregnated filter paper is placed on the mouth of the patient and the patient is asked to breathe through it for 15–20 minutes. Blackening of the paper indicates the presence of phosphine in breath. The sensitivity of the test is 100% and 50% vis-à-vis gastric fluid and exhaled air, respectively.
- However, the most specific and sensitive method for detecting the presence of pH in blood or air is gas chromatography.
- For spot sampling of phosphine in air, detector tubes and bulbs are available commercially.
- Laboratory evaluation is mainly done to assess the prognosis.
- Leukopenia indicates severe toxicity.
- Increased SGOT (serum glutamic oxaloacetic transaminase) or SGPT (serum glutamic-pyruvic transaminase) and metabolic acidosis indicate moderate-to-severe ingestional poisoning.
- Electrolyte analysis shows decreased magnesium while potassium may be increased or decreased.
- Measurement of plasma renin is significant as its level in blood carries a direct relationship with mortality and is raised in direct proportion to the dose of pesticide.
- The serum level of cortisol is usually found to be decreased in severe poisoning.

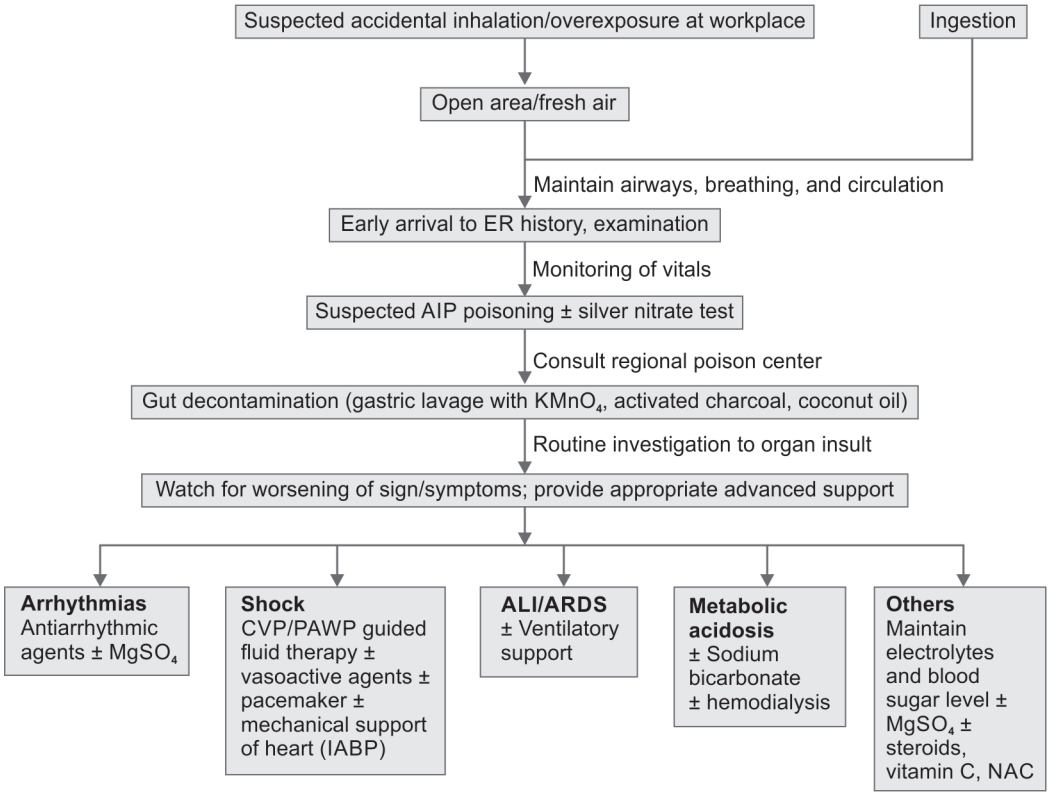
Emergency Department Management of Aluminium Phosphide Poisoning

- Take personal protection measures, including a full-face mask and rubber gloves during decontamination. Secure airway; if required patient should be intubated and mechanically ventilated, there is no role of noninvasive ventilation in $AlPO_4$ poisoning, central venous line should be preferred as IV access (**Flowchart 4**).
- IV access should be established and 2–3 L of normal saline is administered within the first 8–12 hours.
- Vasopressor is started to keep systolic blood pressure >90 mm Hg.
- Gut decontamination with $KMnO_4$, vegetable or coconut oil (within 6 h)



(ETC: electron transport chain)

FLOWCHART 3: Effect of aluminum phosphide on the cardiovascular system causing hypotension and arrhythmias.


Suspected accidental inhalation/overexposure at workplace
Ingestion
Open area/fresh air
Maintain airways, breathing, and circulation
Early arrival to ER history, examination
Monitoring of vitals
Suspected AIP poisoning ± silver nitrate test
Consult regional poison center
Gut decontamination (gastric lavage with $KMnO_4$, activated charcoal, coconut oil)
Routine investigation to organ insult
Watch for worsening of sign/symptoms; provide appropriate advanced support
Arrhythmias
Antiarrhythmic agents ± $MgSO_4$
Shock
CVP/PAWP guided fluid therapy ± vasoactive agents ± pacemaker ± mechanical support of heart (IABP)
ALI/ARDS
± Ventilatory support
Metabolic acidosis
± Sodium bicarbonate
± hemodialysis
Others
Maintain electrolytes and blood sugar level ± $MgSO_4$ ± steroids, vitamin C, NAC

(ALI: acute lung injury; $AlPO_4$: aluminum phosphide; ARDS: acute respiratory distress syndrome; CVP: central venous pressure; PAWP: pulmonary capillary wedge pressure; NAC: n-acetyl cysteine)

FLOWCHART 4: Emergency management of aluminum phosphide poisoning.

- Two important steps, resuscitation of shock and supportive measures, should be taken as soon as possible. In management, the main objective is to provide oxygenation, ventilation, and circulation till phosphine is excreted. Specific management toward $AlPO_4$ toxicity includes reducing absorption of phosphine, reducing cellular toxicity, and increasing excretion through kidney and lungs.
- Various point-of-care devices are useful while managing the $AlPO_4$ poisoning are electrocardiogram, arterial blood gas analysis, ultrasound chest, echocardiography, cardiac enzymes, portable chest X-ray.
- After ingestion, effectiveness of gut decontamination primarily depends on the duration of exposure of poison and should be done as early as possible.
- To reduce the absorption of phosphine, gastric lavage is done with coconut oil.
- Gastric lavage with normal saline or distilled water is contraindicated as phosphine gas is liberated from $AlPO_4$ on coming in contact with water.
- Potassium permanganate (1:10,000) can be used for gastric lavage as it oxidizes phosphine to nontoxic phosphate. There is no well-proven basis to conclude that $KMnO_4$ is efficient against $AlPO_4$ poisoning.
- Slurry of activated charcoal also helps to adsorb phosphine from the GI tract in most of the literature. Activated charcoal has a wide internal surface area consisting of pores (10–20 Å). It efficiently adsorbs toxins of moderate molecular weight (100–800 Da). The molecular weight of $AlPO_4$ is about 58 Da; therefore, the role of activated charcoal in $AlPO_4$ poisoning is again doubtful as liberated phosphine cannot be detoxified.
- Magnesium sulfate helps in scavenging free radicals through glutathione (GSH) recovery; hence, it is effective as a parenteral antioxidant in this poisoning as well as has been tried for its general membrane-stabilizing effect in cardiac cells. It is observed that dose-related mortality rates in patients treated with and without $MgSO_4$ are not significantly different. Magnesium is a weak antiarrhythmic agent and may be useful in controlling few supraventricular arrhythmias and a more potent antiarrhythmic agent can be used.
- Antacids and proton-pump blockers are added for symptomatic relief.

Intensive Care Management of Aluminium Phosphide Poisoning

- *Shock*: Fluid therapy with 2–3 L normal saline in the first 8 hours to maintain CVP of 12–14 cm saline. Adequate hydration and renal perfusion with IV fluid enhance the excretion of poison through urine.
- *If no response*: Inotropes can be added to keep systolic blood pressure >90 mm Hg.
- *Refractory hypotension*: Consider intra-aortic balloon pump (IABP). The role of advanced measures such as the use of IABP to mechanically support the heart has been practiced in tertiary care hospitals. The role of advanced measures such as the use of IABP to mechanically support the heart has been demonstrated in toxic myocarditis with refractory shock due to aluminum phosphide poisoning. IABP can mechanically support the heart, decrease the afterload, and improve perfusion to the vital organs and coronary arteries.
- The possibility of the beneficial effect of extracorporeal life support (ECLS) as a supportive measure for intractable circulatory collapse. Extracorporeal membrane oxygenation (ECMO) is a novel technique for supplying oxygen and it may have a beneficial role in the management of $AlPO_4$ poisoning.

Aluminum phosphide poisoning has a high mortality rate due to the nonavailability of a specific antidote. Only possible measures to save the life in poisoning with unexposed forms of aluminum phosphide are supportive.

SUMMARY

Poisoning is a major global problem and specially in India due to pesticides, its incidence is increasing due to fast industrialization and urbanization. The toxins involved in acute poisoning cases vary from place to place but in India, insecticides and pesticides are the most commonly consumed agents, e.g., organophosphorus carbamate and aluminium phosphide. Number of cases are increasing day-by-day so knowledge of commonly consumed poisons in India particularly important for emergency physicians as it may help in early diagnosis and institution of life-saving treatment.

MULTIPLE CHOICE QUESTIONS

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201 CHAPTER

Anticholinergics

Shikha Tandon

INTRODUCTION

Anticholinergics are substances that block the neurotransmitter acetylcholine in the central and peripheral nervous systems and are administered to reduce the effects mediated by acetylcholine on acetylcholine receptors in neurons through competitive inhibition. There are many medications and plants in which anticholinergic properties are present. Anticholinergic activities can be seen either as therapeutic effects or due to adverse events. Antihistamine or accidental ingestions of hyoscyamine-containing drug by a child to treat colic pain can present as toxicity.

Various plants and their components also have anticholinergic properties and produce a psychoactive hallucinogenic effect if ingested accidentally or taken as abuse. Alkaloids containing plant belladonna have high anticholinergic properties. Ingestions of seeds and berries can also produce anticholinergic toxicity. Atropine is the antidote for organophosphorus insecticides which produces cholinergic syndrome. Anticholinergic toxicity can also be observed on a high dose of atropine given to a person without cholinesterase poisoning.

HISTORY

Historically, anticholinergic agents were known more for their toxicity than for their therapeutic effects. Anticholinergics originate from botanical preparations of the deadly nightshade family (Solanaceae) used for centuries in many cultures. *Datura* is a genus of the Solanaceae family and it grows worldwide. The burning roots, stems, and seeds of these plants release an aerosol of potent alkaloids, one of which is the antimuscarinic compound, atropine. It was the inhalation of this medicinal smoke that was a treatment for obstructive airways disease for many centuries. In addition to atropine, other alkaloids, including scopolamine and hyoscyamine, are released with additional effects including intoxication, hallucinations, and poisoning.

PHARMACOLOGY

The absorption of anticholinergics drugs is through ingestion, smoking, and ocular route. Anticholinergics act as reversible competitive antagonists to the neurotransmitter acetylcholine, thus blocking it to bind at cholinergic receptors present in the endings of the parasympathetic nervous system. There are 2 types of cholinergic receptors described in **Table 1**. Anticholinergics can be broken down into three subgroups based on their respective specificity to various types of cholinergic receptors.

The first group of "classic" anticholinergic agents is the antimuscarinic compounds (atropine, propantheline), which block acetylcholine action, or the cholinomimetic drugs, which bind to muscarinic M-receptive areas of the central nervous system (CNS) and glandular system, myocardium, and smooth muscle.

The second group is represented by ganglioblockers (mecamylamine, trimethaphan), which inhibit cholinergic

TABLE 1: Types of cholinergic (muscarinic and nicotinic) receptors.

Receptors	*Location*	*Stimulates/Action*
Muscarinic	M_1 brain salivary gland	Increases salivary and gastric secretion
	M_2 heart	Decreases in sinus and atrioventricular node rate
	M_3 smooth muscle cells endocrine and iris	Bronchospasm, increase saliva and gastric acid, constriction of the pupil
	M_4 central nervous system	Multiple actions
	M_5 not well understood	Mechanism of action—activation of phospholipase C—increase calcium and decrease in cyclic adenosine monophosphate
Nicotinic	• Central nervous system • Neuromuscular junction • Autonomic ganglion • Adrenal medulla	Mechanism of action—opening of Na and K channels—depolarization

transmission in the autonomic parasympathetic and sympathetic ganglia by blocking (nicotinic) N-receptors.

The third group is represented by neuromuscular junction blockers (tubocurarine, pancuronium), which block nicotinic N-receptors of skeletal muscle.

ETIOLOGY OF ANTICHOLINERGIC TOXICITY

Anticholinergic toxicity is common in the emergency department (ED) but rarely fatal. Overdoses of compounds with anticholinergic activity can be accidental or intentional. This is an important issue as anticholinergics are readily accessible, and many medications/over-the-counter (OTC) drugs have anticholinergic side effects, such as those used in the treatment of motion sickness, nausea, insomnia, parkinsonism, etc.

The majority of anticholinergic agents are orally ingested. The naturally occurring compounds atropine, hyoscyamine, and scopolamine are the prototypical anticholinergics from which others are synthesized. The prototypical agent atropine is used as an antidote for cholinergic toxicity from organophosphates and nerve agents which is a common scenario in developing nations. Atropine is also used as an acute treatment for symptomatic bradyarrhythmia as per the advanced cardiac life support (ACLS) algorithms.

Other therapeutic uses of anticholinergics include antihistamines, antiparkinson drugs, sleep aids, antiemetics, drugs for overactive bladder, tricyclic antidepressants (TCAs), muscle relaxants, and antipsychotics. The effects of multiple anticholinergic medications are synergistic. This is especially important for elderly patients on multiple medications. The most common source of an anticholinergic drug overdose is antihistamines.

Plants are also a common source of accidental and intentional anticholinergic ingestion. Plants that contain belladonna alkaloids are often abused due to their hallucinogenic properties.

HISTORY AND EVALUATION

A thorough history and physical examination are critical to the identification of patients with anticholinergic poisoning. Patients may present with a history of intentional ingestion of common anticholinergic agents such as antihistamines or jimson weed. There are various groups of prescription drugs in which anticholinergic activities are present and overdose can produce toxicity listed in **Table 2**.

Often, the history is less straightforward. Patients may present after a suicide attempt and be unwilling or unable to disclose what they ingested. Young children may be brought in by a caretaker/parent with somnolence/decreased mentation or other anticholinergic symptoms, although the ingestion may have been unwitnessed by the caretaker. Any history of potential co-ingestion should be obtained [commonly antidepressants, benzodiazepines (BDZs), alcohol, other sedatives, etc.].

Due to potential difficulty in obtaining a reliable history, it is critical that the clinician be familiar with the anticholinergic toxidrome. The memory aid "*red as a beet, dry as a bone, blind as a bat, mad as a hatter, hot as a hare, full as a flask*" is helpful to remember the classic signs and symptoms of anticholinergic poisoning.

TABLE 2: Commonly prescribed drugs with anticholinergic properties.

Class	*Drugs*
Antihistamine	Chlorpheniramine, loratadine, cetirizine, meclizine, prochlorperazine, promethazine
Antispasmodic	Dicyclomine, methantheline bromide
Antipsychotics	Chlorpromazine, thioridazine, clozapine, olanzapine quetiapine
Antidepressant	Amitriptyline, imipramine, doxepin
Anti-Parkinson drugs	Benztropine, trihexyphenidyl
Skeletal muscle relaxant	Cyclobenzaprine, orphenadrine
Mydriatic	Cyclopentolate, tropicamide
Belladonna alkaloids	Atropine, homatropine, scopolamine, glycopyrrolate
Plants	• *Datura* species—*Datura stramonium* • Mandragora/Mandrake • *Brugmansia* species

CLINICAL FEATURES

The signs and symptoms of anticholinergic toxicity are due to the blockage of central and peripheral cholinergic receptors. Central anticholinergic syndrome presents as fever agitation, delirium, and coma while peripheral anticholinergic syndrome presents as tachycardia, dry and flushed skin, dry mouth, and urinary retention.

Clinical findings associated with toxicity of cyclic antidepressant are more of wide complex tachydysrhythmia along with anticholinergic effect. An injectable antihistamine may present with euphoria in the patient.

A delirium patient with central anticholinergic syndrome presents with restlessness, irritability, disorientation, confusion, agitation, auditory, and visual hallucination. Repetitive picking of bed cloth or imaginary objective is common. Staccato speech pattern, dysarthria, unable to comprehend, high-pitched cries, jerking movement of extremities, and seizure can be seen.

Hyperthermia can also be seen which is usually agitation induced, associated with other symptoms such as decreased sweating and movement. Hyperthermia leads to rhabdomyolysis, coagulopathy, and multiorgan dysfunction. Mortality is due to status epilepticus, hyperthermia, wide complex tachydysrhythmia, and cardiovascular collapse.

DIFFERENTIAL DIAGNOSIS

Many conditions can cause agitated delirium, especially in the elderly. The side effects of other medications and polypharmacy should be considered. Pure anticholinergic toxicity versus mixed toxicity, as seen with TCAs and phenothiazines, should be considered. Common distractors in making a diagnosis of anticholinergic toxicity are neuroleptic malignant syndrome (antipsychotics such as haloperidol, phenothiazines such as promethazine, chlorpromazine), malignant hyperthermia (depolarizing muscle relaxants, anesthetics such as halothane/isoflurane/desflurane), serotonin syndrome (antidepressants, opioids, CNS stimulants), etc. Overlapping features make it

TABLE 3: Differentiating features of anticholinergic toxicity from other conditions.

Conditions	*Exposure to medications*	*Common features*	*Differentiating features*
Serotonin syndrome	Serotonergic medications	Hypertension	Presence of clonus hyperreflexia, hyperactive bowel sound
Neuroleptic malignant syndrome	Dopamine agonist	Tachycardia	Bradykinesia, no clonus or hyperreflexia
Anticholinergic toxicity	Acetylcholine antagonist	Hyperthermia	Dry skin, absent bowel sound, no clonus, or hyperreflexia
Malignant hyperthermia	Muscle relaxant anesthetic agents	Altered mental status	Extreme muscle rigidity, no clonus or hyperreflexia

confusing unless a thorough clinical history and distinguishing features of each of the poisonings have been kept in mind and catered to while examining the patient. The same has been enumerated in **Table 3**.

MANAGEMENT

Good supportive care is usually all that is required for the treatment of anticholinergic toxicity. Pharmacological sedation with BDZs (lorazepam and diazepam) is strongly recommended and used to counteract agitation of the patient and seizure activity. Intravenous fluid is to be started in case of hypotension and if there is any rhabdomyolysis. Adequate cooling techniques are to be used in case of hyperthermia, and activated charcoal can be administered if the ingestion has been within an hour of presentation to the ED. Soda bicarbonate can be given in case of wide complex tachyarrhythmias.

However, physostigmine may be indicated in severe cases as a specific antidote. Physostigmine is not generally considered a first-line agent and should probably be reserved for cases with potentially life-threatening complications of anticholinergic toxicity that are unresponsive to standard treatment regimens such as severe agitation, seizures, persistent hypertension, and hemodynamic compromise secondary to tachycardia (i.e., unstable narrow complex dysrhythmias). The recommended dose is 0.5–2 mg IV for adults and 0.02 mg/kg IV for pediatric patients with a maximum pediatric dose of 0.5 mg. Because of its short half-life and rapid elimination, repeat dosing may be required after approximately 30 minutes if symptoms recur.

This is hence used as a specific antidote keeping the following important considerations:

- Severe agitation or psychosis unresponsive to other therapies.
- Severe peripheral and central anticholinergic features.
- No history of seizures (rapid infusion in ED can precipitate/induce seizures).
- Normal electrocardiogram (EKG), especially QRS duration (conditions with QRS >0.10 s are associated with brady arrhythmias and asystole).
- No co-ingestion of drugs altering intraventricular conduction, e.g., TCAs, the toxicity of which is associated with QRS prolongation primarily.

Prior to administering physostigmine in the ED, potential complications in the form of increased cholinergic tone should be anticipated. Urinary outlet obstruction can be prevented by the placement of a Foley catheter beforehand and bedside suction should be immediately available to clear excessive salivation, bronchial secretions, or emesis. The patient should be placed on continuous EKG and pulse oximetry monitoring. Close supervision during and immediately following administration is desirable. Resuscitation equipment including atropine should also be readily available to counteract the cardiac side effects of excessive cholinergic tone.

The final disposition of poisoning cases should be an admission in the intensive care unit. Besides the therapeutic measures, other aspects also need to be addressed. A poison control center must be informed and a psychiatry consultation to be sought in cases of intentional self-harm. Elderly population must be educated about the fact that taking multiple medications carries a risk of anticholinergic side effects. Parents must be educated to keep common OTC drugs out of reach of children. People should also be made aware that commonly prescribed drugs, such as cold medications and sedatives, should not be consumed at doses more than prescribed. The key points of treatment are given in **Table 4**.

DISPOSITION

Patients with anticholinergic toxicity with mild symptoms can be discharged to home after a 6-hour observation in the ED. The rest of the patients with anticholinergic toxicity should be hospitalized till the resolution of symptoms or 12 hours after receiving the physostigmine.

SUMMARY

Always consider anticholinergic toxicity in patients taking multiple medications, especially the elderly; hence, polypharmacy should be ruled out. Always consider anticholinergic toxicity in young children who present somnolent or lethargic. Remember the mnemonic "*red as a beet, dry as a bone, blind as a bat, mad as a hatter, hot as a hare, stuffed as a pipe*." There is as such no confirmatory testing readily available in the emergency setting. Anticholinergic toxicity is a clinical diagnosis.

TABLE 4: Key points for anticholinergic toxicity treatment.

Intervention/Drug	*Action*	*Rationale*
Activated charcoal	For gastrointestinal decontamination	Decreased intestinal motility may enhance its effect
Sedation	Benzodiazepines	Strongly recommended to avoid injury in an agitated patient, risk of hyperthermia and rhabdomyolysis can be avoided
Sodium bicarbonate	Wide complex tachyarrhythmias	Severe cases of anticholinergic toxicity present with wide complex arrhythmias due to sodium channel blockade
Cholinesterase inhibition	Physostigmine	Used in severe anticholinergic toxicity with severe agitation and unresponsive to other therapies

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CHAPTER

Antidepressant Antipsychotic

Devendra Richhariya

INTRODUCTION

Antidepressants and antipsychotics are the two most commonly prescribed drugs so emergency physicians should be aware of their potential side effects, multidrug exposure, overdose effects, and toxicity by both therapeutic doses and intentional ingestions.

ANTIDEPRESSANT

Depression is probably one of the oldest diseases of mankind and *Papaver somniferum* is the oldest antidepressant. It was postulated that cerebral monoamine neurotransmitter deficiency is the cause of depression. But now depression is observed as a complicated picture of receptor-neurotransmitters biochemistry and gene expression. Over the years, many pharmacological agents have also evolved to treat the many symptoms of depression.

Antidepressants are drugs that are used in depressive illness for the elevation of the mood. Generally, all antidepressants act directly or indirectly by affecting the monoaminergic transmission in the brain. Over the last two decades, various antidepressants are available and classified (**Table 1**) on the basis of reuptake/metabolism of biogenic amines or pre/post aminergic/cholinergic receptors.

Monoamine oxidase inhibitors (MAO-I) and tricyclic antidepressants (TCA) are considered first-generation antidepressants and their use has declined over the years and have been largely replaced by the newer, second-generation, atypical, serotonergic antidepressant which has a unique pharmacological effect on serotonin–norepinephrine dopamine modulation in the brain.

OVERDOSE AND TOXICITY

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are the first-generation antidepressant and are currently used to treat only atypical and refractory cases of depression as newer antidepressants have better and favorable side-effect profile, less toxicity on overdose, and no dietary restrictions. Isocarboxazid, selegiline, rasagiline, moclobemide, and phenelzine are a few examples of the MAO-I. Tyramine reaction, serotonin syndrome, and medication incompatibilities are associated with MAO-I, and "even one pill can kill" the pediatric age group population.

There is no typical presentation of symptoms of MAO-I overdose and toxicity, and symptoms' presentation is also delayed 6–12 hours (even 24 hours) after ingestions. Headache, agitation irritability, nausea, palpitation, and tremor are the initial presentations. Tachycardia, hyperreflexia, hyperactivity, fasciculation, dilated pupil, nystagmus, and flushing are the *early signs of toxicity*. Muscle rigidity, chest pain, hypertension, diarrhea, hallucination, confusion, and agitation are the features of *moderate toxicity*. Coma, seizures, hypotension, hypoxia, bradycardia, and hyperthermia are the features of

TABLE 1: Practical classification of antidepressants.

Tricyclic antidepressant (TCA)	*Atypical antidepressant*	*Selective serotonin reuptake inhibitors (SSRIs)*	*Serotonin/norepinephrine reuptake inhibitors (SNRIs)*
• Monoaminoxidase inhibitors (MAO-I) and TCA are considered first-generation antidepressants • Amitriptyline, imipramine, clomipramine, trimipramine, doxepin, dothiepin • Nortriptyline, desipramine, amoxapine, reboxetine	• Also known as newer/second-generation/serotonergic antidepressants • Bupropion, mirtazapine, nefazodone • Trazodone, vilazodone, vortioxetine	• Citalopram, escitalopram, fluvoxamine, fluoxetine • Sertraline, paroxetine	• These are also called nonselective inhibitors of serotonin and norepinephrine • Desvenlafaxine, duloxetine, levomilnacipran, venlafaxine

severe toxicity. QT prolongation is specific to moclobemide overdose and toxicity.

Tyramine Reaction

Tyramine is an exogenous dietary amine present in a small amount in many foods but in a high amount in pickled and fermented dietary products. It is normally metabolized by the intestine and hepatic monoamine oxidase, and this process prevents tyramine from entering into the blood. But this process is lost by nonselective MAO-I and gives rise to tyramine reaction. Tyramine reaction is rapid onset within 15–60 minutes of ingestion of amine-containing food. The severity of the reaction depends on the amount of tyramine-containing food ingested. Severe occipital or temporal headache is a typical symptom of tyramine reaction. Other features are hypertension, palpitation chest pain, pallor, neck stiffness, diaphoresis, and mydriasis. Within 6 hours, most symptoms resolve without any treatment but in rare cases, some fatality is reported due to myocardial infarction and intracranial hemorrhage. Electrocardiogram (ECG) should be performed in cases of chest pain and computed tomography (CT) of the head should be performed if a severe headache is reported. Severe hypertension is treated with phentolamine 2.5–5 mg IV every 5–15 minutes until blood pressure is controlled. A rapid-acting direct vasodilator, nitroprusside, can be used 1–4 μg/kg/min IV infusion.

Tricyclic Antidepressant

Although the popularity of TCAs has decreased in recent years, they remain a frequent cause of drug exposure and overdose, in most cases requiring emergent medical care. TCAs are associated with more drug-related deaths than any other class of prescription medication. The relatively low exposure-to-death ratio of TCAs underscores their low therapeutic index and potential for severe toxicity resulting in death. In addition, they are prescribed frequently for other psychiatric and medical conditions such as obsessive-compulsive disorder, attention-deficit disorder, panic and phobia disorders, anxiety disorders, eating disorders, chronic pain syndromes, peripheral neuropathies, nocturnal enuresis, migraine headache prophylaxis, and selected drug withdrawal therapy.

Pediatric and adolescent use has increased significantly over the past few years. The five most commonly reported TCAs involved in drug exposures include (1) amitriptyline (40%), (2) imipramine (17%), (3) doxepin (14%), (4) nortriptyline (12%), and (5) desipramine (6%).

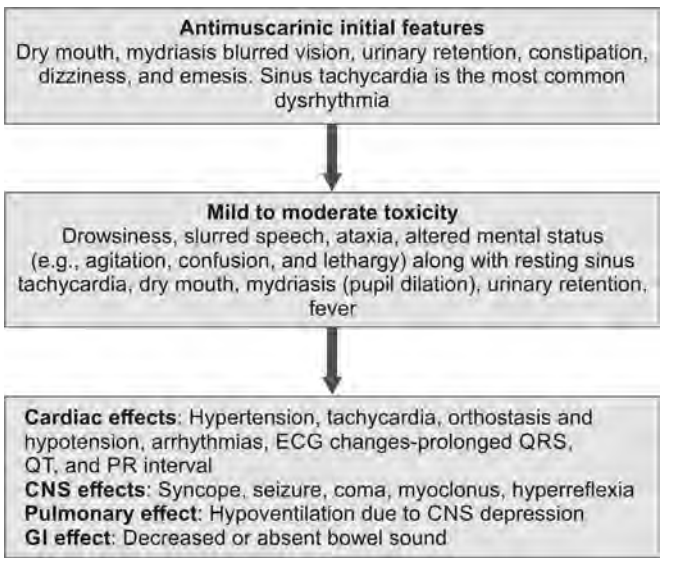
There are different possible *mechanisms for developing TCA-related drug toxicity* while taking therapeutic doses. *First*, mild-to-moderate toxicity will develop commonly if unacclimated individuals are started on higher therapeutic doses. *Second,* toxicity can result when TCAs are combined with other medications having similar pharmacologic actions (e.g., antihistamines, antipsychotics). *Third,* in the population in which TCAs metabolize slowly, higher plasma TCA levels achieved for any given dose. *Fourth,* drug combination formulations with either benzodiazepines or antipsychotic agents have the potential for additional drug toxicity. *Fifth,* patients with comorbidity conditions, such as underlying heart problems or seizure disorders, are more susceptible to TCA toxicity at therapeutic doses. *Sixth*, TCAs with other serotonergic medications produce serotonin syndrome.

Clinical Features and Diagnosis of Tricyclic Antidepressant Toxicity

Tricyclic antidepressant at a therapeutic dose of <1 mg/kg is not toxic. Ingestion of >10 mg/kg TCA is life-threatening. Geriatric and pediatric age group population; patients on cardiotoxic, sedative, and antipsychotic drugs; and patients with an underlying heart and neurologic disease are at a higher risk of developing TCA toxicity (**Flowchart 1**). A combination of the following four criteria is essential for the diagnosis of TCA toxicity: (1) history of TCA drug intake, (2) clinical features, (3) typical ECG findings, and (4) positive urine drug screen for TCA.

Atypical Antidepressant

Atypical antidepressants are also known as *second-generation or newer antidepressants,* and most of them pose serotonergic activities. They are the most popular form of psychopharmacological therapy for major depression, obsessive-compulsive disorder, panic disorder, and eating disorder. *Second-generation, newer or atypical serotonergic antidepressants* are less severe toxic in overdose and are less fatal than TCA and MAO-I. These groups have serotonergic activities and the potential to cause *serotonergic syndrome* in combination with other serotonergic agents. These classes of drugs do not produce tyramine reaction (do not inhibit monoamine oxidase) and also not much inhibition of the cardiac, sodium, calcium, or potassium ion channel. Generalized overdose and toxic symptoms are dizziness, tremor, nausea, vomiting, tachycardia, agitation, and mild hyperthermia. Seizure is more common in bupropion toxicity in comparison to another atypical antidepressants. ECG changes, hypotension, coma, and cardiac arrest are also reported in severe bupropion toxicity. Central nervous system (CNS) depression (dizziness and ataxia) is significant in trazodone atypical antidepressant. Drug-induced priapism is also noted in trazodone atypical antidepressant.


Antimuscarinic initial features
Dry mouth, mydriasis blurred vision, urinary retention, constipation, dizziness, and emesis. Sinus tachycardia is the most common dysrhythmia
Mild to moderate toxicity
Drowsiness, slurred speech, ataxia, altered mental status (e.g., agitation, confusion, and lethargy) along with resting sinus tachycardia, dry mouth, mydriasis (pupil dilation), urinary retention, fever
Cardiac effects: Hypertension, tachycardia, orthostasis and hypotension, arrhythmias, ECG changes-prolonged QRS, QT, and PR interval
CNS effects: Syncope, seizure, coma, myoclonus, hyperreflexia
Pulmonary effect: Hypoventilation due to CNS depression
GI effect: Decreased or absent bowel sound

(CNS: central nervous system; ECG: electrocardiogram; GI: gastrointestinal; TCA: tricyclic antidepressant)

FLOWCHART 1: Features of TCA toxicity.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitor (SSRIs) are a class of drugs that are typically used as antidepressants in the treatment of major depressive disorder and anxiety disorders. SSRIs are the group of antidepressants that act by inhibiting the presynaptic serotonin reuptake without much affecting norepinephrine and dopamine reuptake. They are associated with fewer overdose toxicity and other unwanted pharmacological actions as compared to TCA. Citalopram, escitalopram, fluoxetine, and sertraline are the commonly used SSRIs for depression.

Patients on SSRI complain about various adverse effects such as nausea, vomiting, diarrhea, and constipation. Neurological symptoms such as headache, dizziness, weakness, sedation, fatigue, and tremor are also reported. Extrapyramidal symptoms such as dystonic reaction, akathisia, dyskinesia hypokinesia, and Parkinsonism are also associated with SSRI therapy. Serotonin syndrome is the most serious drug-related adverse effect of SSRI. Fluoxetine is widely used and there is more clinical experience about overdose features. Agitation, seizures, hallucination, hypertension, and hypotension are less frequently observed and all SSRIs show a high therapeutic index. QT and QRS prolongation is more frequently associated with citalopram and escitalopram ingestion.

Serotonin/Norepinephrine Reuptake Inhibitors

Serotonin/norepinephrine reuptake inhibitors (SNRIs) are nonselective inhibitors of serotonin and norepinephrine uptake and no direct effect on presynaptic or postsynaptic neurotransmitter receptors. SNRIs cause tachycardia, hypertension, diaphoresis, tremor, and mydriasis which are the initial clinical features. Altered consciousness and mild-to-moderate sedation are common and progression to coma is rare. Generalized seizure and subclinical rhabdomyolysis are observed in venlafaxine overdose. Severe left ventricular dysfunction and low ejection fraction are observed in large overdose of venlafaxine. Sinus tachycardia and prolonged QRS and QT interval are common ECG abnormalities.

TREATMENT

General Management

Evaluation of the patient should be started by history-taking and physical examination. Altered mental status, hemodynamic status, and respiratory distress should be evaluated. Establish the peripheral venous access and start the intravenous fluid. Start monitoring the cardiac rhythm and take the 12-lead ECG. Arterial blood gas analysis is recommended in a symptomatic patient. Laboratory investigations such as serum electrolyte, creatinine, and blood glucose are recommended. Bladder catheterization (in case of urinary retention as antimuscarinic effect) and nasogastric tube placement (in case of ileus) is recommended. Symptoms generally appear late in initially asymptomatic patient so the patient should be monitored.

Gastrointestinal Decontamination

If the patient is awake, then patent airway and arrival to the emergency department within 1 hour of ingestion are recommended. Activated charcoal of 1 g/kg single dose should be given orally. Activated charcoal bind with TCA and help in decreasing the absorption. An asymptomatic patient with a reliable history of antidepressant overdose can be treated only with activated charcoal. Observe him/her for toxicity.

Sodium Bicarbonate

Cardiac arrhythmias (sinus tachycardia, QT and QRS prolongation in ECG) and hypotension are common in moderate-to-severe antidepressant toxicity. Sodium bicarbonate ($NaHCO_3$) is used to treat refractory hypotension and cardiac dysrhythmias. A bolus dose of $NaHCO_3$ 1–2 mEq/kg followed by repeat dose should be given till the patient improves and blood pH is between 7.50 and 7.55. Instead of repeat boluses, $NaHCO_3$ infusion can also be started (150 mEq mixed with 1 L of 5% dextrose and infusion at the rate of 2–3 mL/kg/h). Monitor serum electrolyte during $NAHCO_3$ infusion (hypokalemia is a concern).

Altered Mental Status

A diminished level of consciousness is more frequent and rapid onset in TCA overdose. Pulmonary aspiration is common in this situation. Cardiotoxicity and seizure can be precipitated. Agitation can also be observed and can be controlled by reassurance and benzodiazepine.

Seizures

Seizures are common in the early hours of the ingestion of TCA. A detailed neurological examination should be carried out if there is repeated seizure or status. Status is particularly associated with two antidepressants, maprotiline and amoxapine. The anticonvulsant of the choice in these conditions is benzodiazepine (diazepam and lorazepam). Barbiturates are used to treat benzodiazepine-resistant seizures. Endotracheal intubation may be required in case of respiratory depression.

Hypotension

Isotonic crystalloid fluid should be started initially as bolus 10–30 mL/kg by keeping in mind pulmonary edema in impaired cardiac contractility. Intravenous $NaHCO_3$ should be considered in hypotension refractory to intravenous fluid. A vasopressor should be considered if there is hypotension refractory to both fluid and $NaHCO_3$. Other supportive therapies such as circulatory and cardiopulmonary bypass, overdrive pacing, and aortic balloon pump should be considered if hypotension refractory to all the above measures is present.

Dysrhythmias

Among all antidepressants, TCA affects heart rate conduction and contractility much more than any other group of antidepressants. Drug-induced cardiotoxicity is increased by coexisting factors such as acidosis, hypotension, respiratory depression, and seizure. First-degree atrioventricular (AV) block should be monitored closely as this may progress to complete heart block. In TCA overdose induced isolated QRS prolongation or/with minimal toxicity, the use of $NaHCO_3$ is controversial but ventricular arrhythmia is treated with $NaHCO_3$. In situations such as renal failure, pulmonary edema, and cerebral edema, where $NaHCO_3$ cannot be used, hyperventilation is an alternative therapy, though it is less effective. Hypertonic saline 3% (1–3 mL/kg over 10 min) is considered if ventricular arrhythmia refractory to $NaHCO_3$

therapy is present. Magnesium sulfate 2 g intravenous is used to treat the torsades de pointes. Overdrive pacing is considered for refractory tachyarrhythmias. All, class I and class III, antiarrhythmic β blockers and calcium channel blockers are contraindicated in TCA-induced dysrhythmias.

Lipid Emulsion

Lipid emulsion therapy is considered beneficial in antidepressant (TCA) induced toxicity because TCAs are highly lipid-soluble. At present, no convincing evidence is present for use of lipid emulsion in antidepressant (TCA) toxicity. In TCA-induced cardiotoxicity which is refractory to other measures, 20% lipid emulsion is used. A *dose* of 100 mL (1.5 mL/kg) IV bolus over 2–3 minutes is given followed by infusion 18 mL/min (total dose 10 mL/kg).

SEROTONIN SYNDROME

Serotonin is a neurotransmitter and found in the dietary intake of tryptophan and helpful in alteration of various clinical statuses such as sleep, anxiety, depression, appetite, emesis, movement disorder, and platelet function. Serotonin syndrome occurs due to the presence of excess serotonin in the blood which overstimulates the serotonin receptors in the central and peripheral nervous systems. Antidepressants (**Table 1**) are the most common drugs which are associated with serotonin syndrome. Serotonin syndrome can be life-threatening and produced by any drug or combination of serotonergic medications. Serotonergic medications other than antidepressants which have the potency to cause serotonin syndrome are *amantadine, amphetamine, bromocriptine, carbamazepine, cocaine, dextromethorphan, fentanyl, levodopa, lithium, linezolid, tryptophan, lysergic acid diethylamide, metoclopramide, pentazocine, sumatriptan, other triptans, and tramadol.*

Serotonin syndrome is a triad of altered mental status (altered cognition and behavior), abnormal neuromuscular activity, and autonomic instability. Most of the patients develop serotonin syndrome at the therapeutic doses of serotonergic drugs. Clinical features are classified into minor or major categories.

Minor clinical features are *cognitive*: insomnia, restlessness anxiety; *autonomic*: tachycardia, hypertension/hypotension, tachypnea, mydriasis; and *neuromuscular*: incoordination, akathisia. Major clinical features are *cognitive*: altered mental status, agitation; *autonomic*: hyperthermia, diaphoresis; and *neuromuscular*: muscular rigidity, hyperreflexia, myoclonus, tremor.

Serotonin syndrome develops within 2–24 hours of ingestion of serotonin medications and symptoms range from mild to severe (**Box 1**). Diagnosis of serotonin syndrome is only based on the history of ingestion of medication, clinical features, and ruling out other medical and psychiatric conditions, as no confirmatory laboratory tests for the diagnosis of serotonin syndrome are available. Differentiating features of serotonin syndrome from the neuroleptic malignant syndrome (NMS) and anticholinergic toxicity are given in **Box 2**.

BOX 1: Severity of serotonin syndrome.

***Mild*:** Mild agitation, mild fever (<40°C), tremor, myoclonus, hyperreflexia, diaphoresis, mydriasis, tachycardia, and hypertension

***Moderate*:** Marked agitation, hyperthermia (>40°C), myoclonus, hyperreflexia, ocular clonus

***Severe*:** Hyperthermia (>41°C), delirium, marked muscular rigidity, marked fluctuation in blood pressure, and heart rate

BOX 2: Differentiating features of serotonin syndrome, neuroleptic malignant syndrome, and anticholinergic toxicity.

- **Serotonin syndrome**
  - H/O serotonergic medication, onset of symptoms within 24 h
  - Myoclonus tremor and hyperreflexia
- **Neuroleptic malignant syndrome (NMS)**
  - H/O dopaminergic agonist intake or withdrawl, take days to weeks to develop symptoms
  - Bradyreflexia, bradykinesia lead pipe rigidity
- **Anticholinergic toxicity**
  - H/O anticholinergic agents, symptoms develops within 1–2 h
  - Dry skin and mucous membrane, reflexes, and muscle tone are normal

(H/O: history of)

Treatment

Discontinuation of serotonergic drugs and initiation of supportive care are the basic treatment. All patients should be hospitalized and seriously ill patients need intensive care and few patients may require endotracheal intubation and mechanical ventilation. Cardiac monitoring, peripheral venous access, and intravenous fluid should be started immediately. ECG should be obtained. External cooling measures should be applied for hyperthermia (the most common cause of death is hyperthermia). Patients with muscle rigidity, seizure, and hyperthermia should be observed for rhabdomyolysis and metabolic acidosis. *Benzodiazepine* is used to control agitation, promote muscle relaxant, and enhance patient comfort. A short-acting intravenous antihypertensive (nitroprusside and esmolol) is used for severe hypertension. A vasopressor (norepinephrine or epinephrine) is used for fluid-resistant hypotension. *Cyproheptadine* (antihistamines and serotonin antagonist) available in oral form only can be used 12 mg initially and then 2 mg every 2 hourly till improvement is seen. Supportive clinical evidence is not available for cyproheptadine use in serotonin syndrome. *Chlorpromazine* is available in a parenteral form and reported to cure serotonin syndrome but causes hypotension which is the potential disadvantage.

Usually, patients with serotonin syndrome improved within 24 hours of holding the serotonergic drugs, and future inclusion of serotonergic drugs should be avoided.

ANTIPSYCHOTICS

First-generation (typical) antipsychotics were introduced in clinical practice in 1950s for the use of positive symptoms of schizophrenia only (hallucination and delusion) and not useful for negative symptoms (apathy poverty of thought, withdrawal, poor motivation). First-generation antipsychotic has limited use and is associated with a high noncompliance rate and

treatment failure because of severe extrapyramidal side effects and tardive dyskinesia. During 1980s, second-generation or atypical antipsychotics were used. These agents have the ability to treat positive as well as negative symptoms of schizophrenia and less propensity to develop extrapyramidal symptoms and tardive dyskinesia. Traditionally, antipsychotics were termed *major tranquilizers or neuroleptics*. These drugs were used to treat other conditions as well such as nausea, vomiting, agitation, headache, suppressing the hiccups, and controlling involuntary motor disorders.

Antipsychotics effects are mediated through various receptors: Dopaminergic, α adrenergic muscarinic, histaminergic, and serotonergic. All antipsychotics bind and inhibit pre- and postsynaptic dopamine-2 (D_2) receptors.

- *First-generation (typical) antipsychotics*: Chlorpromazine, prochlorperazine, haloperidol, fluphenazine, trifluoperazine, promethazine, thioridazine
- *Second-generation (atypical) antipsychotics*: Clozapine, risperidone, olanzapine, quetiapine, ziprasidone
- *Third-generation antipsychotics*: Aripiprazole, brexpiprazole, cariprazine

The most common adverse effects due to antipsychotic overdose are CNS depression, miosis hypotension, and reflex tachycardia. Single-drug overdose is rarely fatal. CNS effects are lethargy, ataxia, dysarthria, confusion, and coma with respiratory depression. ECG changes are QT prolongation, QRS widening, and nonspecific T-wave abnormalities. Diagnosis is established by history of ingestion of antipsychotics. The following supportive laboratory tests should be performed: Blood chemistry, pregnancy test in females of childbearing age, and acetaminophen and salicylate levels if there is a history of coingestion. Perform ECG to evaluate QT interval and QRS complex.

Treatment

Treatment is generally supportive, start intravenous fluid. Cardiac monitoring, pulse oximetry, and blood glucose assessment should be considered. Consider naloxone or thiamine.

*Benzodiazepin*e, e.g., lorazepam in case of seizures, can be administered. Treat hypotension initially with the intravenous fluid and in fluid-resistant case with phenylephrine and norepinephrine.

Magnesium sulfate ($MgSO_4$) is used 2 g intravenous over 10 minutes in a patient with QT_C interval > 500 ms (is at an increased risk of developing torsades de pointes). A patient of torsades de pointes should be treated with $MgSO_4$ 2 g IV bolus followed by 2–4 mg/min. Overdrive pacing is used in refractory cases. $NaHCO_3$ is used (1–2 mEq/kg IV bolus followed by repeat boluses or continuous infusion) to treat intraventricular conduction delay (prolonged QRS) and ventricular dysrhythmias. Lidocaine can be used as an alternative for ventricular arrhythmia. Antiarrhythmic drug such as class 1A, 1C, III (amiodarone) and class IV should be avoided in antipsychotic-induced conduction abnormalities and ventricular dysrhythmias (they may potentiate cardiotoxicity).

EXTRAPYRAMIDAL SYMPTOMS

All groups of antipsychotics can produce extrapyramidal symptoms (*consist of four symptoms: (1) Acute dystonia, (2) akathisia, (3) tardive dyskinesia, and (4) drug-induced parkinsonism)*. First-generation (typical) antipsychotics are known to cause more potent extrapyramidal symptoms than second- and third-generation antipsychotics. Acute dystonia and akathisia develop early in course of therapy and are reversible while tardive dyskinesia and drug-induced parkinsonism develop after prolonged antipsychotic therapy and are unlikely to be reversible.

Acute Dystonic Reaction

There are unpleasant adverse effects of dopamine-blocking agents such as antipsychotic, antiemetics, and antidepressant drugs. These are sudden involuntary contraction of muscle or group of muscles while maintaining the normal mentation and usually occur few days to week of starting the medications. Face, tongue, neck, trunk, back, and extremity muscles are commonly affected. Treatment is by administration of drugs with central anticholinergic activities, diphenhydramine (25–50 mg IV) and benztropine (1–2 mg IV) followed by diphenhydramine 25–50 mg orally and benztropine 1–2 mg orally for 2–3 days.

DRUG-INDUCED HEAT STROKE

Heat stroke is triad of hyperpyrexia (core temperature > 41.1°C), anhidrosis, and disturbance of CNS. Temperature above 41.6–42°C causes significant systemic injury and over 49°C it almost causes immediate cell death and tissue necrosis.

Heat-related illnesses are more common in an individual with a psychiatric illness or on antipsychotic medications and in the elderly population. Anticholinergic medications also increase the risk of drug-induced heat stroke. Suppressed function of the thermoregulatory center in the anterior hypothalamus and loss of sweating ability are the main pathophysiologic mechanisms for the development of drug-induced heat stroke. Early recognition of drug-induced heat stroke is essential; it is also important to differentiate early from NMS. Early cooling is essential, otherwise there will be a high risk of progression of condition to multiorgan failure. The core temperature should be maintained between 38.5 and 39°C. Hypotension usually responds to cooling and intravenous crystalloid should be used for hypotension. Refractory hypotension is an ominous sign.

NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome is a rare but fatal idiosyncratic drug reaction and is due to drug overdose. NMS usually develops soon after starting/adjusting the antipsychotic drugs, and the serum level of antipsychotic drugs remains in the therapeutic range. All typical and atypical antipsychotics can produce NMS.

Neuroleptic malignant syndrome presents with hyperthermia, muscular rigidity, autonomic dysfunction, and altered mental status. Other features are akinesia, tremor, dystonia dysphagia, dyspnea, diaphoresis, sialorrhea, incontinence, tachycardia, fluctuation of blood pressure, flushing, and pallor. Two important laboratory findings are important: (1) Leukocytosis (total leucocyte count 10,000–40,000/μg/L), and (2) Elevated serum creatine phosphokinase (CPK) level. The diagnostic criteria are summarized in **Box 3**. NMS is confused with the serotonin syndrome where the onset is rapid (2–24 hours) and associated features are

BOX 3: Diagnostic criteria for neuroleptic malignant syndrome.

***Minor features*:** Muscle cramps, tremors, tachycardia, tachypnea, hypersalivations, and increased creatine kinase (>4 times of upper limit)

***Major features*:** Hyperpyrexia >38°C (100.4°F), lead pipe muscle rigidity, psychomotor slowing altered mental status, sympathetic nervous system lability, fluctuation hypertension, urinary incontinence, recent history of dopamine agonist, withdrawal of dopamine antagonist, exposure

***Exclusion criteria*:** Rule out infectious, toxic, metabolic, or neurologic causes

nausea, vomiting, diarrhea, shivering, hyperreflexia, and less pronounced muscle rigidity and fever.

Treatment is largely supportive. Antipsychotic or any other culprit medications should be withdrawn. Any other medical conditions with similar features should be evaluated and ruled out. Sedation with benzodiazepine (lorazepam) is important to decrease the agitation and sympathetic activity. Cooling measure is applied to patient temperature in hyperpyrexia, and antipyretics are generally not beneficial. Excessive secretion, dysphagia, decreased airway reflexes, and acidosis hypoxia lead to compromise in airway and breathing, which should be anticipated and patient should be intubated and ventilated. Neuromuscular paralysis and intubation are helpful in reducing the fever and rigidity. Nondepolarizing agents (rocuronium) are preferred over depolarizing agents (succinylcholine) when a patient of NMS is intubated. Other agents used to decrease the severe muscular rigidity are *dantrolene* 1.0–2.5 mg/kg loading followed by 1 mg/kg IV every 6 hourly or *bromocriptine* 2.5 mg orally 3–4 times per day or amantadine 100 mg orally 3 times per day. Mortality in NMS is largely due to complications related to severe muscular rigidity. Muscular rigidity should be promptly reduced to avoid complications such as rhabdomyolysis, renal failure, respiratory failure, disseminated intravascular failure, and cardiovascular collapse.

SUMMARY

Antidepressants and antipsychotics are the two most commonly prescribed drug classes. Several adverse reactions are also reported due to either therapeutic doses or intentional overdoses of antidepressants or antipsychotics. Most of the time, a patient presents with no symptoms or mild symptoms which require no treatment or observation in the emergency department for few hours before discharge. Rarely a patient requires intensive care management. It is expected from an emergency physician to be aware of pharmacology, toxicity, and management of antidepressant and antipsychotic exposure.

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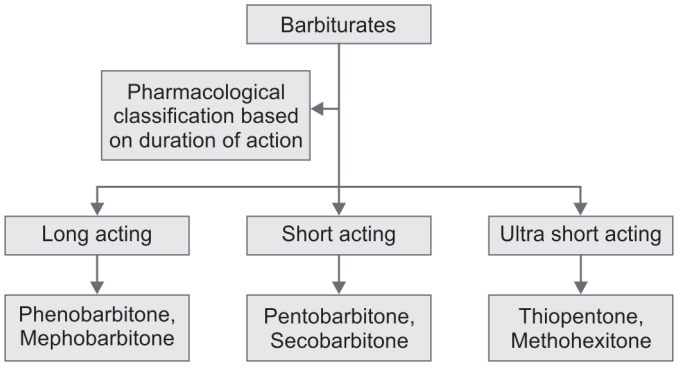
CHAPTER

Anticonvulsants Barbiturates and Phenytoin Toxicity

Vivekanshu Verma

BARBITURATES

Barbiturates are effective as anxiolytics, hypnotics, and anticonvulsants but have physical and psychological addiction potential as well as overdose potential among other possible adverse effects. They have largely been replaced by benzodiazepines and nonbenzodiazepines ("Z-drugs") in routine medical practice, particularly in the treatment of anxiety and insomnia, due to the significantly lower risk of addiction and overdose and the lack of an antidote for barbiturate overdose. Despite this, barbiturates are still in use for various purposes: in general, anesthesia, epilepsy, treatment of acute migraines or cluster headaches, acute tension headaches, euthanasia, capital punishment, and assisted suicide. Phenobarbital has extensive use as an antiepileptic drug in the neonatal and pediatric population (**Flowchart 1**). It is the most cost-effective drug treatment for epilepsy in adults in low-resource countries. Intravenous barbiturates have been used for neurosurgery due to the reduction in cerebral metabolic rate of oxygen consumption. For individuals with severe traumatic brain injury (TBI), high-dose barbiturates may be a consideration but are not indicated for prophylactic administration. In a review of practice in five European countries, about 20% of patients received barbiturates. In the treatment of refractory status epilepticus, a Cochrane review found that thiopental was equally effective as propofol for control of seizure activity.



FLOWCHART 1: Pharmacological classification based on the duration of action of barbiturates.

Thiopental was introduced in 1934 for induction of anesthesia for general anesthesia. Thiopental was the predominant intravenous (IV) anesthetic induction agent until its replacement by propofol. Because of its use in lethal injection protocols, the major supplier of thiopental elected to discontinue production in 2011.

Methohexital has demonstrated safety and effectiveness for procedural sedation of short duration for cardioversion, pediatric outpatient surgery, emergency department fracture reduction, and sedation for elective intubation in neonates. Methohexital has preferential use in electroconvulsive therapy due to its longer seizure duration. Phenobarbital has frequent use in the pediatric population; half-lives range between 59 and 182 hours. Both methohexital and thiopental may be administered rectally in pediatric, particularly if the child is unable to cooperate in IV needle insertion.

Epidemiology

Acute barbiturate toxicity may occur as the result of an intentional or unintentional overdose. Barbiturates have a history of abuse; the Health Department data showed 8,469 cases of barbiturate poisoning in the period between 1957 and 1963.

Pathophysiology

Phenobarbital is known to be an inducer of the cytochrome enzyme system, specifically the 1A2, 2B6, 2C9, and 3A4/5 isozymes, that will reduce the efficacy of warfarin, steroids, oral contraceptives, psychoactive, and immunosuppressants. Phenobarbital will also lower the plasma concentrations of other antiepileptic drugs such as lamotrigine, oxcarbazepine, phenytoin, tiagabine, and valproate. Thiopental and thiamylal have been shown to release histamine, while methohexital and pentobarbital have minimal histamine release.

Clinical Features

Overdosage of phenobarbital symptoms includes central nervous system (CNS) depression, respiratory failure, and hemodynamic instability. Extravasation of thiopental (a vesicant) may cause severe tissue necrosis.

Diagnosis

Phenobarbital has a narrow therapeutic range of 10–30 mg/L, with 80 mg/L reported as being fatal. A Cochrane review found no clear evidence of a benefit to routine serum monitoring of drug levels for antiepileptic drugs. Dose titration to control seizures was found to be effective.

Treatment

No antidote available for barbiturate overdose. Treatment of an overdose includes supportive care, activated charcoal, and urinary alkalinization (**Flowchart 2**). If extravasation of thiopental occurs, treatment measures include hyaluronidase and phentolamine.

PHENYTOIN TOXICITY

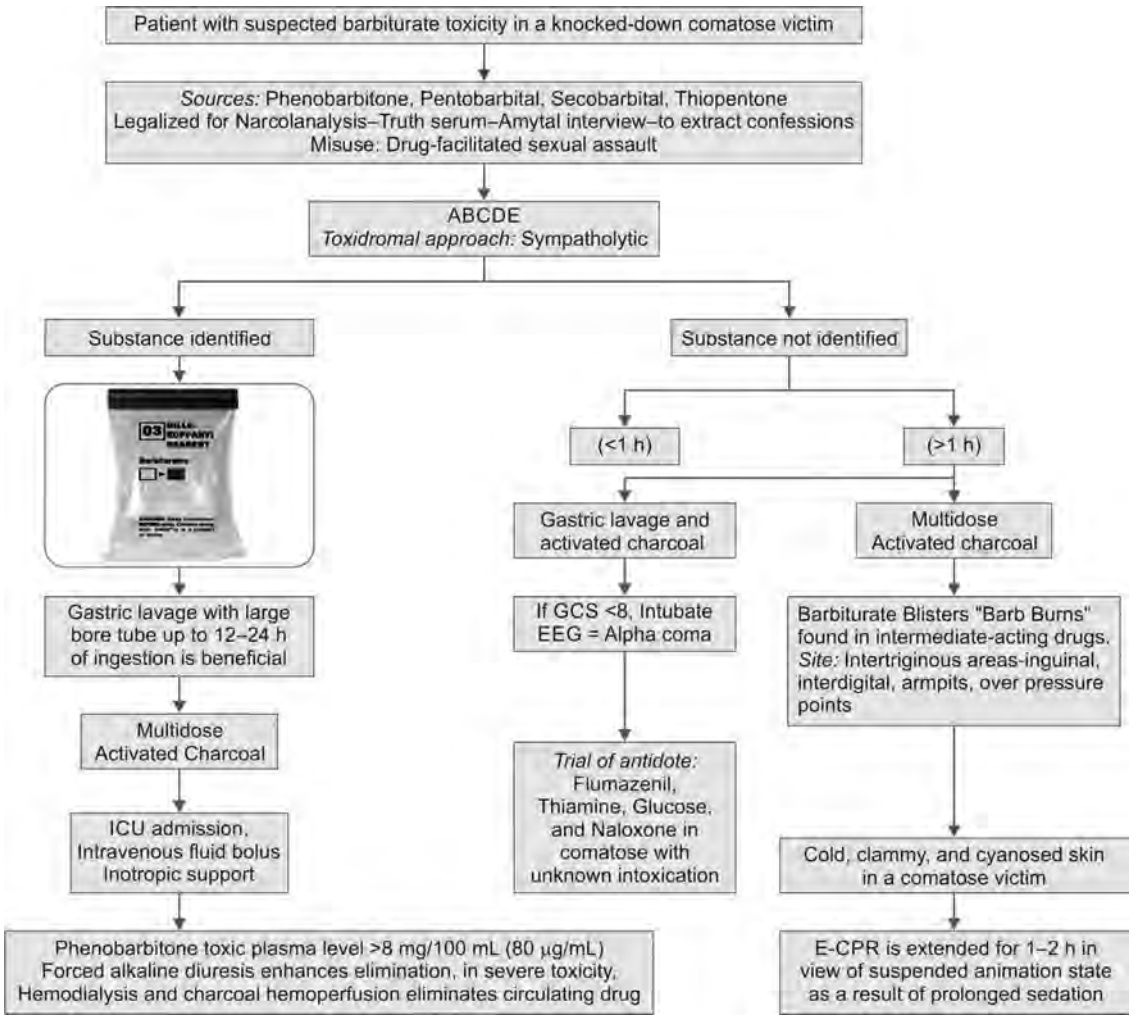
Since its discovery in 1908, phenytoin has become one of the well-studied anticonvulsants. It has also become one of the most widely used anticonvulsants, listed on the World Health Organization's List of Essential Medicines. It has a narrow therapeutic index and it is used daily, considering that potential phenytoin overdose or toxicity from chronic use is vital to early management and prevention of its further toxicity.

Epidemiology

According to the Annual Report of the American Association of Poison Control Centers (AAPCC) National Poison Data System 1971, single-substance phenytoin exposures resulted in 46 major outcomes and 1 death.

Pathophysiology

As in other toxicologic overdoses, the character of the toxicity depends on basic pharmacologic pathophysiology: the route of exposure (oral vs. parenteral), duration of exposure (acute overdose vs. chronic), and dosage, and therefore the nature of metabolism (or deficiency thereof). Phenytoin displays its main signs of toxicity on the nervous and cardiovascular systems. Overdose of oral phenytoin mainly causes neurotoxicity and very rarely causes cardiovascular toxicity. On the other hand, cardiovascular toxicity is the main side effect of parenteral administration.


Patient with suspected barbiturate toxicity in a knocked-down comatose victim
Sources: Phenobarbitone, Pentobarbital, Secobarbital, Thiopentone
Legalized for Narcolanalysis–Truth serum–Amytal interview–to extract confessions
Misuse: Drug-facilitated sexual assault
ABCDE
Toxidromal approach: Sympatholytic
Substance identified
Substance not identified
(<1 h)
(>1 h)
Gastric lavage and activated charcoal
Multidose Activated charcoal
Gastric lavage with large bore tube up to 12–24 h of ingestion is beneficial
If GCS <8, Intubate
EEG = Alpha coma
Barbiturate Blisters "Barb Burns" found in intermediate-acting drugs.
Site: Intertriginous areas-inguinal, interdigital, armpits, over pressure points
Multidose Activated Charcoal
Trial of antidote: Flumazenil, Thiamine, Glucose, and Naloxone in comatose with unknown intoxication
ICU admission, Intravenous fluid bolus Inotropic support
Cold, clammy, and cyanosed skin in a comatose victim
Phenobarbitone toxic plasma level >8 mg/100 mL (80 µg/mL)
Forced alkaline diuresis enhances elimination, in severe toxicity.
Hemodialysis and charcoal hemoperfusion eliminates circulating drug
E-CPR is extended for 1–2 h in view of suspended animation state as a result of prolonged sedation

(E-CPR: extracorporeal cardiopulmonary resuscitation; EEG: electroencephalogram; GCS: Glasgow Coma Scale; ICU: intensive care unit)

FLOWCHART 2: Algorithm for managing barbiturate toxicity.

Note: The Dille–Koppanyi reagent turns phenobarbitone, pentobarbital, amobarbital, and secobarbital into light purple.

Clinical Features

Neurotoxicity

The neurotoxic effects are dependent on plasma concentration and may range from mild nystagmus to ataxia, slurred speech, vomiting, lethargy, and eventually coma and death. Paradoxically, at very high concentrations, phenytoin can cause seizures. Symptoms correlate well with the unbound plasma phenytoin concentration. However, this laboratory value is seldom obtained. The following is a loose correlation of side effects with total plasma phenytoin concentrations (the value obtained in most laboratories):

- <10 mg/L: Rare side effects
- 10–20 mg/L: Occasional mild horizontal nystagmus on lateral gaze
- 20–30 mg/L: Nystagmus
- 30–40 mg/L: Ataxia, slurred speech, tremor, nausea, vomiting
- 40–50 mg/L: Lethargy, confusion, hyperactivity
- >50 mg/L: Coma and seizures

Seizures are very rare and usually occur at very high serum concentrations. The presence of seizures in a patient with suspected phenytoin toxicity due to overdose should prompt the search for other ingested toxins or drugs of abuse.

Cardiac Toxicity

Phenytoin is a class IB antiarrhythmic drug, although it is no longer used as an antiarrhythmic by cardiologists. Its effects on the heart's voltage-gated sodium (Na^+) channels can lead to arrhythmias as well as sinoatrial and atrioventricular nodal blocks, although such effects have rarely been reported following ingestion of the oral form. In the intravenous form, the main toxicity is believed to be from its parenteral vehicle—propylene glycol. Propylene glycol is a cardiac depressant and rapid infusions can lead to bradycardia, hypotension, and asystole. Care must be taken so that phenytoin is not administered intravenously at a rate >50 mg/min.

Other Toxicities

"Purple glove syndrome" is an adverse effect that can occur with phenytoin intravenously. It presents with discoloration and worsened edema of distal limbs, which can lead to extensive skin necrosis and limb ischemia. Phenytoin hypersensitivity has also been reported, generally occurring 1 week to 1 month after initiation of therapy. It presents with a raised temperature and skin rash and rarely leads to hepatitis, myocarditis, and pneumonitis.

Phenytoin has suicidal tendency as its adverse effect, but oral phenytoin–related toxicity is rarely fatal. Injectable phenytoin-related toxicity is mainly due to its fast infusion. Extracorporeal therapy such as dialysis is not routinely indicated to remove phenytoin in acute overdose.

As the mortality associated with phenytoin is very small, the primary indication of extracorporeal toxin removal (ECTR) is to reduce morbidity associated with prolonged incapacitating ataxia due to chronic phenytoin toxicity. However, ECTR should not be initiated solely based on a suspected dose of phenytoin ingested or serum phenytoin level.

The EXTRIP (Extracorporeal Treatments in Poisoning) group recommends ECTR to remove phenytoin by hemoperfusion and therapeutic plasma exchange. ECTR is not routinely indicated but in selected patients [chronic kidney disease (CKD) with kidney dysfunction and hypoalbuminemia, which reduce protein binding] with severe toxicity of chronic phenytoin overdose, with prolonged incapacitating ataxia, charcoal hemoperfusion may be helpful in selected patients. Historically, intermittent hemodialysis (IHD) has not shown to be effective in the removal of phenytoin, but with the use of modern high-efficiency filters, especially in the presence of conditions such as kidney dysfunction and hypoalbuminemia (in these selected patients, which reduce protein binding), IHD with albumin supplemented dialysate during modeled continuous hemodialysis may be effective.

Diagnosis

All patients suspected of possible phenytoin overdose should be evaluated with a broad differential in mind. Blood glucose level should be obtained in all patient. An ECG is suggested on all suspected phenytoin overdose patients, especially patients who have received parenteral phenytoin.

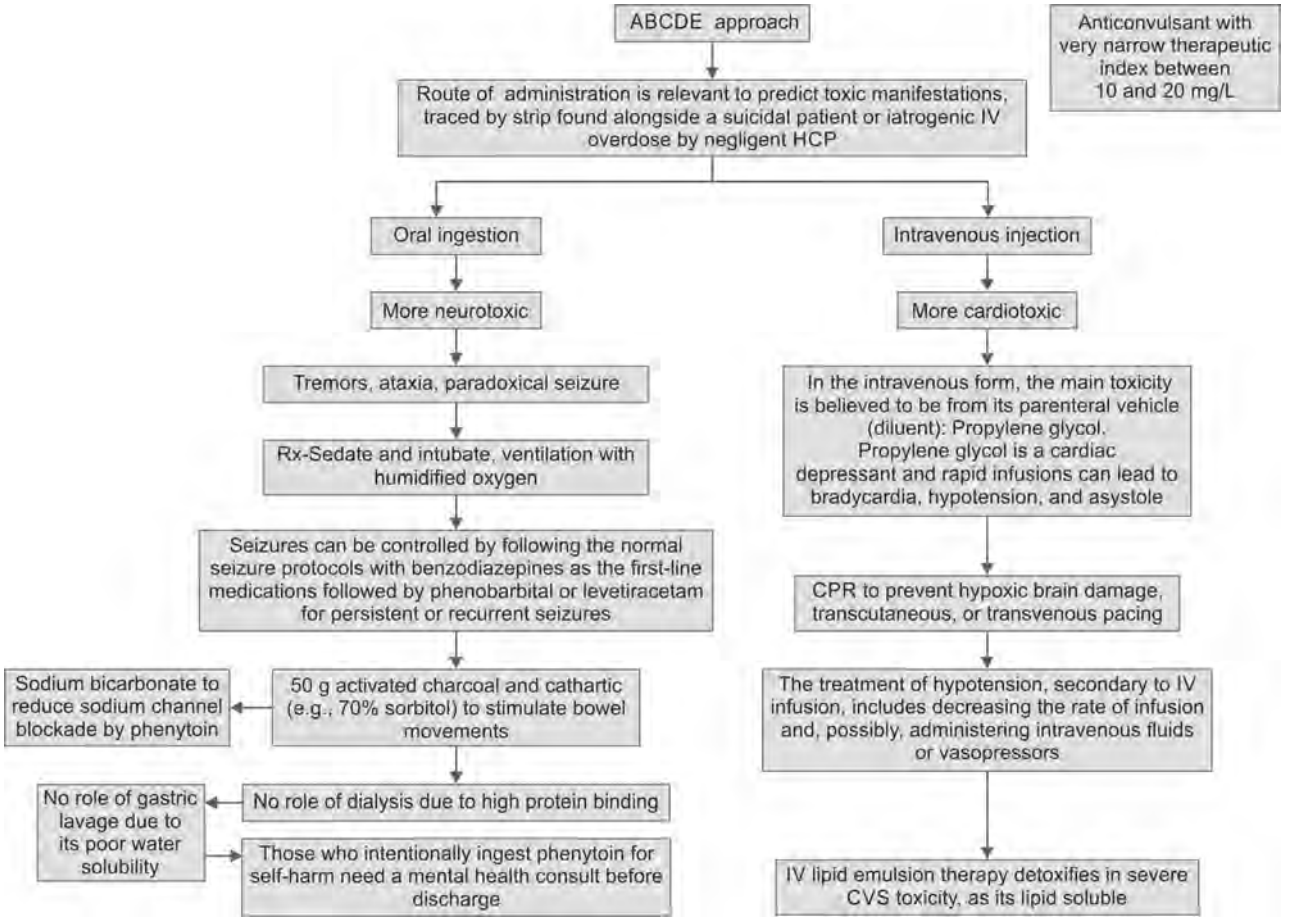
Laboratory work should be obtained including a complete blood count (CBC), basic metabolic panel (BMP), liver function test (LFT), total serum phenytoin concentration, and serum albumin. Urine toxicology, as well as acetaminophen, salicylic acid, and alcohol levels, should also be obtained to complete the toxicological workup. A serum phenytoin level at 10–20 mg/L has a narrow therapeutic window. Serum concentrations of phenytoin are monitored by measuring the total phenytoin concentration. However, phenytoin is generally 90% bound to plasma proteins (mostly albumin), and only its unbound form is pharmacologically active.

Treatment

No specific antidote is available, and the treatment is largely supportive care (**Flowchart 3**). The management of phenytoin toxicity should initially proceed along the lines of the Indian Society of Toxicology Life support (ISTOLS) guidelines of accepted treatment of toxic overdoses. The airway should be assessed, and advanced airway management should be initiated in patients who cannot maintain their airway or respiratory drive. The circulation should be assessed and abnormalities in vital signs addressed. Hypotension can be treated with an initial bolus of isotonic solution. If unresponsive to fluid administration, vasopressors can be initiated with norepinephrine or dopamine being preferred. Bradycardia can also be managed according to standard ISTOLS protocols including atropine, epinephrine and, if needed, transcutaneous or transvenous pacing. Consultation with a medical toxicologist is highly recommended.

Activated charcoal reliably binds phenytoin and prevents absorption. In acute ingestions, one dose of activated charcoal may be of benefit, especially in large acute overdoses, as phenytoin slows gastrointestinal (GI) motility and absorption is delayed. Activated charcoal is also of benefit in acute ingestions of extended-release tablets. Activated charcoal is not recommended if there is a depressed mental state. The role of multidose activated charcoal is controversial. Some studies have shown increased clearance rates although no clinical benefit or improvement in patient outcomes could be demonstrated. Induced emesis, gastric lavage, and whole bowel irrigation are not recommended for phenytoin overdose.

Despite high-plasma protein binding by phenytoin, the drug can be removed by hemodialysis with moderate effectiveness. However, clinical benefits are controversial.


ABCDE approach
Anticonvulsant with very narrow therapeutic index between 10 and 20 mg/L
Route of administration is relevant to predict toxic manifestations, traced by strip found alongside a suicidal patient or iatrogenic IV overdose by negligent HCP
Oral ingestion
Intravenous injection
More neurotoxic
More cardiotoxic
Tremors, ataxia, paradoxical seizure
In the intravenous form, the main toxicity is believed to be from its parenteral vehicle (diluent): Propylene glycol. Propylene glycol is a cardiac depressant and rapid infusions can lead to bradycardia, hypotension, and asystole
Rx-Sedate and intubate, ventilation with humidified oxygen
Seizures can be controlled by following the normal seizure protocols with benzodiazepines as the first-line medications followed by phenobarbital or levetiracetam for persistent or recurrent seizures
CPR to prevent hypoxic brain damage, transcutaneous, or transvenous pacing
Sodium bicarbonate to reduce sodium channel blockade by phenytoin
50 g activated charcoal and cathartic (e.g., 70% sorbitol) to stimulate bowel movements
The treatment of hypotension, secondary to IV infusion, includes decreasing the rate of infusion and, possibly, administering intravenous fluids or vasopressors
No role of gastric lavage due to its poor water solubility
No role of dialysis due to high protein binding
Those who intentionally ingest phenytoin for self-harm need a mental health consult before discharge
IV lipid emulsion therapy detoxifies in severe CVS toxicity, as its lipid soluble

(CPR: cardiopulmonary resuscitation; CVS: cardiovascular; HCP: health care professional; IV: intravenous)

FLOWCHART 3: Algorithm for managing phenytoin overdose and toxicity.

Due to the high-risk nature of hemodialysis, the effectiveness of supportive treatment, and the self-limited nature of acute overdoses, hemodialysis is rarely recommended and should only be used in extreme situations after consultation with a medical toxicologist.

The key to phenytoin toxicity is prevention, which is best done by an interprofessional team. Both the nurse and the pharmacist should educate the patient on the dangers of a drug overdose and the importance of not changing the dose. Those who intentionally ingest phenytoin for self-harm need mental health consult prior to discharge. If the older patient has difficulty reading the label on the vial or not capable of maintaining good hydration while on phenytoin, social work should be involved. In addition, the pharmacist should ensure that there is no polypharmacy and the risk of drug interactions is minimal.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Sedatives Benzodiazepine and Nonbenzodiazepine

Chidrupi Sharma

INTRODUCTION

A sedative is a drug that reduces excitement, anxiety, and responsiveness to any form of stimulation and produces a calming effect on the patient. A sedative drug produces its effect in the form of anxiolysis, hypnosis, amnesia, and sedation, as an anticonvulsant and muscle relaxation. In this chapter, benzodiazepine (BZD) and nonbenzodiazepine sedatives are discussed.

BENZODIAZEPINES

Benzodiazepines are commonly used orally or parenterally. In the emergency department, IV doses are used for seizure control, procedural sedation, and acute psychosis. Oral doses are recommended for anxiety, nervousness, panic disorders, muscle spasms, insomnia, alcohol withdrawal, premenstrual syndrome, etc. (**Table 1**). BZDs when parenterally used, especially in combination with opioids or other sedatives, may cause respiratory depression and hypotension. Parenteral administration of these drugs is always done under the supervision of doctors trained in advanced airway management. BZDs can be classified as short, intermediate, and long-acting BZDs.

- *Short-acting drugs*: Midazolam, alprazolam, oxazepam
- *Intermediate-acting drugs*: Lorazepam, nitrazepam, flunitrazepam
- *Long-acting drugs*: Diazepam, clonazepam, chlordiazepoxide, flurazepam

TABLE 1: Uses of benzodiazepines.

Condition	*Commonly used drugs*
Anxiety disorder	Alprazolam, chlordiazepoxide, clorazepate, diazepam, lorazepam, midazolam
Seizure disorders	Clonazepam, clorazepate, lorazepam, clobazam, diazepam
Insomnia	Estazolam, flurazepam, quazepam, temazepam, triazolam
Procedural sedation	Midazolam, lorazepam
Muscle relaxation	Diazepam
Alcohol withdrawal	Chlordiazepoxide

Mechanism of Action

Benzodiazepines work on the midbrain ascending reticular formation, on limbic systems leading to sedation and anxiolysis, and on the medulla for muscle relaxation. These drugs act by stimulating the α subunit of the γ-aminobutyric acid (GABA) receptors in the central nervous system (CNS), thereby reducing their excitability throughout the CNS, producing sedation, anxiolysis, anticonvulsant effect, and muscle relaxation. These drugs are lipid-soluble. The more the lipophilic nature of the drug, the faster the onset of its action but shorter its duration of activity. The drugs rapidly move into the tissue storage sites such as liver and fat/adipose tissue. Hence, serum levels are not an accurate indicator of the true levels of the drug to assess the duration of action of the drugs. Routes of administration are IM, IV, intranasal, and transbuccal.

Adverse Effects

Benzodiazepines are relatively safe to use. Toxicity is usually seen when used along with other drugs like opioids. Prolonged usage may cause dependence, especially noticed with alprazolam. Abrupt stoppage of the drug can lead to "withdrawal syndrome" which presents with anxiety, insomnia, anorexia, disorientation, confusion, irritability, sleep disorders, delirium, psychosis, and even seizures. Withdrawal may be seen as long as a week after stoppage of the drug. This withdrawal is treated with long-acting BZDs such as clonazepam or other antiepileptic drugs, such as sodium valproate and carbamazepine. Tapering the drug dose gradually is recommended to avoid withdrawal symptoms. Overdose/toxicity is mostly neurological, seen as somnolence, dizziness, ataxia, vertigo, and confusion. Coma as a presentation is seen in combination with other sedative-hypnotic agents. Unusual adverse effects, such as extrapyramidal syndrome and allergic reactions, are very rare.

Benzodiazepine Toxicity

A patient presents with dizziness, confusion, drowsiness, and unresponsiveness/agitation. On examination, there is altered mental status, slurred speech, hypotonia, respiratory depression, ataxia, nystagmus, hypotension, paradoxical agitation, or coma. Differential diagnoses with other sedative-hypnotic drug overdoses, alcohol toxicity, hypoglycemia, stroke, etc., should be kept in mind while examining and planning treatment.

History and clinical examination are the best diagnostic tools for identifying BZD overdose. The patient or the attendants should be asked the time since ingestion, amount consumed, other medications or alcohol consumption along with BZD, history of mental and psychological status, pregnancy status for women in the reproductive age group, any treatment given at home to induce emesis, other comorbid conditions, medications, if any, being used by the patient, etc. Any medication strips seen near the patient or on the scene should be asked to be brought in, as this will help in estimating the dose and the drugs consumed and plan treatment with antidotes and other supportive case and aid in prognosticating the patient's outcome. Examine the patient for injuries, either due to physical abuse or due to self-infliction. A history of accidental or intentional overdosing should be obtained.

Diagnosis

Needlestick glucose levels are done to rule out possible hypoglycemia. Blood, urine, and gastric lavage samples should be sent for toxicological immunoassay screening. Only BZDs that metabolize into desmethyldiazepam or oxazepam are detected in these screening tests, thus leaving a large gray area of undetected BZDs that are not metabolized but maybe present. These are usually performed for medicolegal purposes and the results are not useful in an acute setting. Perform arterial blood gas (ABG) analysis to check for CO_2 narcosis and respiratory acidosis and electrocardiogram (ECG) to check for QT prolongation, tall T waves, and associated drug toxicity, such as tricyclic antidepressants (TCAs). A urine pregnancy test is recommended in all women in reproductive age groups. Renal profile, liver profile, and blood alcohol level examination should be routinely done. A CT scan of the brain is done when there is a strong suspicion of trauma or stroke as a differential for the clinical condition.

Treatment

Airway

In severe toxicity, the patient is very drowsy and can have a threatened airway. Monitor the patient's condition clinically for a compromised airway. Elective intubation with mechanical ventilation should be done as indicated.

Breathing

Respiratory depression leading to hypoxia and hypercarbia can be observed. Supplemental oxygen should be provided. Blood gas analysis should be done repeatedly to guide treatment. Altered mental status and coma can cause aspiration pneumonia. This should be borne in mind before inducing emesis or administering any substance orally or through Ryle's tube.

Circulation

Hypotension is an observed side effect with BZD overdose. Obtain a large-bore IV access. Fluid resuscitation and, if needed, ionotropic support should be provided.

Disability

Systematic repetitive neurologic assessment should be done throughout the stay in the emergency department (ED) and later on to check the effect of treatment on the neurological status. Other clinical conditions mimicking poor neurological status such as stroke, severe head injury, and other conditions leading to raised intracranial pressure (ICP) should be parallelly thought of while assessing a patient with suspected BZD and sedative toxicity.

General Measures

Ryle's tube placement provides access to initiate gastric lavage. Lavage is best effective, especially when done within 1 hour of ingestion of most of the drugs. Activated charcoal is debatably used as poor mentation can make the patient aspirate the gastric contents. Other drug elimination methods, such as hemodialysis and forced diuresis, are not effective. Naloxone can be tried when there is a suspicion of opioid toxicity as a cause for respiratory depression.

Benzodiazepine Antagonist

Flumazenil is a BZD analog having a selective antagonistic effect on BZDs when used in overdose. It antagonizes and abolishes the hypnogenic, psychomotor, and cognitive actions of BZD toxicity. It is commonly used for reversal of coma leading to respiratory depression and anesthesia caused by BZDs during procedural sedation. Flumazenil should be used with caution in cases where there is no clear history of BZDs as a cause of the current clinical condition. Some of the contraindications for flumazenil administration are as follows:

- Overdose with unknown drugs or coingestion of other seizure-inducing drugs
- Chronic BZD use
- Suspected TCA overdose
- Known seizure disorder
- Conditions causing raised ICP such as stroke and head trauma

Flumazenil has high first-pass metabolism and hence is administered intravenously. *Dosage*: It is available as a 1-mg ampoule. IV dose is 0.2 mg repeated to a maximum of 3 mg, repeated every minute and based on the patient's response. Seizures are a side effect of flumazenil administration, especially when there are co-ingestion and toxicity with TCAs. Flumazenil-induced seizures should be treated with phenobarbital or propofol.

Disposition

Admission is warranted for those patients exhibiting signs of severe respiratory depression, hypotension, or significantly altered mental status. Supportive care with effective management of airway, breathing, and circulation (ABC),

administration of antidote, and close monitoring for worsening or improvement of symptoms is done in the ED. Other differentials are worked on and those patients who are still symptomatic or who do not show much improvement are admitted to the intensive care unit.

NONBENZODIAZEPINES

Nonbenzodiazepines are predominantly used in the treatment of acute and chronic insomnia. Described here are four drugs called the "Z drugs:" (1) zolpidem, (2) zopiclone, (3) zaleplon, (4) eszopiclone. The details of the pharmacology of the drug are given in **Table 2**. All Z drugs are only used for the short-term use of insomnia which should last for days to a maximum of 4 weeks.

Zolpidem

Zolpidem is the most commonly used nonbenzodiazepine drug. It is available as tablets for immediate release, extended release, and sublingual use and as an oral spray prescribed specifically for different types of sleep disorders such as difficulty in sleep onset and maintenance or middle of night awakening. Caution should be exercised while prescribing zolpidem and other GABA agonists in this class, for patients with hepatic impairment (precipitates hepatic encephalopathy), chronic obstructive pulmonary disease (COPD), and sleep apnea. Toxicity or overdose presents as dizziness, headache, prolonged reaction time, reduced alertness, drowsiness, hallucinations, etc., "complex sleep behaviors" including sleep-walking, sleep-driving, falls, etc., can lead to very harmful injuries or death, especially in industry workers and drivers. Medications should be stopped immediately if the patient experiences complications. Peak plasma concentrations: 1.6 hours (immediate release), 1.5 hours (extended release), 0.9 hours (spray), 0.6–1.4 hours (sublingual). Elimination half-life is prolonged by about four times in hepatic impairment.

Zaleplon

Zaleplon is a GABA-BZD receptor complex agonist with a duration of action shorter than zolpidem. It is available as 5- and 10-mg capsules and used for short-term insomnia. It should be used cautiously in hepatic impairment. Headache is seen as a common side effect which is treated symptomatically and warrants dose adjustment. It is shown to cause serious complications when used with alcohol, fentanyl, and hydrocodone, and concomitant use is not recommended. Among the Z drugs, zaleplon causes the least adverse effects and withdrawal may be because of its short half-life.

Eszopiclone

Though its mechanism of actions is not clearly known, it is the active isomer of zopiclone. The dosage is available orally as 1-, 2-, and 3-mg tablets. The drug is rapidly absorbed and metabolized in the liver. About 50% of the drug is excreted by decarboxylation from the lungs. Adverse effects are poor coordination, headache, complex sleep disorder, and unpleasant taste, especially seen in the younger population.

Other nonbenzodiazepines such as buspirone, chloral hydrate, γ-hydroxybutyrate, meprobamate, melatonin, and its receptor agonists such as ramelteon and tasimelteon are also some categories of drugs used to treat insomnia.

Overdose/Toxicity

Overdose/toxicity presents as dizziness, CNS depression, drowsiness, coma, confusion, and respiratory depression. Treatment is supportive care with the management of ABCD (airway, breathing, circulation, and disability). Consider activated charcoal at 1 g/kg body weight, if the patient presents within 1 hour of ingestion of the drug. No specific antidote is available for nonbenzodiazepine overdose.

SUMMARY

Nonbenzodiazepine drugs have been shown to have lesser side effects and are more selective than the older benzodiazepine anxiolytic drugs. They produce effective anxiolysis with little or no sedation, anterograde amnesia, or anticonvulsant effects. Dependency and withdrawal syndrome are less with nonbenzodiazepines.

TABLE 2: Nonbenzodiazepine sedatives.

Name	*Time to peak plasma level*	*Oral bio-availability*	*Elimination half-life*	*Dose*	*Time for drug administering before sleep*
Zolpidem	1–2 h	65–70%	1.4–4.5 h	• 5-, 10-mg tablets • 6.25-, 12.5-mg extended-release tablets • 1.75-, 3.5-, 5-, 10-mg sublingual tablets • 5-mg nasal spray called zolpimist	• Immediately before bedtime with 7–8 h before waking • 1.75-mg sublingual tablet to be taken >4 h of sleep remaining in conditions of middle of night awakening
Zopiclone	1.5– 2 h	75–80%	5–6 h	3.75-, 7.5-mg film-coated tablets	Immediately before bedtime with 7–8 h before waking
Zaleplon	0.7–1.4 h	30%	0.9–1.2 h	5-, 10-mg capsules	Immediately before bedtime with 7–8 h before waking
Eszopiclone	1–1.5 h	75–80%	6–7 h	1-, 2-, 3-mg tablets	Immediately before bedtime with 7–8 h before waking

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CHAPTER

Opioids

Olita Shilpakar

INTRODUCTION

Opioid is a term designated for a number of natural substances, originally derived from opium (Greek word: juice of poppy plant, *Papaver somniferum*), and their analogs that bind to specific opioid receptors. *Opiates* are compounds derived from the opioid alkaloids found naturally in the opium poppy plant. Opioids are among one of the widely used drugs since ancient times for sedation and analgesia. In the past few years, opioid abuse is becoming a significant public health issue all over the world resulting in increase of cases of opioid toxicity and opioid overdose deaths.*Opioids are categorized into three forms,* namely (1) naturally occurring compounds (opiates), (2) chemically modified natural compounds (semisynthetic), and (3) completely artificial compounds (synthetic) (**Table 1**). Opioids may act as agonists at all opioid receptors (e.g., morphine and hydromorphone), agonists–antagonists (e.g., pentazocine, butorphanol, nalbuphine) at the opioid receptors and some as antagonists (e.g., naloxone) (**Table 2**).

PATHOPHYSIOLOGY

Opioids act on three major classes of *opioid receptors* which are G protein-coupled transmembrane molecules: μ (mu), κ (kappa), and δ (delta). Stimulation of the μ-receptors results in analgesia, respiratory depression, sedation, miosis, bradycardia, cough suppression, gastrointestinal dysmotility, and euphoria. The κ-receptor stimulation can yield a weaker analgesia, sedation, hallucinations, miosis, and dysphoria whereas the δ-receptors show mood modulation effects along with pain control.

Opioid receptors are distributed throughout the body. Nociception is mediated by the thalamus, amygdala, and the dorsal-root ganglia. Respiratory depression is caused by brain stem opioid receptors along with the dopaminergic neurons which modulate the responses to hypercarbia and hypoxic drive. Stimulation of opioid receptors in the Edinger–Westphal nucleus of the oculomotor nerve controls the pupillary constriction causing miosis. The receptors in the gastrointestinal tract decrease gut motility.

TABLE 1: Categorization and characteristics of opioids.

Types of opioid	*Duration of action (hours)*	*Elimination half-life (hours)*
Opiate		
Codeine	4–6	2.5–4
Morphine	3–4	2–4
Semisynthetic		
Buprenorphine	6–24	20–44
Hydrocodone	4–6	8
Hydromorphone	2–4	2–3
Oxycodone	3–6	3–4
Synthetic		
Fentanyl	1	3–4
Methadone	4–8	12–18
Meperidine	1–3	3–4
Pentazocine	3–4	2–4
Propoxyphene	4–6	6–12
Tramadol	4–6	5–7

TABLE 2: Classification of opioid agonists and antagonists.

Agonists	*Agonist–antagonists*	*Antagonists*
Morphine	Pentazocine	Naloxone
Meperidine	Buprenorphine	Naltrexone
Methadone	Butorphanol	Nalmefene
Hydromorphone	Nalbuphine	
Heroin	Nalorphine	
Fentanyl		
Tramadol		

TOXICOKINETICS

Opiates have a wide diversity of routes of administration, namely intravenous, intramuscular, oral, subcutaneous, buccal, topical, and inhalational routes. When ingested orally, opioids are readily absorbed, achieving peak blood levels within 30–60 minutes following ingestion and up to 90 minutes in sustained-release formulations. Opioid absorption occurs in the small intestine following which they undergo hepatic first-pass metabolism and renal elimination. Different opioids can cross the blood–brain barrier differently due to variability in their lipid solubility. Following nasal insufflation of heroin, peak levels are achieved within 10–15 minutes while intramuscular injection takes about 30–45 minutes and fentanyl patches around 2–4 hours to reach peak levels. In cases of drug overdose, there is alteration in the pharmacokinetics which may increase the severity and duration of action beyond the therapeutic range.

CLINICAL EVALUATION

Clinical Presentation

The classical triad of opioid toxidrome includes respiratory depression, central nervous system depression (CNS), and miosis. These findings may not be consistently present in all the cases and the diagnosis is therefore based on a reliable history and thorough clinical examination.

History

A pertinent history is obtained from family, friends, bystanders, and emergency medical service providers since majority of patients are lethargic or comatose due to opioid overdose. One may find pills, bottles, needles, syringes, and drug paraphernalia. Detailed history regarding the type and quantity of drug ingested and time of ingestion should be ascertained.

Physical Examination

Opioid toxicity characteristically presents with respiratory depression, mental state depression, and pupillary miosis which are considered the hallmarks of the toxidrome. It may encompass with a wide range of clinical findings.

Pulmonary

The most readily recognized abnormality is a decline in the respiratory rate characterized by slow and shallow respirations resulting in hypoxia, hypercarbia, and cyanosis. Morphine overdose may be observed as shallow breathing, hypopnea, bradypnea with a respiratory rate of <12 breaths/min and occasionally with bronchoconstriction presenting with dyspnea, wheezing, and pink frothy sputum.Opioid-induced acute lung injury, previously known as noncardiogenic pulmonary edema, is an infrequent complication of heroin overdose and occurs immediately or up to 24 hours after the ingestion. The pathophysiology of acute lung injury in opioid overdose may be related to a capillary leak phenomenon. Opioid-induced ventilatory impairment (OIVI) is a more complete term comprising opioid-induced central respiratory depression (decreased respiratory drive), decreased level of consciousness (sedation), and upper airway obstruction. All of these may result in decreased alveolar ventilation and increased arterial carbon dioxide levels.

Neurological

Mental state depression is frequently encountered with high doses of opioids. Generalized seizures have been reported in adults, mostly following propoxyphene or meperidine ingestion since opioids can lower the seizure threshold.Young children are also at risk primarily due to paradoxical excitation of the CNS. Neuropsychiatric symptoms such as anxiety, agitation, hallucinations, euphoria, paranoia, and dysphoria may be noted with higher doses. Serotonin syndrome is caused by the combination of opioids such as meperidine and tramadol with selective serotonin reuptake inhibitors and monoamine oxidases and is characterized by hyperthermia, autonomic dysfunction, muscle rigidity, and hyperreflexia.

Eye

Miosis may be present in patients with opioid overdose. Frank mydriasis has also been reported secondary to morphine, meperidine, diphenoxylate, and propoxyphene toxicity along with respiratory depression and cerebral hypoxia.

Skin

Needle track marks in case of intravenous opiate abuse are observed. Morphine and heroin are injected illicitly by street users, subcutaneously known as "skin popping." Poor injection techniques could present with thrombophlebitis, cellulitis, aneurysms, intra-arterial injections, and embolization. Patch marks due to the use of transdermal fentanyl patches could also be observed. Opiates can cause the release of histamine resulting in pruritis, flushed skin, and urticaria.

Cardiovascular

Peripheral vasodilatation may result in orthostatic hypotension. In case of co-ingestion with other drugs, a severe form of refractory hypotension may occur. Ventricular arrhythmias have also been encountered at higher doses.

Gastrointestinal

Nausea, vomiting, decreased gastrointestinal motility, delayed gastric emptying, constipation, and ileus are seen in patients with opioid toxicity.

Others

Other findings include hypothermia, rhabdomyolysis, compartment syndrome, peripheral neuropathy, myoglobinuric renal failure, sensorineural hearing loss, and endocarditis. "Body stuffers" are patients who ingest loosely packaged bags of illicit drugs. Patients who ingest packaged packets of illicit drugs for trafficking purposes are known as "body packers." Heroin is a commonly used drug by both body stuffers and packers. As compared to stuffers, packers may have lethal amounts of drugs in a concentrated form and are at a higher risk of prolonged toxicity.

DIFFERENTIAL DIAGNOSIS

A list of both toxicological and nontoxicological differentials of opioid toxicity is given in **Table 3**.

TABLE 3: Differential diagnosis of opioid toxicity.	
Toxicological	***Nontoxicological***
Clonidine toxicity	Acute hypoglycemia
Benzodiazepine toxicity	Acute subdural hematoma
Barbiturate toxicity	Diabetic ketoacidosis
Sedative-hypnotic toxicity	Hyperosmolar hyperglycemic state
Organophosphate and carbamate toxicity	Meningitis
Cannabinoid toxicity	Pontine and intracerebral hemorrhage
Carbon monoxide toxicity	
Atypical antipsychotics toxicity	

INVESTIGATION

Clinical judgment is of utmost importance in case of opioid toxicity. Laboratory studies or drug screens may aid in the diagnosis but with limitations. A qualitative urine opioid screen can readily detect morphine and its naturally acting counterparts, such as codeine and heroin, which are metabolized to morphine. Positive results can be observed up to 36–48 hours postexposure. False-positive results have been reported in rifampin, diphenhydramine, dextromethorphan, ibuprofen, quetiapine, and fluoroquinolones, presumed to be due to interference with the immunoassay technique.

A chest radiograph should be obtained to evaluate for acute lung injury in case the patient presents with audible wheezes. If a "body packer" or a body stuffer" is suspected, abdominal X-rays might be helpful in making a diagnosis. A 12-lead electrocardiogram should be done to detect any possible cardiotoxicity, e.g., QRS widening or QTc prolongation, as seen in propoxyphene and methadone use.

TREATMENT

Stabilization and Supportive Care

Airway protection and ventilation are the most important measures that should be taken for the stabilization of the patient in the emergency department. Maintain adequate oxygenation and ventilation as required via a bag valve mask, bi-level positive airway pressure, continuous positive airway pressure, or rapid sequence endotracheal intubation and mechanical ventilation with positive end-expiratory pressure.

Decontamination

In case of ingestion of opioids preferably within an hour, oral activated charcoal can be administered at a dose of 1 g/kg body weight. Gastric lavage is not recommended because the risks outweigh the benefits. Whole bowel irrigation can be considered for body packers; however, close monitoring is required because of the high risk of rupture of the packets.

Enhanced Elimination

There are no clinically effective techniques for the enhanced elimination of opioids.

Antidote Therapy

Naloxone is a pure competitive opioid antagonist which has an affinity for μ receptors. It is an oxymorphone derivative which rapidly reverses the effects of opioid intoxication including respiratory depression, CNS depression, and miosis. Naloxone is not effective orally because its bioavailability is minimal but is well absorbed via intravenous, intramuscular, subcutaneous, inhalational, endotracheal, and intranasal routes. The onset of action of naloxone, when administered intravenously, is <2 minutes, the duration of action is between 20 minutes and 2 hours, and the elimination half-life is 60–90 minutes.

An initial dose of naloxone, 0.1–0.4 mg IV, is recommended in patients with CNS depression but with an adequate respiratory status. Subsequent small doses of naloxone of 0.1–0.4 mg IV are administered every 2–3 minutes and titrated until the desired effect is achieved since larger doses can precipitate opioid withdrawal symptoms. If the patient presents with severe respiratory depression, a bolus dose of naloxone, 2 mg IV, should be administered which should be followed by repeated doses of 2 mg IV every 3 minutes till the respiratory depression is reversed or till a maximum dose of 10 mg IV is reached.

In case the symptoms persist or worsen, a continuous naloxone infusion and an endotracheal intubation should be considered. A naloxone infusion dose is calculated as two-thirds of the dose that effectively reversed intoxication, also known as the "wake-up dose," and is administered per hour. Intramuscular, subcutaneous, or intranasal doses can be given as an initial dose of 2 mg and titrated accordingly. The same dose of naloxone is mixed with 3 mL of normal saline and can be used in the nebulized form. Other opioid antagonists are nalmefene and naltrexone which have a longer duration of action and half-lives than naloxone. However, naloxone still remains the antidote of choice for opioid reversal.

DISPOSITION

History and clinical examination are of utmost importance to determine the disposition of cases following opioid intoxication. Patients with opioid toxicity can be safely discharged within 4–6 hours after administration of naloxone if the patient is stable with a normal temperature, respiratory rate of >10 breaths/min, oxygen saturation of >92% in room air, and a Glasgow coma scale of 15. Longer acting or sustained-release opioids and moderate-to-severe overdose patients following multiple doses of antidote require intensive care admission. Psychiatric consultation and behavioral counseling are done prior to discharge of the patient.

OPIOID WITHDRAWAL

Opioid withdrawal occurs when opioids are stopped abruptly in a patient with physiological dependence or following the administration of an antagonist. It is a hyperadrenergic state with symptoms representing the reverse of opioid administration. The initial symptoms start within 6–12 hours of the last opioid use with anxiety, drug craving, yawning, lacrimation, diaphoresis, rhinorrhea, and myalgias which progress to nausea, vomiting, diarrhea, pain abdomen, piloerection, mydriasis, agitation, apprehension, hyperventilation, insomnia, and muscle spasms. These symptoms usually start

6–12 hours following abstinence, peak approximately by the third day, and abate by the fifth day.

Treatment of opioid withdrawal in the emergency room is symptomatic and consists of intravenous fluids and electrolyte replacement along with antiemetics. Administration of an alpha-2-agonist, clonidine, at a dose of 5 μg/kg orally, is known to shorten the withdrawal duration by suppressing the sympathetic hyperactivity. Methadone, a long-acting opioid, is used for maintenance therapy to prevent withdrawal and for treatment in de-addiction clinics.

SUMMARY

Opioids are among the oldest known drugs which refer to any natural, semisynthetic, or synthetic compounds having morphine-like properties. The hallmark of opioid toxidrome consists of respiratory depression, mental state depression, and miosis. The diagnosis is based on clinical evaluation. Management of opioid toxicity comprises airway protection, ventilation, and early administration of naloxone.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Substance Abuse

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HISTORY

Humans have a long history of substance abuse and have used substances for thousands of years. Early civilization used wine from at least the time of the early Egyptians. The earliest recorded use of narcotics dates back to 4000 BC with medicinal marijuana appearing in China around 2737 BC. The extraction of active ingredients from psychoactive substances did not occur until the 19th century.

Substance abuse is a worldwide problem that affects millions of people. It is mainly the young boys and girls who are engaging in drug use for a variety of reasons and many youngsters have already died from the drug use. Substance use poses serious challenges as it affects foremost the health and life of the substance user, then the social well-being of the family, and finally the whole community.

The use of drugs as part of the cultural norms did not create major social problems during traditional periods. However, the types of substance used have been shifted since the last few decades from *Cannabis* to synthetic opiates and chemical substances. Also, the mode of substance uses has changed from smoking/ingesting to injecting and that has become one of the major challenges for infectious diseases such as human immunodeficiency virus (HIV) and hepatitis infections. So, substance abuse has become a multidimensional problem and substance abuse treatment a challenge for the global world.

EPIDEMIOLOGY

In 2017, an estimated 271 million people, or 5.5% of the global population aged 15–64 years, had used substances in the previous year. While this is similar to the 2016 estimate, a longer term view reveals that the number of people who use substances is now higher than it was in 2009. Although that increase was in part due to a 10% growth in the global population aged 15–64 years, data now shows a higher prevalence of the use of opioids in Asia, Africa, Europe, and North America and the use of *Cannabis* in North America, South America, and Asia compared with 2009.

According to the survey, hard drug users have significantly increased in Asian countries. A very large majority of them happen to be young people. Most of the drug users started drug use very early, in fact before they reached 20 years. Only 50% of drug users were employed. *Cannabis* (90.5%), opiates (93.5%), tranquilizers (83.5%), inhalants (12.7%), hallucinogens (8.7%), and stimulants (5.2%) were the drugs used in descending order (**Table 1**). Injecting was again the main mode of drug administration. Peer pressure and curiosity were the main pulling factors for initiation of first-time drug use.

When it comes to tackling challenges inside the emergency room, a variety of stereotypes come to mind in compiling the profile of a substance abuser. Adherence to a belief in these stereotypes is a dangerous trap for the clinician. Physicians are likely to discount the possibility of substance intoxication in

TABLE 1: Commonly abused drugs.

Cannabis (marijuana) (90.5%)	Bhang, charas, ganja, sulfa
Opiates (93.5%)	• Heroin (Brown sugar, Smack, etc.) • Cough syrup (Corex, Phensedyl, etc.) • Pain medication • Propoxyphene (Darvon, Proxyvon) • Buprenorphine (Tidigesic) • Pethidine • Morphine • Pentazocine (Fortwin)
Tranquilizers (83.5%)	• Diazepam (Valium, Calmpose) • Nitrazepam (Nitravet, Dormin, Nitrosun) • Alprazolam (Alprax)
Inhalants (12.7%)	• Dendrite • Paint thinner • Varnish • Petrol
Hallucinogens (8.7%)	• LSD • Ketamine • Acid
Stimulants (sympathomimetic) (5.2%)	• Cocaine • Amphetamines

(LSD: lysergic acid diethylamide)

TABLE 2: Complications of illicit drug use.	
Neurologic	Strokes, SAH, seizures
Cardiac	Endocarditis, arrhythmias
Infectious	• HIV, hepatitis C, hepatitis B, infective endocarditis, STI's syphilis • Botulism, tetanus, osteomyelitis, septic joints • Abscess/cellulitis
Psychiatric	• Anxiety, depression, psychosis, suicide, panic attacks • Social isolation
Traumatic	Penetrating trauma, knife fights, blunt trauma, MVCs

(MVCs: motor vehicle collisions; SAH: subarachnoid hemorrhage; STI: sexually transmitted infection)

a well-dressed professional or in those at the extremes of age, but substance use and abuse span the spectrum of age, sex, economic, and intellectual status. Physicians have a difficult time recognizing such abuse, particularly in patients with chronic pain syndromes. In the emergency room, a patient with chronic pain may not manifest the typical overt sympathetic changes or physical findings of acute pain. Patients may seek treatment because of the perceived failure of their outpatient regimen, because of an acute flare-up, or because of abuse or addiction. Therefore, emergency clinicians constantly walk a tightrope between undertreating legitimate pain and inappropriately rewarding substance abusers with controlled medications.

In assessment and management planning, consider the primary toxic effect of the agent, complications of intoxication, and complications of the administration/injection technique. Complications of a poor injection technique include cellulitis, thrombophlebitis, intra-arterial injection and embolization, mycotic aneurysm, endocarditis, anaerobic infection, and blood-borne virus infection. So, a high index of suspicion is required. Presentation to an emergency department (ED) with acute intoxication or complications of drug use indicates an ongoing hazard and provides an opportunity for intervention (**Table 2**). Patients should be counseled regarding strategies to avoid future overdose and, if willing, should be referred to rehabilitation agencies. The drugs of misuse or abuse most commonly involved in deaths are cocaine, opioids, antidepressants, benzodiazepines, stimulants, and club drugs.

HALLUCINOGENS

Hallucinogens (psychedelics) cause alterations in perception. A hallucination is defined as a perception of an object or sensation that does not exist in reality. Hallucinogens may work by several different mechanisms, including stimulating the serotonergic 5-HT2A receptor, hyperactivation of the dopamine D2 receptor, and blockade of the glutamate *N*-methyl-d-aspartate (NMDA) receptors.

LYSERGAMIDES

Lysergic acid diethylamide (LSD), or acid, is a potent psychedelic drug. Doses of 1–1.5 μg/kg produce psychedelic effects. The typical dose taken for an acid trip is approximately 25–100 μg. LSD is sold as a tablet (microdot), liquid, powder, gelatin square (windowpane), and blotter acid. Sheets of blotting paper are sprayed with LSD, dried, and perforated into small squares. Each sheet is composed of hundreds of squares that are placed sublingually or eaten whole. Massive ingestions are rare.

LSD Blotters (Felix the Cat)

In terms of treatment of lysergamides, if panic attacks occur, proceed with nonpharmacologic and supportive care. Complications include harm to self/others. Look for rhabdomyolysis, seizures, and coagulopathy. Watch out for worsening depression postuse and sedate with benzodiazepam followed by second-line haloperidol for psychosis. Withdrawal symptoms are unknown. More research is needed to find out if behavioral therapies can be used to treat addiction to hallucinogens.

MARIJUANA AND SYNTHETIC CANNABINOIDS

Cannabis in South-East Asia has been used since as early as 2000 BC. In ancient Hindu society, common terms for *Cannabis* preparations include *charas* (resin), *ganja* (flower), and *bhang* (seeds and leaves). South-East Asian drinks, such as *bhang lassi*, are made from *bhang* which is one of the most common legal uses.

Cannabis sativa and *Cannabis indica* plants are some of the earliest plants grown by humans. Bioactive substances derived from these plants are collectively called cannabinoids. Marijuana is smoked, vaporized, or eaten blended into foods. Δ^9-Tetrahydrocannabinol (THC) is the main psychoactive agent of >61 cannabinoid compounds and approximately 300 other substances present in the *Cannabis* plant, and cannabidiol (CBD) is the major nonpsychoactive component. Cannabinoids act primarily at cannabinoid receptors CB1R, found mostly in the central nervous system (CNS), and CB2R, found primarily on peripheral immune cells. The discovery of these cannabinoid receptors and experiences in states with medical marijuana availability have led to an interest in further exploration of the therapeutic potential of cannabinoids.

Clinical Features

Smoking marijuana leads to rapid and predictable signs and symptoms. Ingestion can cause delayed and sometimes unpredictable effects. The most common effects of marijuana smoking include mood changes and typically relaxation and euphoria. A slight rise in heart rate and conjunctival injection are the only reliable physiologic results. Other acute peripheral changes include urinary retention, decreased testosterone levels, and decreased intraocular pressure. Short-term memory is impaired and the ability to perform complex tasks may be adversely affected. Many users report excessive appetite after marijuana use. Peak blood levels occur within 8 minutes of inhalation, with rapid distribution into tissues, especially tissues with a high lipid content. The duration of perceived effects is usually 2–4 hours when the drug is smoked.

Oral ingestion of marijuana edibles may be associated with a longer duration of effect (≥6–12 h), and patients with a

massive oral marijuana ingestion may develop profound ataxia, vomiting, agitation, anxiety, and CNS depression requiring medical care. Edible products often carry high concentrations of THC in relatively small portion sizes and, due to a delayed onset of effect up to 4 hours after ingestion, patients may ingest escalating amounts of the product while awaiting the onset of psychoactive effects.

Though intoxications with marijuana and synthetic cannabinoids may have some similarities, significant differences have been described. First-generation synthetic cannabinoids, such as JWH-018, JWH-073, HU-210, and CP-47, were commonly associated with tachycardia, agitation, nausea and vomiting, altered mentation, and hallucinations. Seizures were also noted with this group of cannabinoids. Second-generation synthetic cannabinoids, such as ADB-PINACA and AB-FUBINACA, have been associated with more profound agitation and aggression, seizures, tachycardia followed by bradycardia, and, less commonly, ischemic stroke and cardiac toxicity. Withdrawal symptoms of marijuana include irritability, trouble sleeping, decreased appetite, and anxiety.

Differential Diagnoses

The presentation that most closely resembles that of marijuana and synthetic cannabinoid intoxication is acute psychosis. Some individuals with underlying and preexisting psychiatric disorders may progress to overt psychosis after heavy or first-time marijuana use. Because marijuana is so readily available, it is commonly a cointoxicant used with ethanol and other psychotropic agents.

Diagnostic Testing

Marijuana screening is rarely helpful in the ED. Urinary metabolites of THC are detectable within 1 hour after smoking of marijuana, but a positive urine test result does not correlate with acute intoxication. A single marijuana cigarette can be detected for 72 hours when a cutoff level of 100 ng/mL is used, and positive urine levels may persist for 3 months after chronic marijuana use.

Management and Disposition

Care of patients intoxicated from marijuana and synthetic cannabinoids consists of prevention of injury and reassurance for those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral administration of benzodiazepines or antipsychotics. Antiemetics (e.g., ondansetron 4–8 mg IV or metoclopramide 10–20 mg IV) may be used to treat nausea and vomiting induced by the cannabinoid hyperemesis syndrome (CHS) associated with the synthetic cannabinoids and heavy, daily marijuana use. Hot showers are often recommended for patients suffering from these symptoms. The precise mechanism whereby hot bathing produces a rapid reduction in the symptoms of CHS is unknown. It has been postulated that hot water may act by correcting the cannabis-induced disequilibrium of the thermoregulatory system of the hypothalamus. Children who are significantly symptomatic may require admission for a 24-hour observation period. Behavioral therapies such as cognitive-behavioral therapy (CBT), contingency management, motivational incentives, motivational enhancement therapy can be used.

AMPHETAMINES

Pharmacology and Pathophysiology

The amphetamines as a class are based on a central structure of phenylethylamine that parallels that of the epinephrine, norepinephrine, and dopamine biogenic amines. Because of the resemblance, amphetamines may be presumed to specifically activate adrenergic receptors. Instead, they act to increase the number of adrenergic neurotransmitters that are released for any given stimulus. This results in higher levels of synaptic excitatory neurotransmission and the clinical effects which follow. Patients on amphetamines present on a spectrum from a mildly "energized" to a full-blown adrenergic crisis.

The central structure of amphetamine is suitable for substitution using very simple chemistry, and amphetamines such as 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine, and "2-bromo-dragonfly" are available. These substances have been synthesized to take advantage of serotonin storage vesicles behavior for greater hallucinogen's "gain". A fairly well-known example is MDMA ("Ecstasy"). MDMA-intoxicated patients may present either as sympathomimetic, as serotonergic or, more likely, as a combination of both. Since these designer amphetamines have some degree of serotonergic activity, a core temperature is of critical importance; these substances can induce hyperthermia directly and interfere with other serotonergic medicines, and interactions with other serotonergic medications [e.g., selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs)] can precipitate serotonin syndrome. The street names of Methamphetamines are Crank, Chalk, Crystal, Fire, Glass, Go fast, Ice, Meth, Speed. Its commercial name is Desoxyn which is used to treat attention-deficit hyperactivity disorder. Its common forms include white powder or pill; crystal meth looks like pieces of glass or shiny blue-white "rocks" of different sizes.

Amphetamines are commonly taken via ingestion, smoking, inhalation, or injection. All are absorbed from the gastrointestinal (GI) system, with peak serum levels within 3 hours. They are weak bases, 20% bound to plasma proteins, and have large volumes of distribution. The half-lives vary between 8 and 30 hours. The main route of elimination is hepatic transformation; however, up to 30% of amphetamine and methamphetamine may be eliminated in the urine.

Amphetamines improve catecholamines release and inhibit their reuptake triggering increased central and peripheral adrenergic receptor activation contributing to sympathomimetic toxidrome. Higher doses bring about central release of serotonin. Substitutions alter the hallucinogenic, behavioral, and cardiovascular effects of the drugs. In overdose, the exact amphetamine may not be distinguishable as effects are more uniform.

Clinical Features

Central nervous system excitation and the peripheral sympathomimetic reaction are primary signs. Euphoria, apprehension, and agitation are common. The patient may present with tachypnoea, mydriasis, tremor, diaphoresis and hyperpyrexia, severe dental problems ("meth mouth"), and intense itching leading to skin sores from scratching. Psychosis can

occur with visual and tactile hallucinations, severe agitation, and paranoia resembling paranoid schizophrenia. Myocardial infarction, aortic dissection, rhabdomyolysis, acidosis, acute cardiomyopathy, shock, renal failure, and coagulopathy are documented. Symptoms may persist for several days. Death is secondary to hyperthermia, arrhythmia, intracerebral hemorrhage, or trauma.

After use of MDMA, hyponatremia with cerebral edema that presents as altered mental status and seizures is documented and can be fatal. Mechanisms that lead to hyponatremia include psychogenic polydipsia and insufficient antidiuretic hormone secretion.

Long-term abuse of amphetamines may be complicated by a necrotizing vasculitis which can involve multiple organ systems and proceed to renal failure, myocardial ischemia, and cerebrovascular disease.

Dependence and withdrawal of amphetamine are recognized. Withdrawal is characterized by neurasthenic symptoms, including somnolence and intense cravings for amphetamines, depression, anxiety, and tiredness. Management is supportive.

Differential Diagnosis

Amphetamine derivative overdose may not be clinically distinguishable from cocaine except for the elevated psychotic symptoms and a longer period of action. The differential diagnosis also includes anticholinergic delirium, serotonin syndrome, alcohol and benzodiazepine withdrawal, sepsis, thyrotoxicosis, and pheochromocytoma.

Clinical Investigations

Physical examination and investigations should be directed at excluding complications and alternative diagnoses. Seizures or coma should prompt investigation for complications, such as intracerebral hemorrhage or electrolyte disturbance. All patients should have a blood glucose measurement.

Treatment

Resuscitation prioritizing immediate life threats should be done. Treatment may be better in a quiet environment, away from unnecessary stimuli. Patients exhibiting psychomotor acceleration or psychosis should be managed with titrated intravenous sedation. Hyperthermia and seizure are important factors which contribute to morbidity and mortality. For effective treatment of hyperthermia and seizures, core temperature should be assessed in all patients and continuous monitoring is recommended if the temperature is elevated. Mild-to-moderate hyperthermia (<39°C) typically responds to benzodiazepine sedation and fluid resuscitation. If temperature continues to rise, intubation and paralysis are indicated. The use of dantrolene is not indicated. Benzodiazepines are first-line therapy for seizures, followed by barbiturates, and then general anesthesia. Seizures in the context of acute hyponatremia require initial rapid sodium replacement. Patients with persistent psychotic features may respond to an antipsychotic agent.

Disposition

The period of treatment in the ED and the need for admission would depend on the severity of intoxication, the effect of co-ingested medications, comorbidities, and complications. Patients with mild intoxication may be observed in the ED and discharged when vital signs and mental status have returned to the normal state. The long half-lives of the amphetamines may dictate inpatient care if symptoms or abnormal vital signs do not resolve within a few hours. Behavioral therapies such as CBT, contingency management, motivational incentives, the Matrix model, 12-step facilitation therapy, or mobile medical application: reSET® can be used.

COCAINE

Pharmacology and Pathophysiology

Cocaine hydrochloride, or benzoylmethylecgonine hydrochloride, is a powder extracted from the leaves of the coca plant Erythroxylon. "Freebase" cocaine is an alkaloid that is prepared by combining hydrochloride of cocaine, water, and baking soda and removing precipitates. If the solvent will evaporate, the crystals of pure cocaine, known as "rock" or "crack," remain. Cocaine reaches the cerebral circulation within seconds after smoking or insufflation. After oral ingestion, GI absorption may not peak for 90 minutes. Cocaine is hydrolyzed by plasma and liver cholinesterase to an active metabolite. About 5–10% of cocaine is excreted in the urine unchanged with a half-life of 60–90 minutes.

Common street names of cocaine are Blow, Bump, C, Coke, Crack, Dust, Flake, Nose candy, Rock, Snow, Sneeze, Toot, White Rock. The commercial name is Cocaine hydrochloride. Unpurified cocaine paste is converted to more usable forms of cocaine. The crystallized freebase of the cocaine alkaloid is known as *crack cocaine*. It is inhaled with the use of a special "crack pipe" designed to tolerate the high temperature required to volatilize pure cocaine. The high lipid solubility and rapid transport from the lungs into the brain contribute to crack's rapid onset of action. The water-soluble salts of cocaine (cocaine hydrochloride and cocaine sulfate) are available as a white crystalline powder that is used intranasally or dissolved and injected intravenously. Oral administration is rare except for patients who are smuggling or concealing drugs.

Cocaine is a CNS stimulant that works through enhanced noradrenaline release, plus noradrenaline, dopamine, and serotonin reuptake blockage. Dysphoria, hysteria, seizures, and coma are accompanied by euphoria with increasing doses. Cocaine stimulates the medullary vasomotor center resulting in hypertension and tachycardia. Small doses may produce transient bradycardia. At high levels, the medullary center may be depressed, leading to respiratory depression.

Peripherally, cocaine blocks the adrenaline and noradrenaline reuptake and induces noradrenaline presynaptic release. This results in a sympathomimetic response mediated by both α- and β-adrenoreceptors resulting in tachycardia, diaphoresis, vasoconstriction, and hypertension. Increased psychomotor activity, vasoconstriction, and direct hypothalamic toxicity, possibly mediated by dopamine receptors, contribute to hyperpyrexia.

Cocaine is an ester-type local anesthetic that blocks fast sodium channels. Hypotension can develop in severe toxicity due to a direct toxic effect on the myocardium. Wide complex tachyarrhythmias with toxicity to cocaine are observed. Sodium channel and potassium channel blockade occur, in addition to sympathomimetic, ischemic, and cardiomyopathic

effects. Arrhythmias are multifactorial; factors include dose, co-exposures, acid-base and electrolyte imbalance, and genetic variability. Transient arrhythmias may account for syncope not attributable to seizures.

Clinical Features

The predominant symptoms are those of excitation in the CNS and sympathomimetic peripheral response. Manifestations of CNS include agitation, impaired mental status, seizures, dyspnea, intermittent neurological focal signs, intracranial hemorrhage, and coma. Cerebral infarction, transient ischemic attacks, subarachnoid hemorrhage, cerebral vasculitis, and migraine-like headache are outlined. Contributing mechanisms include hypertension, vasoconstriction, vasculitis, increased coagulability, altered cerebrovascular autoregulation, and embolization of particulate matter.

Cardiovascular signs include tachycardia, stroke, tachydysrhythmias, supraventricular or ventricular, and syncope. Chest pain may be due to musculoskeletal, pulmonary, or cardiovascular problems. Cocaine-induced myocardial ischemia is multifactorial; increased myocardial oxygen demand, immediate or delayed coronary artery vasospasm, increased platelet aggregation, impaired thrombolysis, and accelerated atherosclerosis all contribute. Aortic dissection associated with cocaine use is reported. A retrospective study of cocaine-intoxicated patients with ischemia-consistent chest pain found that 6% had an acute myocardial infarction.

Smoking cocaine may lead to respiratory complications including thermal airway injury, pneumothorax, pneumomediastinum, noncardiac pulmonary edema, interstitial pneumonitis, and bronchiolitis obliterans. Tachypnea, mydriasis, tremor, diaphoresis, and hyperpyrexia may also be seen. Mesenteric vasoconstriction and vasculitis may lead to bowel ischemia and infarction. Rhabdomyolysis complicated by renal failure and hyperkalemia is reported.

Withdrawal symptoms include depression, tiredness, increased appetite, insomnia, vivid unpleasant dreams, slowed movement, and restlessness.

Differential Diagnosis

The differential diagnosis includes intoxication with other sympathomimetic agents, hallucinogenic agents, anticholinergic delirium, serotonin syndrome, alcohol and benzodiazepine withdrawal, sepsis, thyrotoxicosis, and pheochromocytoma.

Clinical Investigations

The diagnosis is clinical, based on history, sympathomimetic symptoms and signs, and the exclusion of other conditions. Physical examination and investigations are directed at excluding complications and alternative diagnoses. Patients with altered vital signs should have a blood glucose measurement, 12-lead electrocardiogram (ECG), and continuous ECG monitoring.

Treatment

Patients with CNS agitation or cardiovascular sympathomimetic symptoms should get an intravenous benzodiazepine titrated to achieve sedation. Hyperthermia and seizures warrant rapid resuscitation (as in the case of amphetamines) to prevent poor outcomes. Seizures should be managed with benzodiazepines and barbiturates, escalating to general anesthesia if required.

Benzodiazepines, nitrates, and calcium channel blockers reduce hypertension and cocaine-induced vasoconstriction causing chest pain/myocardial ischemia. The use of β-adrenergic receptor blockers in cocaine intoxication is controversial due to the theoretical possibility of unopposed alpha stimulation, which exacerbates hypertension. Combined beta- and alpha-blockade agents (e.g., labetalol) are associated with less complications. Primary angioplasty is the treatment of choice for myocardial infarction due to cocaine-induced ST-elevation. Ventricular arrhythmias should be treated as per Advanced Cardiac Life Support (ACLS) protocol. In addition to defibrillation or cardioversion, intravenous bolus bicarbonate (1–2 mEq/kg) and titrated benzodiazepines are used. One suitable alternative is lignocaine. Ventricular arrhythmias occurring after the acute phase of intoxication are presumed to be secondary to myocardial ischemia and should, therefore, be treated in a standard manner. In patients with nondiagnostic ECG, an investigation should proceed as for nontoxicological chest pain.

Body Packers and Body Stuffers

Body packers are planned; large (usually) amounts of illicit drugs are ingested in their body (usually the GI tract) for the purpose of transport. Body stuffers are unplanned; drugs are ingested without a plan to avoid being caught (usually while being chased by police). Treatment includes cardiac monitoring, whole bowel irrigation with pack count, or immediate transfer to operation theatre if signs of hemodynamic instability, obstruction, or rupture are present. The criteria for discharge include three packet-free stools, reliable packet count consistent with ingestion, and normal contrast study.

Disposition

Disposition depends on the level of toxicity, co-ingested products, complications, and comorbidities. Patients with mild intoxication may be observed in the ED and discharged when the patient is asymptomatic with normal vital signs and mental status. Behavioral therapies such as Cognitive Behavioral Therapy (CBT) contingency management, motivational incentives community based recovery guidance should be introduced.

SUMMARY

Emergency Physicians are at the forefront of recognition of drugs of abuse substances as these are ever changing and involve manipulation of basic chemical structures to avoid legal ramifications. In the era of internet, substances are available from around the world for individuals. Some of these drugs include synthetic cathinone, phenethylamines, piperazines, herbal products, prescription drugs, and many other substances. These substances also known by various common street names. Many drugs of abuse result in psychoactive and sympathomimetic effects with excited delirium. Regardless of the street name or chemical formulations, drug ingested, the mainstay of management includes symptom-based goal directed supportive care with benzodiazepines as useful adjunct.

MULTIPLE CHOICE QUESTIONS

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207 CHAPTER

Alcohol

Ajay Singh Thapa, Devendra Richhariya

INTRODUCTION

Alcohol is one of the most available and consumable fermented drinks worldwide. There are several alcohols (e.g., ethanol, methanol, isopropyl glycol), which consist of at least one organic compound of the hydroxyl functional group (–OH) bound to a saturated carbon atom. The word "alcohol" is derived from the Arabic *kohl* (Arabic: الكحل, Romanized: *al-kuḥl*), a powder used as an eyeliner. The meaning of alcohol was extended to distilled substances in general and then narrowed to ethanol, when "spirits" was a synonym for hard liquor.

Alcohol (ethanol), which is a neuropsychoactive substance, causes numerous systemic effects on the nervous system as well as on other organs and systems. Its effects depend on the percentage of concentration, dose ingested, genetic factors, and the behavior of the consumer. The potential effects of alcohol include impairment in attention, cognition, and dexterity. It also causes aggressive impulses and loss of behavioral control and life-threatening alcohol poisoning. Alcohol intoxication is a major public health issue and plays a large role in alcohol's contribution not only to the global burden of disease through its role in alcohol-related injuries, including intentional injuries, but also to other health conditions that lead, e.g., to cardiovascular deaths.

ALCOHOL INTOXICATION

Globally, an ethanol intoxication is associated with numerous complications, including road-traffic accidents, domestic violence, homicide, and suicide. Preventable death from alcohol poisoning remains a major public health concern. Alcohol is one of the ancient fermented brews that existed at least as early as 10000 BC. In ancient India, alcohol was distilled and used between 3000 BC and 2000 BC as a Sura.

In recent contemporary societies, alcoholic beverages are considered as a routine part of the social lifestyle in most of the populations of the world. Alcohol has considerable toxic effects on the digestive and cardiovascular systems. Alcoholic beverages are classified as carcinogenic by the International Agency for Research on Cancer and increase the risk of several cancer types. Alcohol, as an immunosuppressant, increases the risk of infectious diseases, including tuberculosis and human immunodeficiency virus (HIV).

Epidemiology

Worldwide alcohol consumption contributes to around 3 million deaths each year as well as to the disabilities and poor health of millions of people. Generally, unsafe use of alcohol is responsible for 5.1% of the global burden of disease. Harmful use of alcohol is accountable for 7.1% and 2.2% of the global burden of disease for males and females, respectively. Alcohol is one of the leading risk factors for premature mortality and disability among the working population aged between 15 and 49 years.

Disadvantaged and especially vulnerable populations have higher rates of alcohol-related death and hospitalization. The amount of lifetime alcohol use and a combination of circumstance, frequency of alcohol consumption, and the amount consumed per occasion increase the risk of the various range of health and social harms. The substitutes and illegally fermented alcohols can cause an extra health risk from toxic contaminants. The World Health Organization is currently developing an action plan (2022–2030) to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority.

Pathophysiology

Ethanol (CH_3CH_2OH) is a water-soluble, low molecular weight, hydrocarbon that rapidly crosses cell membranes. Absorption of ethanol occurs via the gastrointestinal system, primarily in the duodenum and the remainder of the small intestine (~80%) and stomach (~20%). When the stomach is empty, peak blood ethanol levels are reached between 30 and 90 minutes after ingestion.

The primary pathway of ethanol metabolism occurs in the liver via alcohol dehydrogenase (ADH). ADH is also located in the gastric mucosa. The enzyme is found in decreased quantities in women. Less "first-pass metabolism," combined with a smaller volume of distribution, may explain the enhanced vulnerability of women to acute complications of ethanol intoxication. Ethanol is metabolized to acetaldehyde by ADH. Acetaldehyde is metabolized to acetate by acetaldehyde dehydrogenase (ALDH). Acetate is used by the muscle cells to produce acetyl-CoA using the enzyme acetyl-CoA synthetase, and the acetyl-CoA is then used in the "Kreb's cycle." Hypoglycemia occurs due to ethanol's inhibition of

gluconeogenesis, especially in children, and may cause lactic acidosis, ketoacidosis, and acute kidney injury.

In the central nervous system (CNS), alcohol enhances the inhibitory neurotransmitters γ-aminobutyric acid type A (GABA-A) receptor, 5-HT3 receptor, and glycinergic and cholinergic receptors causing sedative effect followed by coma and respiratory failure. It also inhibits excitatory neurotransmitters such as N-methyl-D-aspartate (NMDA), dihydropyridine-sensitive L-type calcium channel, and G-protein activated inwardly rectifying K^+ channels leading to the behavioral and symptomatic effects of alcohol intoxication.

Clinical Presentation

A patient's clinical features depend on the amount of alcohol and time of consumption as well as on the percentage of alcohol in the beverages. The clinical picture of intoxication levels differs from person to person and in the same person from time to time. The condition of liver functions may alter the presentation of disease due to their ability to metabolize to the acetoacetate by ADH enzymes. A picture of an average intoxicated person is given in **Table 1**.

TABLE 1: Blood alcohol concentration and related clinical presentation.

Blood alcohol concentration (BAC)*	***Clinical presentation***
0.00–0.05	Most of these people appear clinically normal. Some of them have a euphoria. Reaction time is slowed down two times
0.05–0.10	Loss of inhibitions, self-criticism, and exaggerated self-confidence. Loss of concentration and normal judgment. Affected coordination. Reaction time is slowed down four times
0.10–0.15	Further loss of self-criticism, emotional instability, memory problems. Early ataxia, apraxia, and agraphia. Reaction time is slowed down further. Orientation concerning time, place, and person may be affected
0.15–0.25	Ataxia, agraphia, apraxia. Coordination severely affected. Loss of orientation. Emotional instability. Balance disturbances. Apathy and emotional eruptions. Numbness and slowed reaction to pain stimuli. Partial amnesia
0.25–0.35	Worsening of the above-mentioned. Total loss of muscle coordination. Apathy and sometimes stupor. Total loss of orientation. Amnesia
0.35–higher	Stupor followed by coma. General anesthesia and paresis. Suppression of the vital centers in the brain with cardiorespiratory collapse and death

*To convert serum ethanol level (mg/dL) to BAC, move the decimal point three places to the left. For example, a 100-mg/dL serum ethanol level is equivalent to a 0.10 (g/dL) BAC or 0.10% (weight/volume). This means that one tenth of 1% of blood in their body is alcohol or a person has 1 part alcohol per 1,000 parts blood.

Diagnosis

There are various nonspecific clinical features, which may cause difficulty to identify the intoxication. However, the Diagnostic and Statistic Manual of Mental Disorders (DSM-5) elaborated the criteria for the diagnosis as follows:

- Recent ingestion of alcohol
- Clinically significant problematic behavioral or psychological changes (e.g., inappropriate sexual or aggressive behavior, mood liability, impaired judgment) that developed during, or shortly after, alcohol ingestion.
- One (or more) of the following signs or symptoms developing during, or shortly after, alcohol use:
  - Slurred speech
  - Incoordination
  - Unsteady guilt
  - Nystagmus
  - Impairment in attention or memory
  - Stupor or coma
- The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

The definitive diagnosis is based on the measurement of blood alcohol concentration (BAC). In some countries, the law enforcement officers may use the breathalyzer test for a rapid test as an alternative. Alcohol intoxication is often defined as a BAC of >5.4–17.4 mmol/L (25–80 mg/dL or 0.025–0.080%). This can be measured by blood or breath testing. Alcohol is broken down in the human body at a rate of about 3.3 mmol/L (15 mg/dL) per hour.

Management

Acute intoxication of alcohol is an emergency due to the risk of death from aspiration of vomit, and respiratory depression occurs while the patient is unresponsive. The management of acute toxicity is good supportive care. In the emergency department (ED), gastric lavage is not advocated because it may be harmful and cause aspiration and death. The activated charcoal is not useful because it does not bind and adsorb the alcohol in the gastrointestinal tract. Utmost important in ED is to maintain and secure the airway by basic airway management (chin lift and jaw thrust) or endotracheal intubation followed by mechanical ventilation. Circulation failure and dehydration must be prevented by giving intravenous fluids. Hypoglycemia is a major problem as it inhibits gluconeogenesis and causes complications such as CNS depression, pancreatitis, and local phlebitis. Hypoglycemia should be corrected and euglycemia should be maintained.

Metadoxine, also known as pyridoxine-pyrrolidone carboxylate, administered orally at 500–1,000 mg/day or parentally at 300–600 mg/day enhances elimination of alcohol from blood and improves the clinical conditions. The role of vitamin B1 (thiamine) in chronic alcohol is to prevent Wernicke's encephalopathy (WE) secondary to thiamine deficiency. It is also beneficial in acute intoxication. WE is characterized by abnormal mental status, ataxia, and nystagmus and requires daily treatment with thiamine, 100 mg intravenously every 6 hour, until a normal diet is resumed. Pyridoxine 50 mg/6 hour inhibits the metabolism of glyoxylic acid and favors the formation of less toxic metabolites.

Hemodialysis can be considered in life-threatening situations, e.g., blood alcohol concentration >400 mg/dL, pH <7.1 despite sodium biocarbonate infusion and coma.

Prognosis depends on the initial alcohol blood level and overall general physical conditions. Heavy alcohol consumption may cause memory loss and adverse health conditions. A normal liver detoxifies the alcohol over a period of time and improves the clinical conditions if given good supportive care.

ALCOHOL WITHDRAWAL SYNDROME

Ethanol is a CNS depressant and in low concentration, it produces euphoria and behavioral excitation (increase glutamate binding with the NMDA receptors). But by ingestion of a high concentration of ethanol, acute intoxication occurs due to GABA effects through delta subunit of the receptors. Cerebellum, cortical areas, thalamic relay circuitry, and brainstem are mainly involved in acute intoxication. Tolerance and physical dependence develop with prolonged use of ethanol. GABA receptor downregulation increases glutamate production by NMDA to maintain CNS neurotransmitter hemostasis. Sudden stopping of chronic alcohol consumption results in autonomic overactivity and neuropsychiatric complications, such as delirium and seizures, by unmasking these compensatory changes with a glutamate-mediated CNS excitation.

Clinical Features

Alcohol withdrawal syndrome (AWS) occurs due to sudden stopping or reduction of chronic alcohol consumption which gives rise to a wide variety of clinical presentations ranging from nausea and vomiting, loss of appetite, diaphoresis, insomnia, tachycardia, anxiety, craving, hand tremors, fever, agitation, and hyperexcitation to more concerning features such as hallucination, seizures, and delirium tremens (DTs; **Table 2**). Alcohol withdrawal starts after 6 hours of stopping the alcohol consumption and symptoms may last for 10–15 days.

Chronology of the Symptoms

Symptoms start around 6 hours after cessation or decrease in intake and last up to 4–48 hours (early withdrawal). Hallucinations of visual, tactile or auditory qualities, and illusions while conscious are symptoms of moderate withdrawal. They can last up to 6 days. The appearance of acute symptomatic seizures may emerge 6–48 h after the last drink. 19 DT (onset 48–72 h after cessation of drinking) represent characteristics of severe withdrawal that may last for up to 2 weeks (late withdrawal). The chronological development of the various symptoms is illustrated in **Figure 1**.

Diagnosis of Alcohol Withdrawal Syndrome

The DSM-5 outlines diagnostic criteria for AWS using two main components so that the AWS is diagnosed when the following two conditions are met: (1) A clear evidence of cessation or reduction in heavy and prolonged alcohol use, and (2) The symptoms of withdrawal are not accounted for by a medical or another mental or behavioral disorder.

TABLE 2: Common signs and symptoms of alcohol withdrawal syndrome.

Symptoms	*Signs*
Autonomic symptoms	Tachycardia, tachypnea, dilated pupil, hypertension fever, nausea and vomiting, diarrhea, diaphoresis
Motor symptoms	Hand tremors, tremulous, body ataxia, seizure, gait disturbance, dysarthria, hyperreflexia
Awareness symptoms	Irritability, insomnia, agitation, delirium, disorientation
Psychiatric symptoms	Anxiety, illusion, delusion, hallucination, paranoid ideas, disinhibition, combativeness
Time-dependent evolution of alcohol withdrawal symptoms	• 6–24 h (minor symptoms): Nausea and vomiting, anxiety, tremor • 24–36 h: Alcohol withdrawal hallucinations, mostly tactile • >36 h: Withdrawal, seizures, GTCS single or multiple • >48 h: Delirium tremens—agitation, disorientation, hallucination

(GTCS: generalized tonic-clonic seizure)

Useful Markers in an Emergency Department Setting

According to various studies, a high-risk patient with severe AWS (DT) can be predicted on the basis of medical history or a history of similar events, and if the patient is unconscious, laboratory markers are helpful in suspected cases. The quantitative, measurable detection of drinking is important for the successful treatment of alcohol-use disorder (AUD). Therefore, the importance of direct and indirect alcohol markers to evaluate consumption in the acute clinical setting is increasingly recognized. A summary of relevant markers in the emergency setting is given in **Table 3**. Severe alcohol withdrawal symptoms should be differentiated from hyponatremia, hepatic encephalopathy, infections (pneumonia, meningitis) thyrotoxicosis, head injury, psychosis, and drugs intoxication (tricyclic antidepressant, lithium, atropine).

Neuroimaging is recommended to rule out any other neurologic condition, especially those associated with first-onset seizures or generalized tonic-clonic seizures.

Tools for Predicting and Assessing Severity of Alcohol Withdrawal Symptoms

The PAWSS (Prediction of Alcohol Withdrawal Severity Scale) is the first validated tool to identify patients at risk for severe alcohol withdrawal symptoms such as seizure and DT. This will help in starting prophylaxis for AWS before severe symptoms occur. There are several validated scales for the assessment of symptoms and pharmacotherapy intervention. Practicability and objectiveness depend on the qualitative and quantitative awareness of the patients. If a patient is uncooperative or

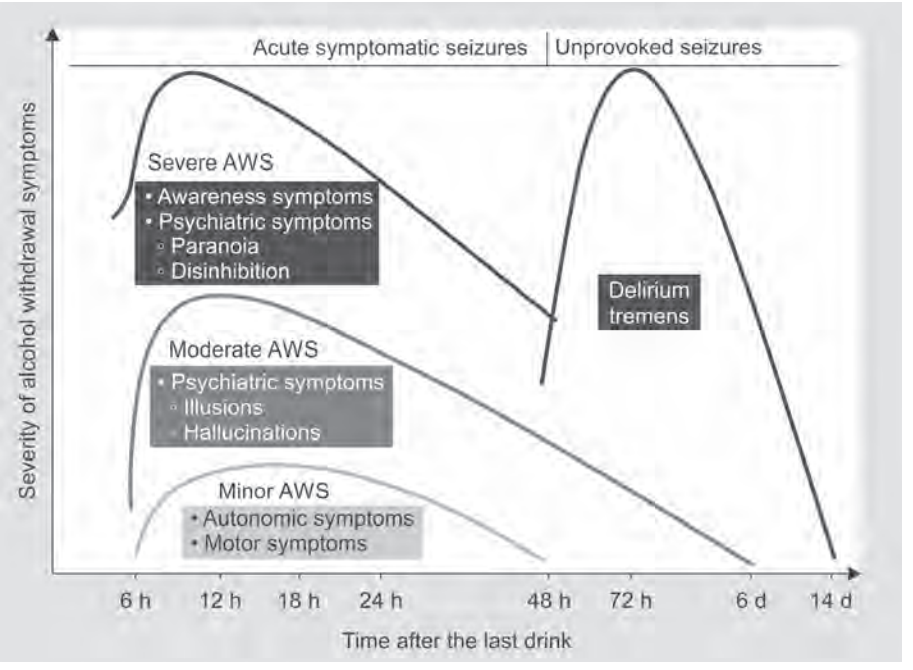

FIG. 1: Chronological development of the alcohol withdrawal symptoms (AWS).

TABLE 3: Relevant markers of alcohol-use disorder in an emergency department setting.

Markers	***Significance***
Ethanol	Estimated in breath, blood urine up to 6–24 h, 90–95% specificity
Hypokalemia	Estimated in blood up to days to weeks, 40% specificity. Serum levels <2.5 mEq/L indicates alcohol-use disorders
Thrombocytopenia	Estimated in blood up to days to 10–12 days, 70–75% specificity. Rebound thrombocytosis after cessation of alcohol abuse
Mean corpuscular volume	Estimated in blood up to days to months, specificity 80%, dose-dependent increase
γ-glutamyl transferase	Estimated in blood up to days to weeks, specificity 80%, marker of liver injury due to alcohol-use disorder
Ratio AST/ALT >2	Estimated in blood AST 18 h ALT 36 h, specificity 80%, marker of liver injury due to alcohol-use disorder

(ALT: alanine transaminase; AST: aspartate transaminase)

sedated, these tools are replaced by those generally applicable to patients admitted to the intensive care unit such as the Richmond Agitation-Sedation Scale. Alcohol Withdrawal Scale is less dependent on patient participation and his/her response that cover the whole spectrum of withdrawal syndromes including delirium. The most widely used tool for clinical estimation of the severity of AWS based on observations and patient participation is Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). Five clinical parameters (heart rate, respiratory rate, temperature, sweating, tremor) and five psychological parameters (agitation, anxiety, tactile disturbances, disorientation, and hallucinations) are used for assessment.

Treatment

Treatment of AWS is mainly based on control of agitation, autonomic hyperactive symptoms, and DT. Later, detoxification therapy and motivation for prolonged abstinence are recommended. Intravenous benzodiazepine is used as the initial therapy. No specific benzodiazepine is superior to one another (**Table 4**). Adjunctive therapeutic agents can also be added. Chronic alcohol use is associated with abnormal magnesium metabolism. Magnesium is an important part of many coenzymes and acts as inhibitors of neurotransmitter. It competes with glutamate in its receptor-binding sites and decreases NMDA-induced hyperexcitability. Electrocardiogram (ECG) for QT interval and lab value should be estimated to balance the deficiency. Early thiamine supplementation is helpful in faster recovery from WE regardless of the initial clinical presentation. WE is a classic triad of confusion, ataxia, and ophthalmoplegia. According to the European Federation of Neurological Society (EFNS) guideline for diagnosis of WE, two of the following four signs are required: (1) Dietary deficiencies, (2) eye signs, (3) cerebellar dysfunction, and (4) either an altered mental state or mild memory impairment. Severe alcohol withdrawal symptoms, especially with delirium, are difficult to differentiate from WE. Prevention of WE with parenteral thiamine is easy and uncomplicated and should be administered to all patients at risk, including those experiencing alcohol withdrawal symptoms and prior to any parenteral carbohydrate-containing fluids.

METHANOL POISONING

Methanol is methyl alcohol, also known as wood alcohol or wood naphtha. It is a colorless, water-soluble liquid with a typical aromatic odor and slightly bitter taste. Industrial methylated spirit consists of 95% ethyl alcohol and 5% methyl alcohol. Mineralized methylated spirit contains 90% ethyl alcohol and 10% methyl alcohol. Surgical spirit contains 95% ethyl alcohol and 5% methyl alcohol in which oil of wintergreen

TABLE 4: Alcohol withdrawal syndrome.

Uncomplicated alcohol withdrawal symptoms	*Complicated alcohol withdrawal symptoms*	
	Alcohol withdrawal seizure	*Alcohol withdrawal delirium tremens*
• IV diazepam 10–20 mg or • IV lorazepam 2–4 mg and • IV ondansetron 4 mg (if vomiting)	IV lorazepam 2 mg	• IV lorazepam 2–4 mg can be repeated with double dose till mild sedation or • IV diazepam 10–20 mg over 2 min can be repeated with double dose till mild sedation
• Lorazepam 2 mg orally • Diazepam 10–20 mg orally • Oxazepam 15–30 mg orally		• If symptoms are refractory to benzodiazepine, • IV phenobarbital 65 mg every 30 min or propofol 5 µg/kg/min (requires intubation as respiratory depression is more than benzodiazepine)
Alcohol-induced psychotic disorder is treated with antipsychotic drugs and abstinence from alcohol		

is added for sweetish aromatic flavor for easy detection and pleasant use. It is used in many home chemicals, duplicating fluids, varnishes, stains, paint thinners, and dyes. Methylated spirit is very cheap and frequently available; hence, it is easily adulterated and used as country liquor among poor people who cannot afford ethyl alcohol for their drink.

Absorption, Distribution, and Excretion

The specific gravity of methanol is 0.81 (ethanol is 0.79), i.e., 1 L contains 810 g of methanol. It is rapidly absorbed from the intestine and to a small extent from the stomach. Its rate of absorption is more than glucose. The absorption depends upon concentration (the higher the concentration, the rapid the absorption) and the condition of the stomach (in empty stomach—rapid absorption) and is completed within 3 hours. If the concentration is below 20%, it increases gastric secretion. After absorption from blood, it mostly goes to the intracellular and extracellular fluid of the tissue and less to body fat. When the absorption is completed, urine and cerebrospinal fluid (CSF) contain 20% more alcohol than blood. About 90% of the alcohol is oxidized in the liver. Rest is excreted through urine and exhaled air. Its oxidation and excretion are much slower than ethyl alcohol. In the presence of ethyl alcohol its absorption, metabolism, and excretion are further delayed.

Mechanism of Toxicity (Metabolism)

Methanol itself is a less toxic agent. It becomes highly toxic when it is mixed with ethyl alcohol as it is adulterated. The rate of oxidation is very slow, only about 15% of that of ethyl alcohol. When taken with ethyl alcohol, it is metabolized only after complete metabolization of ethyl alcohol. In course of oxidation, formaldehyde and finally formic acid are formed which are highly toxic. Ethyl alcohol is preferentially metabolized by ADH resulting in reduced methanol toxicity.

Action, Clinical Features, and Fatality

- *Central nervous system toxicity*: It depresses CNS causing headache, dizziness, vertigo, dyspnea, cyanosis, cardiac depression, and muscular weakness. It is a less respiratory depressant than ethyl alcohol, but its delayed effects are very dangerous which include optic nerve atrophy resulting in complete blindness. The delayed toxicity may take 6–72 hours (usually 12–24 hours) to develop.
- *Ocular toxicity*: It is a delayed feature, which includes blurring of vision, which gradually leads to total or partial blindness. On examination pupillary dilatation, retinal edema, and hyperemia of the optic disk may be found. About 20% of the victims become totally blind; others have a different form of visual disabilities.
- *Renal toxicity*: There may be scanty micturition, which is acidic and contains acetone and format; sometimes there may be total anuria.
- *Gastrointestinal tract toxicity*: It includes nausea and abdominal pain. About 40% of the methanol users have high amylase level.
- *Respiratory toxicity*: There may be dyspnea, respiratory distress, and death usually due to respiratory failure.

Laboratory Diagnosis

Methanol poisoning causes an elevated osmolar gap, which may be detected by the difference between the measured and the calculated osmolarity. Osmolarity is calculated by the formula:

$$\text{Osmolarity} = (2 \times \text{Na}) + (\text{BUN}/2.8) + (\text{Glucose}/18).$$

A serum level of 200 mg/dL of methanol adds approximately 62 mOsm/L to the osmolar gap.

Methanol also produces high anion gap acidosis, which is due to excessive production of formic acid and lactic acid.

Management

The intoxicated person must be hospitalized and kept under close observation, even after initial recovery. He must be treated by an ophthalmologist for his visual problems. Initial management is given in the following text.

There is no evidence of effectivity of stomach wash although it is advocated. Oxygen inhalation and artificial respiration are recommended in moderate cases. In a severe case, the patient should be intubated and mechanical respiration should be given. Circulation should be maintained by giving fluids and sympathomimetics. Fluid–electrolyte balance should be maintained and dehydration should be combatted. Acidosis should be controlled by infusing sodium bicarbonate. Renal failure should be monitored carefully. Sedation can be given cautiously to prevent delirium and restlessness. Eyes should be protected from light and should be under regular observation.

Ethyl alcohol therapy is given to delay the absorption and metabolism and thus to prevent the damaging effect of methanol.

In methanol poisoning, start folinic acid 1 mg/kg (maximum dose is 50 mg): Repeat every 4 hourly to protect against ocular toxicity. Since alcohol (ethanol and methanol) is metabolized by ADH so the primary treatment is to block this

enzyme. *Fomepizole,* also known as 4-methylpyrazole, can be used alone or with hemodialysis to treat methanol and ethylene glycol poisoning. A dose of 15 mg/kg loading is administered followed by 10 mg/kg every 12 hour (total of four doses) till serum ethanol is <20 mg/dL. In case of dialysis, 4 hourly doses are required as it is dialyzable. Studies highlighted greater safety of fomepizole than ethanol (alternative) in the treatment of methanol poisoning.

The (alternate) antidote for methanol poisoning is ethanol. Absolute alcohol is suitable for IV use. Ethanol is given orally or IV to maintain a blood ethanol level of 100–150 mg/dL. This will block methanol metabolism. In mild poisoning, oral ethanol is adequate. Give 10% ethanol 7.5 mL/kg IV, over 30–60 minutes, as a loading dose. The recommended maintenance dose for nondrinkers is 10% ethanol 1 mL/kg/h IV. For chronic ethanol drinkers, the maintenance dose is 10% ethanol 1.96 mL/kg/h IV. If the patient is undergoing hemodialysis, the maintenance dose is 3 mL/kg/h. A solution of about 10% ethanol can be made by mixing 60 mL of absolute alcohol suitable for IV use in 500 mL of 5% dextrose.

Ethanol can be administered orally if the IV preparation is not available. Concentrations <20% are preferred to avoid gastric irritation. A loading dose of 95% ethanol, 0.8 mL/kg followed by 0.1 mL/kg/h can be given. If the patient is undergoing hemodialysis, increase the dose up to 0.2 mL/kg/h and administer via a nasogastric tube. For chronic ethanol drinkers, the maintenance dose is 0.2 mL/kg/h. The alcohol should be diluted in water or fruit juice.

If no alcohol is available in the hospital, give arrack (gin or whisky) 1.8 mL/kg as a loading dose and 0.2 mL/kg/h as maintenance dose orally, after diluting with water or fruit juice. If the patient is undergoing hemodialysis, the maintenance dose is 0.7 mL/kg/h. Dose should be loading with 50 g of 50% ethyl alcohol (e.g., 125 mL of gin, whisky, or vodka) orally followed by a further oral dose for 3–4 days or an IV infusion of 10–12 g ethanol/hour, to achieve a blood concentration of about 500–1,000 mg/L.

Ethanol should be given until methanol is undetected in the blood. A serum ethanol level of 100 mg/dL is essential to achieve the best counter-effect of methanol. The above regimens should be maintained for 2–3 days unless contraindicated for any reason or until plasma methanol concentration is <20 mg/dL. The blood ethanol level should be monitored hourly initially, and at longer intervals thereafter, depending on the facilities available. As prolonged ethanol administration can cause hypoglycemia, especially in children, determine blood glucose levels and give glucose orally or 5% or 50% dextrose IV. If convulsions are present, give diazepam 5–10 mg IV (pediatric dose: 0.2 mg/kg). Repeat if necessary.

Hemodialysis is effective in removing the absorbed poison and its metabolites. Indication for dialysis: (1) If ingest >30 g methanol, (2) develop metabolic acidosis (pH 7.1 rise in creatinine) or mental, visual, or fundoscopic abnormalities attributable to methanol, and (3) has a blood methanol concentration >500 mg/L. Hemodialysis is more effective than peritoneal dialysis. If dialysis is used, increased quantities of ethanol (17–22 g/h) must be administered.

Medicolegal Importance

Most of the poisonings are accidental, due to adulteration with methylated spirit and other narcotics, but postmortem reports always go in favor of suicide as it is self-taken. Homicide is very much uncommon.

SUMMARY

Alcohol is one of the most available and consumable fermented drinks worldwide. Alcohol (ethanol), which is a neuropsychoactive substance, causes numerous systemic effects on the nervous system as well as on other organs and systems. Globally, an ethanol intoxication is associated with numerous complications, including road traffic accidents, domestic violence, homicide, and suicide. AWS occurs due to sudden stopping or reducing of chronic alcohol consumption which gives rise to a wide variety of clinical presentations. Treatment of AWS is mainly based on control of agitation, autonomic hyperactive symptoms, and DT. Methanol becomes highly toxic when it is mixed with ethyl alcohol as it is adulterated. Vulnerable populations have higher rates of alcohol-related death and hospitalization. Knowledge about alcohol-related problems and their management is extremely important for an emergency physician.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Cardiovascular Drug Overdose

Rahul Solanki

INTRODUCTION

Cardiovascular drugs such as β-adrenergic antagonists (BAAs), calcium channel antagonists (CCAs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, etc. are widely used for cardiovascular diseases.These are among the most significant determinants of morbidity and mortality in the entire world. Because of the widespread use of these drugs, their overdose is also common. Mostly, the overdose is unintentional but the intentional use is not uncommon. The proportion of intentional overdose is also significant typically in the younger population with less burden of cardiovascular disease. Sudden cardiac death in a young healthy person is most likely to be drug-related. Poisoning is the leading cause of cardiac arrest in patients younger than 40 years of age but infrequent in elderly patients. Drug-induced adverse cardiovascular events include:

- Myocardial injury—most common. Presence of electrocardiogram (ECG) changes and elevated biomarkers
- Shock—second most common. Hypotension or hypoperfusion requiring vasopressors
- Ventricular dysrhythmias—third most common. Ventricular tachycardia/fibrillation, torsade de pointes
- Cardiac arrest—loss of pulse requiring cardiopulmonary resuscitation (CPR)

Adverse cardiovascular events from hospitalized drug overdose patients are as high as 17%. This high morbidity implies that physicians should always exercise caution while prescribing these drugs. Determinants of dose such as age, renal, and liver function should also be kept in mind. To manage these, a patients proper assessment of hemodynamic status remains important so that pathophysiological derangement can be dealt with effective therapy.

Besides many other drugs, BAA and CCA remain invaluable for the treatment of many cardiovascular and other medical conditions. Unfortunately these drugs are also responsible for cardiovascular collapse after an accidental or intentional overdose. Data suggests that BAA and CCA come only after cocaine as the most common cause of death due to overdose.

β-ADRENERGIC ANTAGONISTS AND CALCIUM CHANNEL ANTAGONISTS

The BAA and CCA are sources of significant morbidity and mortality as both are used widely. Both have a similar presentation in overdose. So the line of treatment is also similar. Both are often refractory to standard supportive care. As both inhibit calcium entry into the cells, both have common clinical features of hypotension and bradycardia.

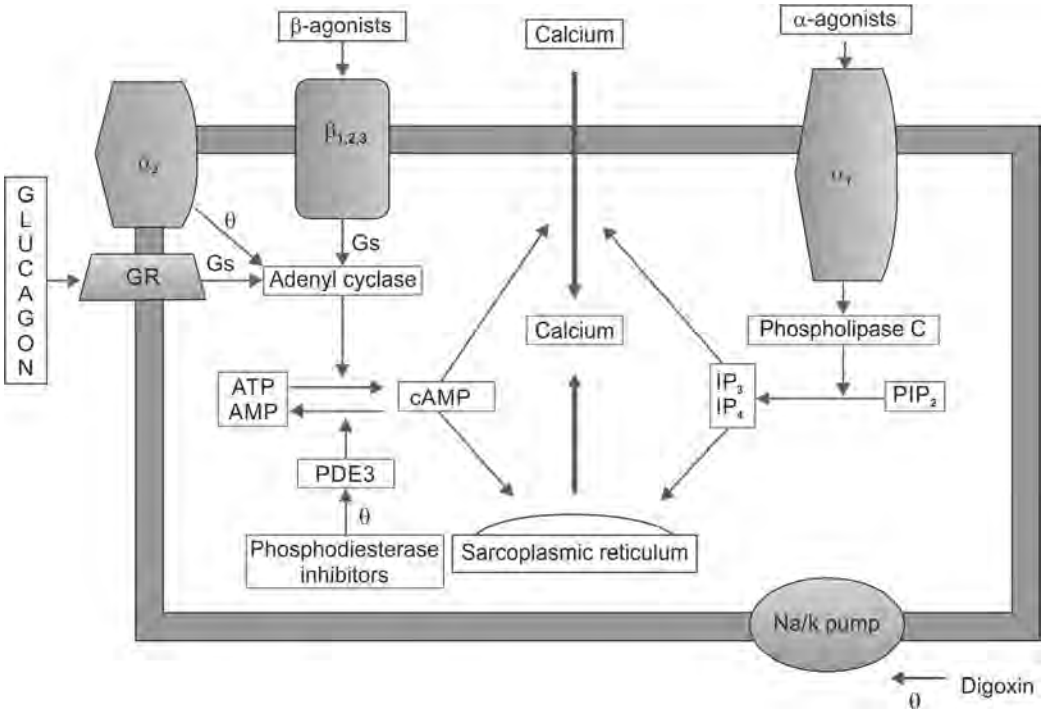
Beta-adrenergic Antagonists

There are three types of β-adrenergic receptors:

1. β_1 receptor primarily regulates myocardial tissue and affects the rate of contraction via impulse conduction.
2. β_2 receptor regulates the smooth muscle and affects bronchiolar and vascular relaxation.
3. β_3 activity increases cardiac inotropy and affects lipolysis.

Calcium Channel Antagonists

Calcium channel antagonists prevent the opening of voltage-gated calcium channels found in the myocardial cells, smooth muscle cells, and β cells of pancreas and reduce calcium entry into the cells during phase 2 of action potential (**Fig. 1**). Inotropy is reduced within the cardiomyocytes as there is lack of intracellular calcium. Vasodilation of vascular smooth muscle also occurs because of calcium channel blockade. Dihydropyridines, such as amlodipine and nifedipine, act predominantly on peripheral vasculature. Nondihydropyridines, such as verapamil and diltiazem, not only are more cardioselective but also have peripheral vascular activity. This leads to a decrease in sinoatrial (SA) and atrioventricular (AV) nodal conduction, myocardial contractility, and peripheral vascular resistance (PVR). Impaired impulse generation can cause sinus bradycardia, complete AV dissociation, and sinus node arrest. Decreased PVR reduces afterload and systemic blood pressure. Because dihydropyridine CCA preferentially acts in the peripheral



(cAMP: cyclic adenosine monophosphate; GR: glucagon receptor; Gs: g protein complex; IP3: inositol triphosphate; PDE3: phosphodiesterase3; PIP: phosphor inositol diphosphate)

FIG. 1: Schematic representation of the action of inotropic drugs on intracellular calcium in myocytes.

vascular system, initial vasodilation with reflex tachycardia may occur. In large overdoses, receptor selectivity is lost and the toxicity of each class is difficult to be differentiated. The voltage-gated calcium channel inhibition of pancreatic β cells results in decreased insulin release.

Clinical Features

Cardiovascular

Cardiovascular adverse effect characterized by hypotension and bradycardia (sinus pause/arrest, junctional escape rhythm, idioventricular rhythm, and AV block) is common to both BAA and CCA. BAA toxicity is typically associated with widened QRS due to sodium channel blockade. It may also have compensatory peripheral vasoconstriction as opposed to vasodilation. Noncardiogenic pulmonary edema is commonly associated with CCB overdose.

Central Nervous System

Lipophilic BAAs (propranolol) are likely to cause sympathetic nervous system (SNS) depression whereas hydrophilic BAAs (atenolol) generally do not produce the same degree of sedation. Although BAA themselves may cause central nervous system (CNS) depression, an inadequately perfused brain also manifests clinically with an altered mental status. Other CNS manifestations include confusion, agitation, and seizures.

Endocrine

Calcium channel antagonist toxicity is likely to result in hyperglycemia. In fact, the degree of hyperglycemia correlates with the degree of cardiotoxicity. But in BAA toxicity, hypoglycemia may occur (especially in children). BAA can also lead to hyperkalemia. It may be difficult to determine the causative agent because of the similar clinical manifestations of BAA and CCA due to their common cardiac effects. Peripheral vasoconstriction and cool extremities, hypoglycemia or euglycemia, sodium channel blockade as well as CNS depression would favor the diagnosis of BAA toxicity whereas peripheral vasodilation, hyperglycemia, noncardiogenic pulmonary edema, and a normal sensorium would suggest CCA toxicity.

In patients who are severely poisoned and not resuscitated properly, tissue hypoperfusion results in lactate-associated acidosis and resultant academia. Similarly, CNS effects including drowsiness, confusion, agitation, and seizures may be observed secondary to hypoperfusion. Acute lung injury, acute kidney injury, and gastrointestinal (GI) ischemia may develop secondary to hypoperfusion and are indicators of poor prognosis.

Management

Gastrointestinal Decontamination

Airway, ventilation, and cardiovascular have precedence over GI decontamination as there is not sufficient evidence that it improves outcome. But in a patient with normal vital signs and who is alert, awake, and oriented, it should be done with activated charcoal. Whole bowel irrigation is done in a patient having an overdose of sustained-release preparation. Polyethylene glycol-based preparation at the rate of 2 L/h (500 mL/h in children) should be used until the rectal effluent is clear. Whole bowel irrigation should be avoided with the onset of symptoms of hypotension and bradycardia as they coincide with depressed GI function and ileus.

Resuscitation and Initial Treatment

All poisoned patients need continuous cardiopulmonary monitoring and immediate and reliable intravenous access. A central venous catheter is required in hypotensive patients as they may need vasopressors. Initial fluid resuscitation with 1–2 L of crystalloid bolus may be required. Be careful to avoid volume overload. IV atropine should be given if there is symptomatic bradycardia or conduction disturbance (dose of 0.5 mg every 3–5 min, total dose 3 mg). If there is shock, its underlying mechanism should be ascertained by echocardiography. This will be helpful in selecting the most appropriate vasoactive agent. Invasive methods, such as pulmonary artery catheter or pulse contour cardiac output, may be used to assess the cardiac output and hemodynamic parameters in patients having shock.

Specific Treatment

Various specific options are available and can be used stepwise and most steps can be selected depending on the response, but sometimes the patient is so unstable due to the severity of the poisoning that several steps will be used simultaneously. Available options are glucagon, calcium chloride/calcium gluconate, high-dose insulin euglycemic therapy (HIET), lipid emulsion, vasopressors, pacemakers, and extracorporeal therapy.

Glucagon

Clinical experience in humans and minimal adverse effect profile support the use of glucagon early in the course of both BAA and CCA toxicity. The first-line therapy in BAA poisoning in patients having symptomatic bradycardia and hypotension is high-dose glucagon (0.1 mg/kg) as it can bypass the β-adrenergic receptor and activate adenylate cyclase (*see* **Fig. 1**). Hemodynamic improvement should occur within 5 minutes of the initial bolus of glucagon. This is immediately followed by a continuous infusion of glucagon at a rate of 2–10 mg/h (maximum dose 10 mg/h) as it has a short duration of cardiac effects. There is no established maximum dose for the continuous infusion; one patient required 411 mg which was given over 41 hours following propranolol overdose. Adverse effects of glucagon include nausea and vomiting and are dose-related. Emesis may be problematic in patients having depressed mentation and difficult airway status. As glycogenolysis is stimulated by glucagon, hyperglycemia may occur which typically does not require any intervention. Vomiting and hyperglycemia occur commonly in diabetics or during continuous infusion. An acute decrease in response to glucagon (tachyphylaxis) may occur after repeated administration. Glucagon is expensive and might not be available in sufficient quantity, so other options such as HIET, and vasopressors can be used.

Calcium Chloride/Calcium Gluconate

Calcium chloride, calcium gluconate, or both can be used. They are expected to increase inotropy and improve blood pressure but have little effect on the heart rate and conduction block. Intravenous calcium is used as a first-line agent in CCA toxicity and to treat BBA toxicity as well depending on improvement in blood pressure and cardiac output.

There are no clear guidelines regarding the form or dose of calcium to use as it is available in two forms.

Calcium chloride contains more calcium in terms of milliequivalents than calcium gluconate. A 10-mL vial of 10% calcium chloride solution contains 13.5 mEq of calcium whereas a similar volume and concentration of calcium gluconate provide 4.5 mEq. When given as equivalent doses, the chloride and gluconate form provide a similar increase in ionized calcium.

Calcium Chloride

About 10 mL of 10% solution (1 g) calcium chloride should be given by central venous access over 5–10 minutes because tissue injury which may occur due to extravasation of calcium preparation is a concern. It can be repeated every 10–20 minutes to a total of 3 g or after the bolus dose, continuous infusion is initiated at a rate of 0.2–0.4 mL/kg/h because bolus administration increases ionized calcium only for a brief period (5–10 min).

Calcium gluconate can be given by a peripheral vein. Starting dose of 30 mL of 10% solution over 5–10 minutes is followed by an infusion of 0.6–1.2 mL/kg/h.

Calcium infusion is titrated to affect either improved blood pressure or contractility. Initially, a serial ionized calcium level is required every 30 minutes and then every 2 hours with a target of maintaining ionized calcium at nearly twice the normal. The required large doses of calcium are usually tolerable without any problem. Rarely calcium administration has potential adverse effects such as hypotension, conduction blockade, bradycardia, and asystole, if given too rapidly. Calcium should not be given inadvertently in a digitalis intoxicated patient who has resultant excessive myocyte calcium overload and asystole. The safest form of available preparation is calcium gluconate.

High-dose Insulin Euglycemic Therapy

Supportive care and traditional treatment are not always sufficient in severe poisoning. HIET for CCA and BAA has been found to have more effect on hemodynamics than traditional measures such as vasopressors. It has emerged as the treatment of choice for severe CCA and BAA toxicity.

High-dose insulin euglycemic therapy exerts its therapeutic effect through two pathways: (1) Increased inotropy, and (2) Vascular dilation. Insulin improves inotropic action through the PI3K pathway and through augmented glucose uptake into myocardial cells, improving energy supply and use. It increases endothelial nitric oxide synthase activity, thereby causing vasodilation of peripheral arterioles in coronary, systemic, and pulmonary vasculature, thus improving perfusion and increasing cardiac output independent of increased inotropy. HIET should be started early when severe poisoning is suspected, even before the hemodynamic instability is profound as the onset of effect usually takes 15–60 minutes and failure of this effect has been seen when it is instituted late. Other causes of treatment failure are insufficient dosing and concomitant use of vasopressor.

The dosage of infusion is not clearly established, mostly a bolus dose of 1 unit/kg of regular human insulin along with 0.5 g/kg of dextrose. This is followed by an infusion of insulin at a rate of 0.5 units/kg/h which can be titrated upward to 2 units/kg/h or high if no improvement is seen after 15–30 minutes. As an improvement in hemodynamic is seen, the dose needs to be uptitrated to a systolic BP of ≥100 mm Hg. If no response is seen in 30–60 minutes, the dose needs to be increased. The glucose requirement does not necessarily increase with an increased

dose of insulin. The concentration of insulin preparation should be 10 units/mL. Similarly, D25W or D50W administration by a central venous catheter may be used to avoid large fluid volume with more dilute solutions. If blood glucose is >300–400 mg/dL, the dextrose bolus is withheld. Glucose should be monitored every 30 minutes for the first 4 hours and titrated to maintain euglycemia (euglycemia is defined as blood glucose between 100 and 250 mg/dL) and then hourly thereafter.

Serum potassium is monitored every hour for the first 4–6 hours with a target potassium level >3 mEq/L. Magnesium and phosphorus levels also need to be monitored. Potassium concentration should also be monitored closely because insulin shifts potassium intracellularly. Replace potassium when it falls below 2.5 mEq/L.

Adverse effects with HIET are predictable and infrequent. They are hypoglycemia, hypokalemia, hypophosphatemia, and hypomagnesemia. To summarize, HIET is a safe and effective therapy for significant CCA and BAA toxicity. Hypodynamic myocardium is the best indication for its use. Early detection of depressed contractility and early initiation of HIET will increase the chance of survival.

Vasopressor

The selection of vasopressor is guided by the type of shock. The goal of therapy should be to improve tissue perfusion and not just to achieve a target blood pressure. There is no single agent that is superior for cardiovascular drug toxicity. In BBA and CCA toxicity, large doses of multiple agents may be required and response might be unpredictable. Norepinephrine appears to be the choice of drug initially due to its strong α_1 agonist [increased systemic vascular resistance (SVR)] and moderate β_1 agonist (increased contractility) activity. Despite having both positive chronotropic and inotropic effects, epinephrine worsens tissue ischemia by hyperglycemia, lactic acidosis, and insulin resistance without improving tissue perfusion in large doses. As there is a lack of efficacy and worsening survival, use of vasopressin has been discouraged. It may be used as an adjunct in severe vasodilatory shock which is not responding to other catecholamines. The dose of vasopressin should never exceed 0.04 IU/min as it can cause reduced cardiac output and limb ischemia. Adverse effects of catecholamine administration include tissue injury, hypotension, and detrimental metabolic consequences. Central intravenous administration is preferable as a potent α-agonist may extravasate from the peripheral intravenous site. Isoproterenol and dobutamine having β-agonist activity and a little α-agonist activity may decrease peripheral resistance and worsen hypotension. an adrenergic agonist may be detrimental during shock as it enhances free fatty acid use by the heart. Because of this detrimental metabolic effect on the heart from catecholamine and marginal efficacy, other cardiotonic agents are a better initial choice when a depressed myocardial function needs to be improved.

Sodium Bicarbonate Therapy

Both BAA and CCA drugs antagonize myocardial sodium channel. Thus, toxicity from these drugs may include widened QRS along with bradycardia. Sodium bicarbonate is used to treat academia and sodium channel blockade. Hemodynamic improvement is also seen after sodium bicarbonate treatment.

Dose: 1–2 mEq/kg (2–4) vials bolus followed by a continuous infusion of 150 mEq/L sodium bicarbonate plus 40 mEq potassium chloride (KCL) at 200 mL/h.

Other Therapies

Phosphodiesterase Inhibition (Amrinone Milrinone Enoximone)

They improve inotropy independent of β-adrenergic receptor by increasing intracellular cyclic adenosine monophosphate (cAMP). But their action on vascular smooth muscle also causes vasodilation and hypotension. They can be considered third-line agents as there is limited evidence of poisoning.

Intravenous Lipid Emulsion

It is recommended as rescue therapy for BAA and CAA toxicity. Its mechanism of action appears to be intravascular sequestration of the toxic drug to an intravascular lipid phase, thereby decreasing the free blood concentration of the drug. It might provide energy to the cardiac myocyte. By increasing the intracellular calcium level, it may also improve the contractility.

Dose: 1.5 mL/kg of 20% lipid emulsion followed by 0.25 mL/kg/min for 30–60 minutes. Maximum dose is 12.5 mL/kg in 24 hours. Adverse effects include pancreatitis, lung injury, and lipemic serum interfering with biochemical tests and there is a possibility of paradoxically increasing absorption of the toxic drug from the GI tract.

Hemodialysis

Hemodialysis can be used in some BAA such as atenolol, nadolol, and sotalol as the binding is <25%, volume of distribution is 2 L/kg, and renal elimination is present. Most other BAA and all three classes of CAA are lipophilic, highly protein-bound, and primarily undergo hepatic metabolism. So extracorporeal drug removal has limited usefulness following overdose of BAA and CCA.

Pacemaker

Pacing may be considered in a case of unstable bradycardia or high-grade conduction disturbances or if shock persists after the administration of the first-line therapy such as calcium, HIET, and vasopressor. However, pacing often fails to achieve electrical capture and if capture occurs, blood pressure is not always restored. The disconnect between electrical capture and lack of improved contractility or increased blood pressure lies in the lack of intracellular calcium necessary for contraction. This is equally true for CCA whereby there is an increased limit required for calcium to enter the myocardium during diastole.

Extracorporeal Life Support

Severe BAA and CCA overdose is responsible for about two third of all deaths due to overdose with cardiotoxic drugs. A subset of patients with shock refractory to traditional approach might benefit from extracorporeal measures. Extracorporeal therapies allow time for drugs to be redistributed or metabolized till the heart function recovers but ineffective in refractory vasodilatory shock. Some reports of successful management of severely poisoned cases with continuous venovenous hemofiltration with charcoal hemoperfusion have been reported. There is

also usefulness of veno-arterial extracorporeal membrane oxygenation (ECMO) in the management of severely poisoned patients having cardiogenic shock or mixed shock with a significant cardiogenic component. Complications include local bleeding and limb ischemia. Timely indication of ECMO has shown to provide a survival benefit, especially in patients refractory to medical therapy.

The overall objective of the therapy is to improve organ perfusion. Since the pathophysiology of the shock could be multifactorial, a multimodal approach for management is needed, based on a careful assessment of the hemodynamic status. Therapy must be individual and multiple simultaneous interventions might be required for the best possible outcome.

CARDIOACTIVE STEROID TOXICITY

Digoxin is a cardioactive steroid (CAS) mostly used in the treatment of congestive heart failure and/or rate control of ventricular response due to atrial fibrillation or flutter. Despite the declined use of CAS, their acute and chronic toxicity is still troublesome even today because of their narrow therapeutic index. Acute overdoses in children are often unintentional and are due to an error in dosing or mistaken ingestion of an adult's medication. The geriatric population is at a particular risk for toxicity because of changes in the absorption, protein binding, elimination, or interaction with other medications. Severe toxicity due to CAS has been reported from consumption of products used for increased sexual performance, male enhancement, herbal colon cleansing, and rodenticides (**Flowchart 1**).

Pathophysiology

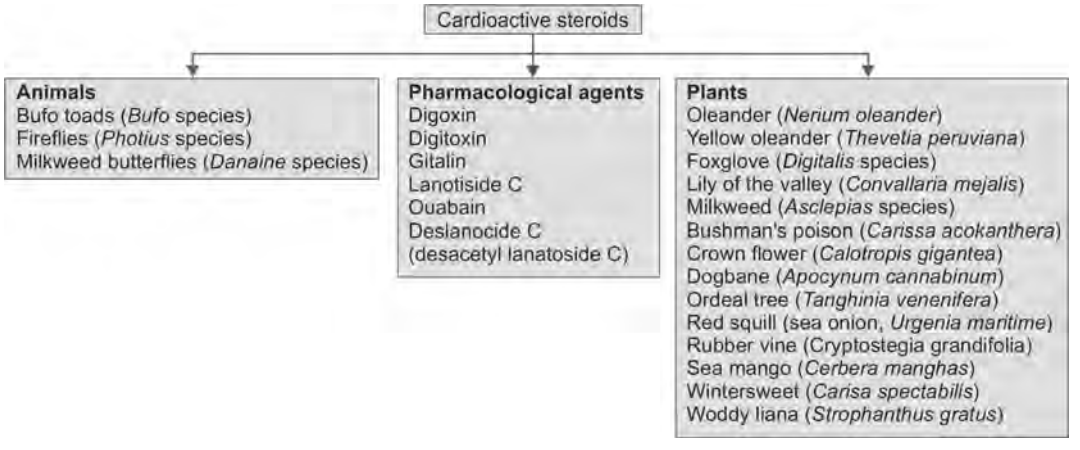
Cardioactive steroids are positive inotropes; as a result, they inhibit active transport of sodium and potassium across cell membrane during repolarization by binding to and inhibiting the sodium–potassium ATPase ($3Na^+$ $2K^+$ ATPase). The end result is an increase in the force of contraction of cardiac muscle due to increased intracellular calcium which induces myocyte sarcoplasmic reticulum to release further calcium. The repolarization interval of cardiac muscle is increased and also shortened by CAS. The conduction through SA and AV nodes is decreased by the concomitant rise in vagally mediated parasympathetic tone. The ECG will show these changes in the form of a prolonged PR interval and a decreased ventricular response rate to atrial stimuli. Ventricular repolarization is also affected via increased intracellular calcium resulting in QT interval shortening and ST-T wave forces opposite to the direction of QRS forces (digitalis effect—scooped ST segment). Hypokalemia increases the chances of arrhythmias by enhancing the automaticity of the myocardium and impairing the activity of $3Na^+$-$2K^+$ ATPase.

Clinical Features

Presentation of CAS toxicity depends on different factors such as age, comorbid condition, renal function, acute or chronic ingestion, identity, and magnitude of the particular drug ingested. All these factors play an important role in determining clinical manifestations. Acute CAS toxicity may occur from accidental, suicidal, homicidal, or recreational exposure to CAS. It should always be kept in mind that the presentation of the patient will depend on the time of ingestion and quantity of the drug. Because of its insidious onset and nonspecific symptoms, it is often difficult to diagnose chronic toxicity. CAS can result in almost any arrhythmia except rapidly conducted supraventricular tachyarrhythmias (due to combined AV node blockade as vagal tone is increased and there is increased ventricular contractility). An ectopic ventricular rhythm is the most common sign of cardiac toxicity. Bidirectional ventricular tachycardia can be said to be nearly pathognomonic of CAS toxicity. When there is evidence of impaired SA/AV nodal conduction combined with increased automaticity, CAS toxicity should be suspected. **Box 1** shows ECG changes in patients taking CAS.

Acute Toxicity

The arrhythmias of CAS are characterized by a depressed AV node and sensitized myocardium and often unresponsive to atropine. An asymptomatic period of minutes to hours may occur after a single toxic dose of CAS. Initially, there can occur symptoms such as nausea, vomiting, and/or abdominal discomfort which may be accompanied by CNS effects such as confusion, somnolence, and weakness due to hemodynamic changes. If GI symptoms recur after several hours, then the possibility of CAS toxicity is less. Hyperkalemia is rarely high enough to cause clinical toxicity. It is also an important



FLOWCHART 1: Cardioactive steroids.

BOX 1: ECG changes in patients taking cardioactive steroids.

- Sinus bradycardia
- Atrial fibrillation or flutter with slow ventricular response
- Atrial tachycardia with high-grade atrioventricular block
- Bidirectional ventricular tachycardia (pathognomonic)
- Premature ventricular contractions (most common finding)
- Ventricular tachycardia
- Ventricular fibrillation
- "Scooped" T waves (suggestive of therapeutic use, not necessarily overdose)

(ECG: electrocardiogram)

BOX 2: Risk factors for chronic cardioactive steroid toxicity.

- Dehydration
- Change in renal function (remain unrecognized)
- Inappropriate dose adjustment in patients with renal insufficiency
- Drug–drug interactions (verapamil, quinidine amiodarone, etc.)
- Use of macrolide (decreased gut flora that normally metabolizes cardioactive steroids)

TABLE 1: Causes of false-positive digoxin levels and digoxin drug–drug interactions.

Medical conditions and drugs causing false-positive results of digoxin levels	*Drug–drug interactions of digoxin*
Poor renal clearance	Angiotensin-converting enzyme inhibitor
Pregnancy	Amiodarone
Acromegaly	Diltiazem
Hypothermia	Quinidine
Elevated bilirubin levels	Verapamil
Spironolactone	Carvedilol
	Spironolactone

prognostic feature and manifestation of acute toxicity. Acute digitoxin overdose with a potassium level above 5.5 mEq/L was also associated with 100% mortality before the introduction of specific antibody therapy.

Chronic Toxicity

Chronic toxicity may produce vague clinical presentation such as GI upset, drowsiness, headache, visual disturbance, and delirium. It is also associated with hyperkalemia like acute toxicity which is likely to increase mortality and digoxin antibody requirement. Bradyarrhythmias occurring later in acute and chronic toxicity are due to direct toxin action on myocytes rather than AV nodal blockade. Thus, they are often unresponsive to atropine. Ventricular dysrhythmias are more common in chronic toxicity than acute toxicity. Chronic toxicity may present with nonspecific symptoms such as weakness, anorexia, abdominal pain, and nausea/vomiting. Factors such as volume depletion, renal insufficiency, electrolyte abnormality, or drug–drug interactions result in chronic toxicity. **Box 2** shows risk factors for chronic digoxin toxicity. Neuropsychiatric symptoms are more common in chronic toxicity as compared to acute toxicity. They are confusion, drowsiness, delirium, hallucinations, photophobia, chromatopsia (purple or yellow halos around lights), and decreased visual acuity. When a patient presents with unexplained bradycardia, nausea, vomiting, history of congestive cardiac failure or atrial flutter or fibrillation, one must rule out CAS toxicity.

Diagnosis

Continuous cardiopulmonary monitoring and hemodynamics should be evaluated in all patients with suspected cardiovascular toxicity. A 12-lead ECG is obtained to QRS or QT interval widening. It is done in all patients. Chest radiograph, pulse oximeter, and serum biochemistry are also obtained. A change in blood glucose level may suggest coexistent BAA or CCA ingestion. Serum lactate is the most specific biomarker for end-organ injury in drug-induced shock. Acute CAS toxicity may elevate the serum potassium level. If a patient presents with hyperkalemia with normal renal function and bradycardia, one must rule out CAS toxicity and serum digoxin concentration may be useful. Empiric therapy may be needed in patients having significant toxicity so an emergent digoxin assay could be performed. Digoxin is absorbed and distributed over many hours so while interpreting its concentration, it is important to consider the timing of ingestion. A serum concentration of >2 ng/mL suggests significant digoxin toxicity. So a digoxin concentration is assessed no sooner than 6 hours after ingestion except in pediatric poisoning and in suicidal cases. In nondigoxin cardioactive poisoning, interpretation of serum digoxin is a challenging task. Endogenous digoxin such as immunoreactive substances may be responsible for false-positive results as they are similar in structure and function to exogenous CAS (**Table 1**).

Management

Early GI decontamination and pharmacologic treatment should be started before the patient becomes unstable. All patients should be evaluated promptly and carefully monitored even if the vital signs are normal. All patients with hypotension should be given a crystalloid fluid bolus of 10–20 mL/kg or repeated as required. Volume depletion and renal insufficiency are the main causes of chronic CAS toxicity. *Digoxin-specific antibody treatment*: Unstable patients with acute life-threatening dysrhythmias require emergent empiric treatment with digoxin-specific antibody fragments. Since these patients have life-threatening toxicity of CAS, digoxin-specific antibody fragment administration is definitive therapy (**Box 3**). The total digoxin load will determine the dose of fab (**Table 2**). Hyperkalemia is a major complication of digoxin-specific antibody fragment. It should be corrected before giving the dose (**Box 4**).

BOX 3: Indications for digoxin-specific antibody fragments.

- Digoxin ingestion of 10 mg or more in an adult (4 mg in a child)
- Any potential cardioactive steroid dysrhythmia
- Brady dysrhythmia refractory to atropine
- Chronic poisoning with end-organ manifestations (e.g., altered mental status, gastrointestinal distress, renal impairment)
- Nondigoxin cardioactive steroids poisoning
- Hyperkalemia exceeding 5 mEq/L in acute digoxin toxicity
- Shock or hemodynamic instability
- Digoxin concentration* ≥15 ng/mL at anytime or ≥10 ng/mL after 6 h of ingestion

*To convert mmol/L to ng/mL, multiply by 0.78 (digoxin concentrations are reported in mmol/L by few laboratories).

TABLE 2: Dosing of digoxin-specific antibody fragments.*

Clinical picture	*Dose*
Acute toxicity, empiric dosing	10–20 vials (adult or pediatric)
Chronic toxicity, empiric dosing	3–6 vials (adult), 1–2 vials (child)
Ingested digoxin dose is known	$\text{Vials} = \frac{\text{Amount ingested (mg)} \times 0.8}{0.5 \text{ (mg per vial)}}$
Serum digoxin concentration† is known	$\text{Vials} = \frac{[\text{digoxin concentration (ng/mL)} \times (\text{weight (kg)}]}{100}$

*Each vial binds ~0.5 mg digoxin.

†To convert mmol/L to ng/mL, multiply by 0.78 (digoxin concentrations are reported in mmol/L by few laboratories).

Intravenous phenytoin can also be used in symptomatic supraventricular tachycardia in a dose of 100 mg bolus and can be repeated after 5 minutes. Though phenytoin and lidocaine are second-line drugs for the management of ventricular tachyarrhythmias, they can rarely be used as first-line drugs while fab is being procured/prepared or in some extreme situation. The dose of lidocaine in ventricular dysrhythmias is 1.5 mg/kg IV bolus which is followed by continuous infusion at a rate of 2.5–4 mg/min in adults and 50 μg/kg/min in children. In some cases where dysrhythmias are refractory to lidocaine and phenytoin, amiodarone can be used. Magnesium is also useful in some refractory cases (IV 1.5 g given over 20 min). If cardioversion is required, it should be done using low energy levels (20–100 J).

Management of Dyselectrolytemia

Hypokalemia is treated with supplemental potassium to achieve a level of >4 mEq/L. Hyperkalemia is treated by using insulin—glucose, bicarbonate, or exchange resins, and hemodialysis is used in renal failure and refractory cases. β-agonists may precipitate tachyarrhythmias so they should be avoided. Hypomagnesemia may occur in patients having chronic CAS poisoning which is associated with diuretic use. Myocardial irritability is reduced by the correction of the magnesium level. Transcutaneous and transvenous pacing is not likely to be beneficial in dysrhythmias caused by CAS poisoning. CAS have a large volume of distribution and high protein binding so hemodialysis and hemoperfusion are not effective in the elimination of these drugs.

BOX 4: Complications of digoxin-specific antibody fragments.

- Acute hypokalemia (severe hypokalemia should be treated before administration)
- Allergic reaction (allergies to papaya extracts or papain can also increase the risk)
- Rarely rapid atrial fibrillation after digoxin removal may occur
- Acute decomposition of underlying congestive cardiac failure

ANTIHYPERTENSIVE

Antihypertensive agents are ACE inhibitors, angiotensin II receptor blocker, CCA, sympatholytic drugs (α-adrenergic antagonists), BAA, adrenergic neuron-blocking agents, centrally acting agents, ganglion blocking agents, vasodilators (arterial, venous), and diuretics.

Angiotensin-converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors are mostly used for hypertension. They act on peptidyl dipeptide carboxyl hydrolase enzyme and inhibit the conversion of angiotensin I to angiotensin II in the lung and vascular endothelium. Adverse effects include cough, hypotension, bronchospasm, proteinuria, renal insufficiency, pancreatitis, and angioneurotic edema.

A patient may remain asymptomatic. Other features are hypotension, renal failure, and hyperkalemia.

Discontinue the offending agent and substitute with an alternative drug, activated charcoal.

Hypotension: IV colloids/crystalloids—10–20 mL/kg isotonic fluid. If not controlled, dopamine/noradrenaline can be used. For patients unresponsive to volume and pressor infusion, angiotensin is used in a dose of 8.5–18 μg/min with infusion. Naloxone is also used in the treatment of hypotension caused by ACE inhibitor overdose. In a patient with angioedema, early endotracheal intubation should be considered along with adrenaline, corticosteroids, and diphenhydramine. Sodium cromoglycate is given for the cough induced by ACE inhibitors. Hemodialysis may be beneficial.

Angiotensin II Receptor Blocker

It acts as an antagonist at angiotensin II receptors and thus inhibits its effects. Cough and angioneurotic edema do not occur with them as the bradykinin pathway is not affected, e.g., losartan/valsartan. Adverse effects include azotemia, oliguria in cases of congestive heart failure, and renal artery stenosis as the renal function depends on the function of the renin–angiotensin aldosterone system. Hepatotoxicity, which is reversible, is found. Clinical features include tachycardia/bradycardia, hypotension, and hyperkalemia. Vagal stimulation is the reason for bradycardia. Management consists of symptomatic and supportive treatment including cardiac

and hemodynamic monitoring, intravenous fluid resuscitation with crystalloids.Vasopressors are used in refractory cases not responding to crystalloids. Hemodialysis is ineffective as most agents are highly protein bound.

Calcium Channel Antagonists and β-adrenergic Antagonists

They have been discussed previously.

Sympatholytic Drugs

Alpha-adrenergic Antagonists

Alpha-1 adrenergic receptors are selectively blocked, e.g., prazosin, terazosin, phentolamine, tamsulosin, phenoxybenzamine, indoramin, tolazoline, and urapidil.

Adverse effects include palpitation, dizziness, vomiting, abdominal pain, and diarrhea which may occur when a large amount is ingested orally. Terazosin may cause headache or asthenia. Indoramin overdose can cause seizures. Priapism is also reported in some cases. Management is largely conservative and supportive includes intravenous fluids,vasopressors (noradrenaline preferred over dopamine). Priapism is a surgical emergency and require immediate urology consultation.

Centrally Acting Agents

Clonidine

Clonidine is an imidazoline compound having potent α_2-adrenergic activity. Besides its use in hypertension, it is also used in conditions such as opiate, ethanol, and nicotine withdrawal, migraine prophylaxis, and attention deficit disorder. Adverse effects include drowsiness, dry mouth, insomnia, orthostatic hypotension, agitation, myalgia, arrhythmias, and GI upset. Paralytic ileus may occur. Avoid abrupt withdrawal of clonidine as it can be life-threatening. Overdoses cause bradycardia which may progress to heart block hypotension, hypothermia, CNS depression, miosis, and periodic apnea. Paradoxical hypertension may occur sometimes. Hypothermia may occur within 1 hour of the ingestion and may last up to 48 hours. It is usually mild and resolves spontaneously within 6–8 hours.

All patients with an altered mental status, bradycardia, and hypo- or hypertension require close observation for frequent monitoring of the vital signs for a minimum period of 6–12 hours or until the patient remains asymptomatic for 4 hours. GI decontamination with activated charcoal is beneficial.

Bradycardia and hypotension may be responsive to only atropine in patients with heart rate below 60/min. In case of hypotension, give 10–20 mL/kg isotonic fluid. In persistent hypotension, use dopamine or noradrenaline. IV infusion of sodium nitroprusside is given at a rate of 0.5–10 μg/kg/min for paradoxical hypertension. Tolazoline (α-adrenergic antagonist) can be used in a dose of 5–10 mg as an IV infusion every 15 minutes (maximum dose 40 mg). Naloxone is used to reverse the deleterious effect on respiration and cardiovascular system function. It is also helpful in lessening the "paradoxical hypertension" effect and least effective in hypotension. The initial dose of naloxone for opiate overdose is 0.4–2 mg IV bolus (in both adults and children) and it is repeated at 2–3-minute interval according to the response. It should be administered cautiously in pediatric patients as it will cause hypertension in them which is treated by phentolamine. Hemodialysis, hemoperfusion, and forced diuresis are not likely to enhance the elimination of clonidine.

Methyldopa

Methyldopa is an antihypertensive whose specific mechanism of action is not clear. To lower blood pressure, it acts centrally via α-methylnoradrenaline which is an active metabolite.

Methyldopa can cause hemolytic anemia, pancreatitis, hepatitis, and myocarditis. Other features include headache, drowsiness, depression, edema, bradycardia, nightmares, nasal stuffiness, sexual dysfunction, galactorrhea, gynecomastia, and dry mouth. A positive Coombs test is found in about 20% of patients. Acute overdose of methyldopa can lead to severe hypothermia, nausea, vomiting, dry mouth, dizziness, weakness, bradycardia, lethargy, coma, paresthesia, headache, involuntary movements, and psychic disturbance. All patients should be admitted and treated in the intensive care unit. Fluid resuscitation should be started in hypotensive patient with 10–20 mL/kg isotonic fluid. Bradycardia can be treated with atropine. Hemodialysis and hemoperfusion may be beneficial in severe poisoning refractory to traditional therapy.

Vasodilators

Sodium Nitroprusside

Sodium nitroprusside has a vasodilatory effect due to the release of nitric oxide after being metabolized in red blood cells (RBCs). Cyanide is also released which can cause significant toxicity in presence of renal insufficiency or low thiosulfate stores (critically ill patients, infants, malnourished). It is used in the treatment of hypertensive emergencies and to induce controlled hypotension during anesthesia to reduce bleeding in surgical procedures. It is also used in congestive cardiac failure.

At a high rate of infusion, there is restlessness, anxiety, muscle twitching, and diaphoresis. When the rate of infusion of sodium nitroprusside is >5 μg/kg/min, toxic accumulation of cyanide with severe lactic acidosis can occur. Concomitant administration of sodium thiosulfate can prevent this. The risk factors for the development of nitroprusside toxicity are renal impairment, hypoalbuminemia, cardiopulmonary bypass procedures, and moderate-to-high dose of nitroprusside administration.

Acute toxicity is characterized by vasodilation and hypotension which can be complicated by nausea, vomiting, headache, sweating, palpitation, and substernal discomfort. An increased cyanide level in the blood may lead to the development of severe acidosis. Thiocyanate may lead to the development of neurotoxic syndrome manifesting by toxic psychosis, hyperreflexia, confusion, weakness, tinnitus, seizure, and coma.

Immediate discontinuation of the infusion is required to control the hypotension caused by sodium nitroprusside which may be followed by IV fluid replacement and vasopressor support. Maintain high PO_2 by giving 100% oxygen. Sodium nitrite and sodium thiosulfate are given in patients having dyspnea, headache, and impaired mental

status. In acidotic patients, sodium bicarbonate is given IV 1 mEq/kg. Serial arterial blood gas (ABG) determines further administration of sodium bicarbonate. Hemodialysis is beneficial in correcting resistant acidosis and increasing thiocyanate clearance, thus helping thiosulfate–cyanide reaction to thiocyanate.

Hydralazine

Hydralazine causes direct relaxation of arteriolar smooth muscle but is not a dilator of capacitance vessels such as the coronary artery. It is used in the treatment of hypertensive emergencies in pregnancy.

Adverse effects include dizziness, headache, lacrimation, blurred vision, palpitation and tachycardia, myocardial ischemia, glomerulonephritis, serum sickness, and lupus syndrome. In slow acetylators, a lupus-like syndrome may develop after a long-term use of hydralazine in a dose of >400 mg/day. Decontamination, IV fluids, and noradrenaline are the choices if required. In patients having myocardial ischemia or persistent tachycardia, BAA and CCA can be used. Pyridoxine is given for peripheral neuropathy.

ANTIARRHYTHMICS

Antiarrhythmics are used to prevent life-threatening arrhythmias and maintain sinus rhythm. As they have a narrow therapeutic index, they promote arrhythmias and increase mortality. Only twice the daily dose can be lethal because of their potent modulation of cardiac electrical activity. The Vaughan–Williams classification of antiarrhythmic drugs is as follows:

- *Class I*: *Sodium channel blockers*
  - IA: Moderate to marked sodium channel blockade—Disopyramide, procainamide, quinidine
  - IB: Mild-to-moderate sodium channel blockade—Lignocaine, phenytoin, mexiletine, tocainide
  - IC: Marked sodium channel blockade—Encainide, flecainide, moricizine, propafenone
- *Class II*: *BAA*—Atenolol, esmolol, metoprolol, bretylium, and timolol
- *Class III*: *Potassium channel blockers*—Acecainide, bretylium, amiodarone, sotalol
- *Class IV*: CCA
- *Unclassified*: Adenosine

Sodium Channel Blockers

Electrocardiogram changes, such as QRS widening and ventricular dysrhythmias, should prompt the physician to consider the possibility of sodium channel blocker toxicity. A syncopal event (e.g., quinidine syncope) may be the clinical manifestation of transient ventricular dysrhythmia.

All classes of drugs can cause significant cardiovascular toxicity which includes AV blocks, bradyarrhythmia, ventricular dysrhythmias, hypotension, and asystole. Extracardiac effects include CNS toxicity including paresthesia, dizziness, ataxia, tremors, sedation, confusion, seizure, coma, and respiratory arrest. CNS toxicity warrants immediate cardiovascular system evaluation as it may occur before cardiovascular toxicity. Disopyramide antagonizes muscarinic receptors causing mydriasis, tachycardia, hyperthermia, delirium, anhidrosis, erythema, ileus, and urinary retention. Quinine and quinidine can cause cinchonism which includes loss of vision, vertigo, and hearing impairment as the retina and inner hair cells damage occur due to toxicity. Drugs of classes IA and IC can also affect pancreatic beta cells by blocking potassium channel and releasing insulin causing hypoglycemia. Some agents may cause immune-related hypersensitivity reaction where symptoms include fever, rash, hepatitis, and blood dyscrasias. Drug-induced lupus has been reported with procainamide, quinidine, and tocainide.

Potassium Channel Blockers

Patients taking potassium channel blockers for therapeutic use or an overdose are at increased risk of torsade de pointes as they increase the duration of QTc interval. Episodes may resolve spontaneously only causing syncope or may persist and degenerate to ventricular fibrillation and sudden death (**Table 3**).

Management

General management includes a focus on airway, breathing, and circulation. Continuous cardiopulmonary monitoring is advised in all patients having antidysrhythmic toxicity. ECG should be done as early as possible. Decontamination with activated charcoal is beneficial. All patients with severe sodium channel blocking (defined as QRS > 120 ms, bradyarrhythmia, or hypotension) should be given sodium bicarbonate. Serum pH of 7.50–7.55 should be maintained. Sodium bicarbonate treatment causes kaliuresis and hypokalemia which in turn lead to difficulty in serum alkalinization. Hypokalemia also increases QTc interval and contributes to toxicity. So it is avoided to replace potassium liberally. Sodium lactate may also be useful. Dose of sodium bicarbonate is 1–2 mEq/kg IV bolus. Repeat as required to reverse QRS widening and dysrhythmia. Maintain an arterial pH 7.4–7.55.

Acidosis caused by seizures can potentiate cardiotoxicity, so it should be treated aggressively by using benzodiazepines, barbiturates, and propofol. In case of hypotension, give IV isotonic solution at a rate of 10–20 mL/h. If hypotension persists, direct-acting vasopressors should be given. Advanced cardiovascular life support (ACLS) protocol with cardioversion, IV magnesium sulfate, electrolyte correction, and overdrive pacing is indicated for recurrent polymorphic ventricular

TABLE 3: Potassium channel blocker toxicity.

Drugs	*Effects*
Amiodarone	• Thyroid dysfunction • Pulmonary fibrosis • Corneal deposits • Decreased inotropy with intravenous dosing • Skin pigmentation • Hepatitis • Peripheral neuropathy
Bretylium	Hypotension preceded by the initial sympathomimetic effect
Dofetilide	Torsade de pointes
Ibutilide	• Atrioventricular block • Torsade de pointes

tachycardia. Isoproterenol infusion can also be used along with them as it decreases temporal dispersion of refractoriness.

In stable monomorphic ventricular tachycardia, lignocaine and amiodarone are the first-line therapy.

Dose of lignocaine is 1–1.5 mg IV bolus. An additional bolus can be given over 3–5 minutes for refractory ventricular tachycardia/ventricular fibrillation (VT/VF). The total dose is not to exceed 3 mg/kg or >200–300 mg during a 1 hour period. During cardiac arrest, only bolus therapy is advised. Begin maintenance infusion of 1–4 mg/min once the circulation has been restored. Repeat 0.5 mg/kg bolus if arrhythmias recur during infusion and increase the rate of infusion incrementally (maximum infusion rate is 4 mg/min). The pediatric dose is 1 mg/kg initial bolus intravenously followed by continuous infusion of 20–50 μg/kg/min. In case of disopyramide overdose, do not use procainamide or quinidine or bretylium.

Along with conventional supportive measures and CPR, high doses of calcium chloride (0.5 g slowly every 5 min up to a maximum of 3 g) are effective in reversing some of the cardiac effects.

In case of class IC overdose, class IA drugs (quinidine, procainamide, disopyramide) are relatively contraindicated because of cross-over in electrophysiologic properties. The class IC drugs are moderately refractory to traditional antiarrhythmic drug therapy and cardioversion/ventricular pacing.

In class IC overdose, class IB (lignocaine, phenytoin, mexiletine, tocainide) may be the best alternative based on the electrophysiologic properties but they can also exacerbate toxicity.

Acute lung injury may occur with disopyramide and it may be delayed up to 24–72 hours after exposure. Mechanical ventilation and positive end-expiratory pressure (PEEP) may be required if a high FiO_2 is needed. Hemodialysis and hemoperfusion are effective in enhancing the elimination of the drug.

Amiodarone (Class III: Potassium Channel Blocker)

Amiodarone primarily prolongs cardiac action potential without changing the resting membrane potential. Vasodilation occurs as a result of noncompetitive α and β antiadrenergic activity. Substantial overdose in a patient can lead to bradycardia/heart block, torsade de pointes, and hypotension. Adult respiratory distress syndrome may be rapidly progressive. Pulmonary toxicity (pulmonary fibrosis/interstitial pneumonitis) may occur causing cough, dyspnea, fever, chest pain, weight loss, and abnormal pulmonary function tests. Rapid IV infusion can cause hypotension, ventricular arrhythmias, bradycardia, and heart block. Hypo- or hyperthyroidism or both can occur. Hepatotoxicity, acute pancreatitis, epididymitis, peripheral neuropathy, blue-green color discoloration of skin and nails, corneal microdeposits, bone marrow granuloma may also occur.

Decontamination can be done up to several hours after ingestion. Only stomach wash is advised. Oral Cholestyramine (4 g/h for 4 h) may reduce the half-life of amiodarone. Corticosteroids are used in pulmonary fibrosis. ECG monitoring is important even after several days of ingestion. Isoprenaline and direct current (DC) cardioversion is done in case of severe cardiovascular collapse. Beta adrenergic agonists or pacemaker in a case of bradycardia. They are also beneficial in sinus arrest. Amiodarone-induced nonsustained polymorphic tachycardia is treated with IV $MgSO_4$. Vasopressors are used in hypotension. Hemodialysis and hemoperfusion are not beneficial.

Adenosine

Adenosine is a nucleotide found in all cells. It is released from myocytes under various physiological and pathological conditions. It is used effectively in the treatment of reentrant supraventricular tachycardia when administered as a rapid IV bolus. It is a degenerative product of adenosine triphosphate (ATP) which in itself may be associated with a higher incidence of adverse effects than adenosine. Significantly lower doses of adenosine should be used in patients receiving dipyridamole as it potentiates the effect of adenosine by competitively inhibiting the transport of adenosine into the cells. Methylxanthines are competitive antagonists of adenosine so they may not be effective in patients taking methylxanthines. Prolonged bradycardia may occur if adenosine is given to patients with CCA toxicity.

Symptomatic and supportive treatment is recommended. Theophylline can be used in prolonged chest pain in patients having ischemic heart disease. The adverse effect of adenosine can be reduced by using a smaller initial dose. Inosine can be used before ATP to alleviate its adverse effects.

SUMMARY

Cardiovascular drugs are used widely in cardiovascular diseases and are among the most significant determinants of morbidity and mortality in the entire world. Because of the widespread use of these drugs, their overdose is also common. Mostly, the overdose is unintentional but the intentional use is not uncommon. The proportion of intentional overdose is also significant typically in younger population with less burden of cardiovascular disease. Sudden cardiac death in a young healthy person is most likely to be drug-related. Poisoning is the leading cause of cardiac arrest in patients younger than 40 years of age but infrequent in elderly patients. To manage these patient's proper assessment of hemodynamic status remains important so that pathophysiological derangement can be dealt with effective therapy. Extracorporeal support, e.g., intraaortic balloon pump cardiac bypass can be added in cases of severe toxicity and refractory to medical therapy.

MULTIPLE CHOICE QUESTIONS

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Salicylates, Acetaminophen, and Nonsteroidal Anti-inflammatory Drugs

209 CHAPTER

Ajay K Mishra, Jitendra Chandrakar

INTRODUCTION

Salicylates, acetaminophen (APAP), and nonsteroidal anti-inflammatory drugs (NSAIDs) are few of the common over-the-counter drugs used for relieving pain and fever. These drugs are also available in various combinations with other medicines, and their ease of availability makes them one of the most common among drug overdose and toxicity.

MECHANISM OF ACTION

All these drugs act as inhibitors of the cyclooxygenase enzyme responsible for prostaglandin synthesis, thus preventing prostaglandin-mediated inflammation and fever. APAP and NSAIDs are reversible inhibitors while salicylates cause irreversible inhibition of cyclooxygenase.

SALICYLATES

Salicylates are widely used all over the world for their anti-inflammatory, antipyretic, analgesic, and antiplatelet properties. *Aspirin is the most widely used salicylate* found in almost every other household.

Pharmacology

Salicylates are rapidly absorbed from the gastrointestinal (GI) tract and peak absorption occurs within 2–4 hours with serum concentration remaining elevated for >12 hours following an overdose in large quantity. Salicylates conjugate with glucuronic acid and glycine in the liver. Free salicylic acid and conjugated forms get eliminated by the kidney. Salicylates follow first-order kinetics at therapeutic concentrations while at serum concentration > 30 mg/dL, it follows zero-order kinetics.

In case of overdose, the kinetic changes from first order to zero order; hence, the metabolic rate becomes constant. Absorption is delayed due to aspirin-induced pylorospasm and formation of bezoar in the stomach. With elevated concentrations, the volume of distribution increases and protein binding decreases, resulting in more amount of free drug reaching the tissues. Saturation of the hepatic metabolic pathways and pH-dependent urinary excretion of salicylate leads to an increase in the half-life of salicylates at toxic concentrations.

Toxic dose: 200–300 mg/kg
Lethal dose: ≥500 mg/kg

Pathophysiology

- Salicylates stimulate the medullary respiratory centers causing hyperventilation and respiratory alkalosis.
- They mainly impair cellular respiration by inhibiting Kreb's cycle and uncoupling of oxidative phosphorylation, thus increasing the production of lactic acid causing metabolic acidosis. This decrease in pH causes an increase in the unionized form of the drug which can then easily cross the cell membranes and blood–brain barrier.
- They impair the glucose metabolism causing hypoglycemia and sometimes hyperglycemia.
- There is significant potassium loss because of vomiting, increased renal excretion, and inhibition of the active transport system.
- Salicylates also cause pulmonary and cerebral edema, the exact mechanism of which is not known.

Clinical Features

The patient may present initially with nausea, vomiting, tinnitus, impaired hearing, hyperventilation, and hyperthermia. Subsequently, the patient may develop severe dehydration. With an increase in acidemia, the patient develops central nervous system (CNS) symptoms, e.g., altered mental status, seizures, or coma.

Investigations

- Serum salicylate concentration should be measured after 6 hours of consumption, followed by a second sample after 2 hours to look for a serial rise in concentration which is indicative of continued absorption. A serum concentration of >100 mg/dL is associated with high mortality and is an indication for hemodialysis.
- Renal function test—to look for renal impairment

- Serum potassium
- Prothrombin time (PT) and international normalized ratio (INR)—to look for coagulopathy due to hepatotoxicity
- Blood gas analysis—to know the acid–base status, anion gap, and lactate levels and to guide the treatment
- An ECG—to look for changes due to hypokalemia.
- Chest X-ray—to look for pulmonary edema
- CT/MRI brain—if the patient presents with CNS symptoms

Management

Treatment objectives include cardiorespiratory stabilization, prevention of absorption, correction of acid–base abnormalities and fluid deficits, and increasing the elimination and excretion.

- Rapid assessment and stabilization of airway, breathing, and circulation
- Intubation should be avoided as it may worsen the toxicity and should be reserved only for patients with respiratory failure.
- Hypotensive and severely dehydrated patients should be aggressively hydrated with IV fluids. If the patient does not respond to fluid resuscitation, then vasopressors may be considered.
- *Gastric decontamination:* Gastric lavage is useful if done within 1 hour of ingestion. To reduce the absorption, activated charcoal should be given as early as possible. Due to delayed gastric emptying in salicylate overdose, repeated doses of activated charcoal can be given to prevent continued absorption.

  Whole bowel irrigation (WBI) is advisable for toxic doses of enteric-coated or sustained-release drugs, especially when such patients present >2 hours after ingestion when activated charcoal is not much effective.
- Dextrose should be given for hypoglycemia or to prevent neuroglycopenic symptoms in euglycemic patients.
- *Serum and urinary alkalization:* Alkalization therapy by using sodium bicarbonate remains the mainstay of treatment in salicylate toxicity. Sodium bicarbonate causes ion trapping, i.e., it increases the serum pH, thus ionizing more drug in the serum and subsequently decreasing tissue distribution. Sodium bicarbonate also alkalinizes the urine and hence prevents reabsorption of ionized salicylate in the kidneys and increases its excretion. An initial bolus of 1–2 mEq/kg should be administered followed by an infusion of 100–150 mEq in 1 L of sterile water with 5% dextrose at 1.5–2 times the maintenance dose of IV fluids. The target is to maintain a serum pH of 7.45–7.55 and a urine pH of 7.5–8. Alkalization should be continued till (1) serum salicylate level is <40 mg/dL, (2) serum pH has returned to the normal level, (3) metabolic acidosis has resolved, and (4) the patient is asymptomatic.
- Hypokalemia, if present, should be corrected and prevented for alkalization therapy to be effective.
- *Hemodialysis:* The indications of hemodialysis in salicylate poisoning are as follows:
  - Serum salicylate concentration > 90 mg/dL
  - pH ≤ 7.20
  - Altered mental status
  - Cerebral and/or pulmonary edema
  - Fluid overload
  - Renal failure

Disposition

Patients who have CNS symptoms, pulmonary edema, dehydration, acidosis, electrolyte imbalance, renal dysfunction, or increasing serum salicylate levels during repeated testing should be admitted to a hospital, preferably in the critical care unit. Patients can be discharged only if asymptomatic or serum salicylate levels are on decreasing trends.

ACETAMINOPHEN

Acetaminophen (chemical name: N-acetyl-para-aminophenol) or *paracetamol* is the 25th most commonly prescribed drug worldwide for pain and fever. APAP toxicity, due to either intentional ingestion or therapeutic misadventure, is one of the leading causes of hepatic failure and mortality in the USA.

Pharmacology

Acetaminophen is rapidly absorbed mainly in the small intestine with peak plasma concentrations reaching within 1 hour and complete absorption within 4–5 hours of ingestion. The therapeutic dose of APAP is 10–15 mg/kg/dose in children (up to a maximum of 75 mg/kg/day) and 325–1,000 mg/dose in adults every 4–6 hours (not to exceed 4,000 mg/day). Therapeutic concentration ranges between 10 and 20 µg/mL. Elimination half-life is usually 2–4 hours. Toxicity occurs usually after a single dose of ≥150 mg/kg or in multiple staggered doses.

Pathophysiology

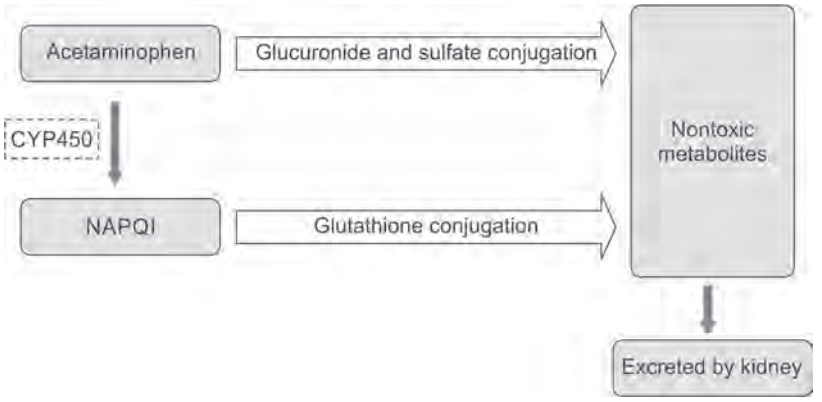
At a therapeutic dose, around 90% of APAP is metabolized in the liver and around 2–3% is excreted unchanged in the urine. The rest of the metabolism takes place via the cytochrome P450 oxidase pathway and gets converted to a toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). This NAPQI gets conjugated with glutathione to form nontoxic metabolites which are excreted in urine (**Fig. 1**).

In case of overdosage, the glucuronide and sulfates get saturated and more of NAPQI is produced. With the depletion of glutathione stores in the liver due to excess of NAPQI, the concentration of toxic metabolite NAPQI increases leading to liver damage and hepatic necrosis (**Fig. 2**).

Patients taking substances or medications that induce the cytochrome P450 system (alcohol, anticonvulsant, or antituberculous drugs) or those with glutathione depletion (poor nutrition, alcoholics, and acquired immunodeficiency syndrome patients) are at an increased risk of hepatic toxicity. The clinical features of APAP toxicity have been divided into four stages (**Table 1**).

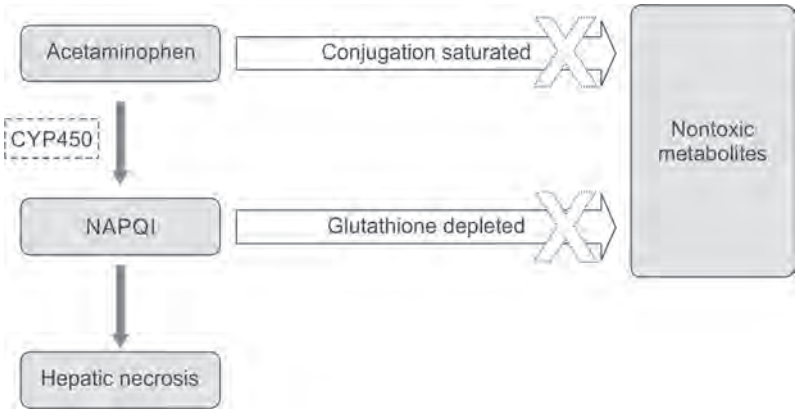
Investigations

- Serum APAP concentration—should be obtained 4 hours after ingestion
- Liver function tests (LFT)—may not be abnormal until >18 hours after the overdose. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most sensitive markers of liver damage.
- INR—a very sensitive marker of liver damage and the best prognostic parameter



(NAPQI: *N*-acetyl-*p*-benzoquinone imine)

FIG. 1: Metabolism of acetaminophen at therapeutic dose.



(NAPQI: *N*-acetyl-*p*-benzoquinone imine)

FIG. 2: Metabolism of acetaminophen at toxic dose.

TABLE 1: Clinical features of acetaminophen toxicity.

Stages	*Time course*	*Clinical manifestations*	*Laboratory abnormalities*
Stage 1	<24 h	Asymptomatic or anorexia, nausea, vomiting	Hypokalemia
Stage 2	2–3 days	• Improvement in anorexia, nausea, and vomiting • Abdominal pain, hepatic tenderness, jaundice	Elevated serum transaminases, elevated bilirubin, and prolonged prothrombin time if severe
Stage 3	3–4 days	• Recurrence of anorexia, nausea, and vomiting • Encephalopathy, anuria, jaundice	Hepatic failure, metabolic acidosis, coagulopathy, renal failure, pancreatitis
Stage 4	>4 days	Clinical improvement and recovery (7–8 days) or deterioration to multiorgan failure and death	Improvement and resolution or continued deterioration

- Renal function—creatinine is a useful prognostic marker and low urea may suggest malnutrition and therefore glutathione depletion.
- Blood sugar levels—to look for hypoglycemia
- Blood gas analysis—to check for acid–base disturbances. Metabolic acidosis, if present, is a poor prognostic sign.

Management

Treatment objectives include supportive care, prevention of drug absorption, and administration of an antidote.

- Rapid assessment and stabilization of airway, breathing, and circulation
- *Gastric decontamination*: Gastric lavage is useful if done within 1–2 hours of ingestion. To reduce the absorption, activated charcoal should be given within 4 hours of ingestion if no contraindications are present.
- Antiemetics should be given to control nausea and vomiting.
- *Antidote*: *N-acetylcysteine (NAC) is the antidote for APAP toxicity*. It binds to the toxic metabolite NAPQI and prevents hepatic damage.
  The IV dosing schedule is as follows:
  - 150 mg/kg in 200 mL of 5% dextrose over 1 hour, followed by

- 50 mg/kg in 500 mL 5% dextrose over 4 hours, followed by
- 100 mg/kg in 1,000 mL 5% dextrose over 16 hours

The oral dosing schedule is as follows:

- 140 mg/kg PO as a loading dose, followed by
- 70 mg/kg PO every 4 hours for a total of 17 doses

N-acetylcysteine can cause side effects ranging from local erythema and urticaria around the infusion site to angioedema or life-threatening anaphylaxis. If anaphylaxis occurs, the infusion should be stopped immediately and anaphylaxis should be treated. Once anaphylaxis settles, the entire dose of acetylcysteine may then be administered, possibly at a slower rate of infusion (e.g., at a rate of 50 mg/kg/h) or by the oral route regimen.

The timing of the overdose decides the treatment to be followed in case of APAP toxicity (**Table 2**). Paracetamol treatment nomogram (*Rumack–Matthew nomogram*) should be used to interpret the measured serum paracetamol levels. NAC should be continued if (any one of the following):

- Paracetamol level is on or above the treatment line between 4 and 15 hours after a single ingestion.
- Serum paracetamol is still detectable 15 hours after single ingestion.
- Serum paracetamol is detectable 4 hours after uncertain time of ingestion.
- INR > 1.3
- ALT > 53 IU/L

Liver transplantation: It is needed in patients with severe APAP -induced liver injury which not improving by NAC and supportive care. The Modified Kings College Criteria for paracetamol toxicity are used to identify patients who may require transplantation:

- pH < 7.3 or
- Arterial lactate >3.5 mmol/L after 4 hours of early fluid resuscitation or arterial lactate >3.0 mmol/L after 12 hours of fluid resuscitation, or
- PT > 100 seconds (INR > 6.5), and
- Creatinine > 300 μmol/L, and
- Grade 3 or 4 hepatic encephalopathy

Disposition

Patients who are asymptomatic and fit into the criteria for treatment with NAC can be admitted to the emergency observation unit or ward. Patients with severe hepatotoxicity or having a risk of fulminant hepatic failure should be treated in the intensive care unit.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are a group of drugs having anti-inflammatory, analgesic, and antipyretic properties. They are classified as nonselective cyclooxygenase (COX) inhibitor (traditional NSAIDs) or selective COX-2 inhibitor.

Pharmacology

NSAIDS get completely absorbed from the upper small intestine and within 1–2 hours reach peak serum levels. They are weak acids, tightly bound to plasma proteins, and thus have a low volume of distribution (0.1–0.2 L/kg). NSAIDs are metabolized by hepatic transformation, mainly oxidation and glucuronidation, and excreted in the urine. Their elimination half-lives vary from short acting (<6 h, e.g., ibuprofen, diclofenac, ketoprofen, indomethacin) to long acting (>6 h, e.g., naproxen, celecoxib, piroxicam).

Clinical Features

Most of the patients with NSAIDs overdose remain asymptomatic and very few patients show minor CNS or GI symptoms, e.g., nausea, vomiting, drowsiness, blurred vision, and dizziness.

TABLE 2: Management of acetaminophen poisoning according to timing.

Timing	*Total dose*	*Investigation*	*Management*
Single ingestion in <1 h	>150 mg/kg	Delay blood sampling until 4 h postingestion	Activated charcoal (50 g orally), IV antiemetic, admit for observation while sampling awaited at 4 h
Single ingestion in >1 h but <4 h	>150 mg/kg	Delay blood sampling until 4 h postingestion	Activated charcoal (50 g orally), IV antiemetic, admit for observation while sampling awaited at 4 h
Single ingestion in >4 h but <8 h	<150 mg/kg	Blood sampling for serum paracetamol level	If the result is expected to be available before 8 h of ingestion, treatment should be guided by the result
	>150 mg/kg	Blood sampling for serum paracetamol level	If the result is not expected to be available before 8 h, NAC should be started immediately without waiting for the result
Single ingestion 8–24 h	<150 mg/kg	Blood sampling for serum paracetamol level	Treatment should be guided by the result
	>150 mg/kg	Blood sampling for serum paracetamol level	NAC should be started immediately without waiting for the result
Single ingestion >24 h	>150 mg/kg	Blood sampling for serum paracetamol level	NAC should be started immediately without waiting for the result
Timing unclear or ingestion is staggered		Blood sampling for serum paracetamol level	Treatment should be started immediately without waiting for the result

(NAC: N-acetylcysteine)

The most commonly ingested NSAID in overdose is ibuprofen. Usually, minor toxicity is seen in ingestion of doses >100 mg/kg whereas significant clinical toxicity is seen after ingestion of massive overdose, i.e., >400 mg/kg. Massive ingestions (particularly ibuprofen and naproxen) can cause high anion gap metabolic acidosis resulting in cardiac dysrhythmias and electrolyte abnormalities.

Acute kidney injury and renal papillary necrosis can result after a massive overdose and are more prone in patients with protracted hypovolemia and hypotension. This renal dysfunction is usually reversible and improve with supportive measures.

Central nervous system effects range from drowsiness to coma. Seizures are seen in many NSAIDs overdose, e.g., ibuprofen, diclofenac, indomethacin, and mefenamic acid.

Indomethacin overdose can cause hematological toxicity, e.g., aplastic anemia and agranulocytosis. NSAIDs can also cause allergic reactions ranging from urticaria to anaphylaxis.

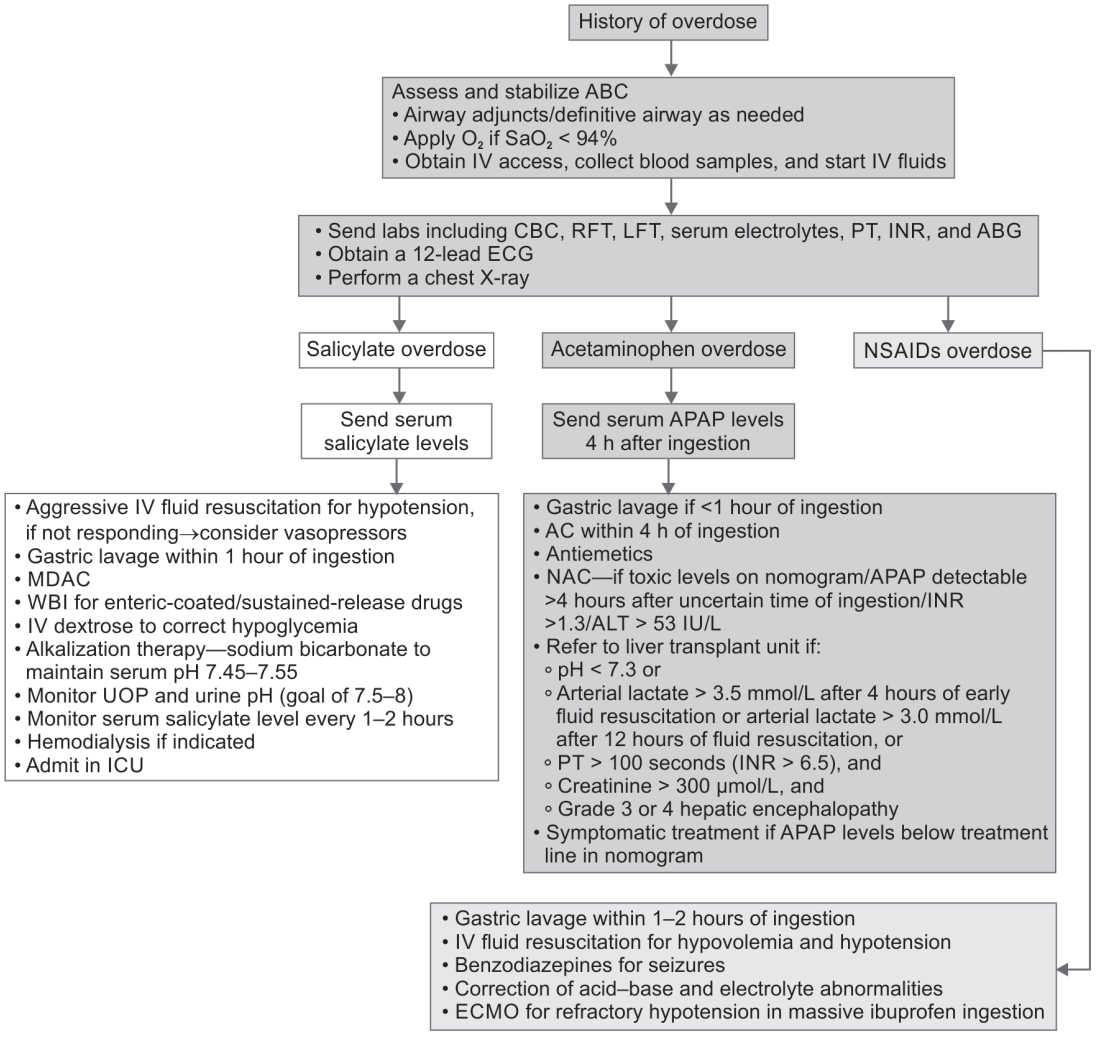
Investigations

- Blood gas analysis to rule out acid–base abnormalities and electrolyte disturbances
- ECG to look for any dysrhythmias
- Renal function test to assess renal dysfunction
- Serum NSAIDs levels are not of much use, but serum salicylates and APAP levels should be checked to rule out coingestions.
- Brain imaging, if indicated according to clinical history, to rule out other causes of CNS symptoms

Management

Management of NSAIDs overdose is usually supportive and no specific antidotes are available.

- Rapid assessment and stabilization of airway, breathing, and circulation


History of overdose
Assess and stabilize ABC
• Airway adjuncts/definitive airway as needed
• Apply O_2 if SaO_2 < 94%
• Obtain IV access, collect blood samples, and start IV fluids
• Send labs including CBC, RFT, LFT, serum electrolytes, PT, INR, and ABG
• Obtain a 12-lead ECG
• Perform a chest X-ray
Salicylate overdose
Acetaminophen overdose
NSAIDs overdose
Send serum salicylate levels
Send serum APAP levels 4 h after ingestion
• Aggressive IV fluid resuscitation for hypotension, if not responding→consider vasopressors
• Gastric lavage within 1 hour of ingestion
• MDAC
• WBI for enteric-coated/sustained-release drugs
• IV dextrose to correct hypoglycemia
• Alkalization therapy—sodium bicarbonate to maintain serum pH 7.45–7.55
• Monitor UOP and urine pH (goal of 7.5–8)
• Monitor serum salicylate level every 1–2 hours
• Hemodialysis if indicated
• Admit in ICU
• Gastric lavage if <1 hour of ingestion
• AC within 4 h of ingestion
• Antiemetics
• NAC—if toxic levels on nomogram/APAP detectable >4 hours after uncertain time of ingestion/INR >1.3/ALT > 53 IU/L
• Refer to liver transplant unit if:
◦ pH < 7.3 or
◦ Arterial lactate > 3.5 mmol/L after 4 hours of early fluid resuscitation or arterial lactate > 3.0 mmol/L after 12 hours of fluid resuscitation, or
◦ PT > 100 seconds (INR > 6.5), and
◦ Creatinine > 300 µmol/L, and
◦ Grade 3 or 4 hepatic encephalopathy
• Symptomatic treatment if APAP levels below treatment line in nomogram
• Gastric lavage within 1–2 hours of ingestion
• IV fluid resuscitation for hypovolemia and hypotension
• Benzodiazepines for seizures
• Correction of acid–base and electrolyte abnormalities
• ECMO for refractory hypotension in massive ibuprofen ingestion

(AC: activated charcoal; ABC: airway, breathing circulation; ABG: arterial blood gas; APAP: acetaminophen; CBC: complete blood count; ECG: electrocardiogram; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; INR: international normalized ratio; IV: intravenous; LFT: liver function test; MDAC: multiple-dose activated charcoal; NAC: N-acetylcysteine; NSAIDs: nonsteroidal anti-inflammatory drugs; PT: prothrombin time; RFT: renal function test; UOP: urine output; WBI: whole bowel irrigation)

FLOWCHART 1: Summary: Algorithm for salicylates acetaminophen NSAIDs toxicity.

- Although very little evidence is available, gastric lavage and activated charcoal may be considered for massive overdosage presenting within 1–2 hours of ingestion.
- In case of hypovolemia and hypotension, rapid IV crystalloid infusion should be given.
- Acid–base abnormality and dyselectrolytemia should be corrected through supportive measures.
- Seizures should be treated with benzodiazepines.
- Extracorporeal membrane oxygenation can be considered for refractory hypotension in case of massive ibuprofen ingestion.

Disposition

Patients with small ingestions, <100 mg/kg, and asymptomatic can be discharged from the emergency room after giving primary supportive therapy. Patients with massive ingestions, >400 mg/kg, suspected coingestions of salicylates or APAP, acid–base abnormalities, or CNS symptoms will require hospitalization for further management.

SUMMARY

Salicylates, APAP, and NSAIDs are the common drugs which are available over the counter and used for relieving pain and fever. These drugs are also available in various combinations with other medicines, and their ease of availability makes them one of the most common among drug overdose and toxicity. The emergency physician should be aware of the clinical features of their toxicity and guideline for the management (**Flowchart 1**).

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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210 CHAPTER

Hydrocarbons and Volatile Substances

Atanu B Bhattacharya

INTRODUCTION

Hydrocarbons are a group of organic compounds having carbon and hydrogen elements. It is the basis of many structures, from plants to vegetables which are consumed, and of various substances derived from petroleum such as fuels, polymers, various oils, and solvents and used in the manufacturing of drugs and dyes. Some of the compounds are in a liquid form while some in a gaseous form and some are volatile in nature at room temperature and pressure while others are converted by the combustion process. The state of the hydrocarbon is determined by the length of its chain and its branching. Compounds of hydrocarbon that get converted to a gaseous state are termed *volatile organic compounds* (VOCs). Benzene, toluene, xylene, and tetrachloroethylene are a few common VOCs. They can create petrochemical smog in the environment and are potentially toxic and carcinogenic. *Most of the VOCs are mixed hydrocarbons and abused by sniffing, huffing, and bagging*. Substances being commonly abused as volatile substances are fuels and solvents.

CLASSIFICATION AND PROPERTIES

Hydrocarbons are classified on the basis of their structure: (1) Acyclic or aliphatic, which are then divided into alkanes (C_nH_{2n+2}), alkenes (C_nH_{2n}), and alkynes (C_nH_{2n-2}); (2) Aromatic hydrocarbons (arenes) (**Table 1**).

The toxicity of hydrocarbons depends on their viscosity, measured in Saybolt universal seconds (SUS), the cutoff point being SUS = 60. The less the viscosity, the more hazardous it becomes with a higher risk of aspiration. Low surface tension and high volatility are associated factors for more toxicity of hydrocarbons including the chemical activity of the hydrogen side chain (**Table 2**).

High volatility causes hypoxia and direct irritation to the lungs. Toxicity can thus occur by either ingestion or inhalation and less by direct contact to the skin. Petroleum distillates are ingested more while halogenated hydrocarbons are mostly inhaled; even direct exposure to skin can occur. Ingestion can be deliberate or accidental and inhalation happens mostly as an abusing agent and sometimes accidental. Inhalation abuse happens by either sniffing, huffing, or bagging. Sniffing is by inhalation from a container directly or by putting the substance in a container. Huffing is by putting the liquid in a cloth or cloth-like substance and then inhaling it while bagging is putting the volatile hydrocarbons in a bag (plastic or paper) and then breathing and rebreathing through it.

PATHOPHYSIOLOGY

A combustible hydrocarbon such as *Kerosene* is found abundantly in the household and in the community and is one of the frequent causes of poisoning, both as accidental and as suicidal poison. The main effects of these poisons are

TABLE 1: Classification of hydrocarbon with its uses.

Hydrocarbon group	*Example*	*State at room temperature*	*Uses*
Aliphatic	Methane, propane, butane, gasoline, kerosene, mineral spirits, mineral oil, mineral seal oil, diesel oil, n-hexane, naphtha	Gas and liquid	Fuels, liquid fuels, solvents, furniture polish, degreasers, multiple uses in the chemical industry
Aromatic	Toluene, xylene, benzene	Liquids	Used in plastics, pharmaceutical, rubber, chemical, and solvent industries, degreasers
Halogenated	Methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, Freon, methyl bromide, lindane,	Liquids	Solvents cleaning fluids, degreasers, fire extinguishers, paint strippers, fumigants
Others	Turpentine, pine oil, oil of wintergreen, pennyroyal	Liquids	Solvents, household disinfectants, incense

TABLE 2: Properties of hydrocarbons and their effect.

Properties of hydrocarbons	*Inference from the term*	*Effects*
Viscosity	The property to oppose the flow or the liquidity of a substance	Less viscosity, more free flow, and more chances of aspiration
Volatility	The property of liquids to get converted to gas	Causes direct effect on the lungs and causes hypoxia by displacing O_2
Surface tension	Property of the liquid to adhere to a surface	Low surface tension, more chances of aspiration
Lipophilicity	The ability of a substance to attach to the lipid molecule	Crosses the blood–brain barrier and is stored in tissues for long

on the gastrointestinal (GI) tract and then on the lungs due to aspiration. The aspiration is mostly due to the vomiting but can be without vomiting as well, attributable to its low viscosity. Other alkanes such as turpentine oil having high viscosity and low volatility and have less chances for aspiration but are readily absorbed through the GI tract and lungs (on inhalation), and they have toxic effects on the GI tract and the central nervous system (CNS). They are usually excreted by the kidneys after metabolization. Ingestion has a variable absorption rate; the higher the molecular weight, the lesser the absorption.

Alkanes, such as methane, ethane, propane, butane, and pentane, are in the form of gases and when inhaled have local toxic effects on lungs. The effect on the lungs is manifested by injury to the basement membrane between the alveoli and the capillary bed leading to hypoxia and pneumonitis. After absorption, high concentrations are detected in adipose tissues, liver, and other organs such as kidney, brain, lung, heart, thymus, or testes as well. These gases have narcotic properties and can cause hypotension and respiratory arrest as well. The inhaled hydrocarbon gets into the adipose tissues and liver and is stored there for a long time even after the exposure stops. Polycyclic aromatic hydrocarbons (PAH) induce liver enzymes CYP450, CYP1A1 and CYP1A2, CYP1B1, CYP2B, CYP2C, and CYP3A. These enzymes are responsible for the metabolism of hydrocarbons (PAH) in the body. Hydrocarbons after absorption from the lungs by diffusion through the alveoli reach the capillaries and cross the blood–brain barrier due to their lipophilic nature and have high concentration in the brain affecting the gamma aminobutyric acid (GABA), dopamine, and opioid receptors.

After ingestion of PAH, the intestinal CYP450 induced along with other cytochrome enzymes mentioned are responsible for the metabolism. Hydrocarbons cause destruction to stratum corneum and duration of contact, denuded skin, and multiple exposure increase skin absorption. Few hydrocarbons, such as carbon tetrachloride and methylene chloride, get metabolized to toxic substances inside the body leading to involvement and failure of organs, especially the liver.

CLINICAL PRESENTATION

The symptoms of hydrocarbon poisoning are attributed to its main effects on the lungs, GI tract, and brain. Ingestion of hydrocarbon in its liquid form can lead to cough, vomiting, choking sensation, and burning sensation in the stomach. Ingestion in children causes cyanosis and can lead to respiratory difficulty. The respiratory difficulty in children and adults is mostly due to the aspiration which occurs during the episodes of vomiting. Less viscosity, along with low surface tension of substances such as kerosene and gasoline, has more propensities for aspiration from the upper GI tract to the trachea causing hypoxia and pneumonitis. Aspirated hydrocarbon causes the loss of surfactant in the alveolar lining leading to collapse of the affected alveoli and ventilation–perfusion (V/Q) mismatch.

The signs and symptoms of aspiration would start as early as half an hour after ingestion and peaks in about 2 days with coughing and signs of respiratory distress (tachypnea, dyspnea, choking sensation, grunting, labored breathing, hypoxic, and cyanosis). The symptoms vary from mild to severe and on examination can have rales and rhonchi. A patient can develop alveolitis, pulmonary edema, pulmonary infiltrates, collapse of lung, pneumothorax, pneumomediastinum, pneumopericardium, hemoptysis, and fever as well. Upper airway involvement causes irritation, hyperemia, and inflammation.

Organs such as brain get involved though systemic absorption or due to inhalation and further diffusion which is manifested by the depressant effect on the brain as manifested by decreased sensorium, lethargy, and convulsions. It causes demyelination, loss of axons, and deposit of iron in the brain. Hydrocarbons toxicity can cause fatal arrhythmias, sudden cardiac death (sniffing effect), myocardial dysfunction, and intravascular hemolysis. It can cause damage to the kidneys causing acute glomerulonephritis, chronic interstitial nephritis, and renal tubular acidosis. Dermatitis of the exposed skin, deranged hepatic enzymes, and fatty infiltration of liver are a few of the other systemic manifestations encountered. Acute liver failure can occur with halogenated hydrocarbons (carbon tetrachloride and methylene chloride) where the degraded toxic metabolite results in hepatic necrosis. These chlorinated hydrocarbons, such as carbon tetrachloride and methylene chloride, are also found to be carcinogenic.

Sudden sniffing death syndrome is a known entity of hydrocarbon inhalation mostly due to halogenated hydrocarbon but may occur with other hydrocarbon inhalation as well. Sudden onset of tachyarrhythmias occurring as a reactive response to endogenous catecholamine leads to this syndrome.

Specific aromatic hydrocarbons such as benzene can cause aplastic anemia, acute myelogenous leukemia, myelodysplastic syndrome, and lymphomas.

Chronic inhalation of hydrocarbons causes permanent cerebral changes in the form of cerebellar degeneration, dementia, chronic encephalopathy, neuropathy, memory, and attention deficits due to loss of neurons, axonal degeneration, and gliosis.

RED FLAGS

- Shortness of breath following hydrocarbon ingestion/inhalation suggests aspiration.
- Swelling and inflammation of the mouth and oropharynx warrants early airway intervention.
- Sudden onset of arrhythmias and cardiac arrest can occur with hydrocarbon sniffing.
- Halogenated hydrocarbons' ingestion can lead to fulminant hepatic failure.
- Acute kidney injury can occur with hydrocarbon toxicity which may require dialysis.

EVALUATION

History

A history suggestive of consumption of a hydrocarbon, preferably with the details, should be sought. Sudden onset of vomiting in children or adults with a characteristic smell could clinch the cause of the condition. The smell of kerosene, turpentine oil, and sweet gasoline-like odor of benzene would give a clue to the consumption. An occupational history is important as exposure can occur in the workplace. The details about the route of exposure, quantity consumed, time at which exposure occurred, time of onset of symptoms, and nature of symptoms need to be documented. There is a need to identify hydrocarbon with other additives and toxicity (**Table 3**).

The symptoms soon after ingestion, along with symptoms on arrival, should be assessed. The quantity of the hydrocarbon consumed and the time at which the person seeks medical care are important. In chronic abusers, typical skin changes occurring, especially bagging in and around mouth and nose which can be identified.

Evaluation of airway (A), breathing (B), and circulation (C) should be undertaken along with checking the sugar. An arterial blood gas (ABG) analysis could give a clue to the metabolic status of the patient. An X-ray should be done to look out for signs of aspiration. An ECG could suggest any ongoing arrhythmia. An evaluation of the patient should focus on the GI tract and lung involvement along with the involvement of the brain. Evaluation of the other organs should be done if the history and examination, along with the identified poison, can cause particular organ damage.

Physical Examination

Examination findings may reveal presence of facial swelling, ulceration, and other skin changes. Look at the tongue and oral cavity for swelling, redness, ulceration, and any signs of burns. A thorough general examination (pallor, cyanosis, clubbing, icterus, pedal edema) and a head-to-toe examination along with systemic examination of respiratory system(mainly focuses on signs of pneumothorax and mediastinal shift). Evaluation of cardiac status would require a look for signs of failure, arrhythmias assessed by tachycardia with or without pulse, pedal edema, and right hypochondriac tenderness. Pain over the epigastric region could occur due to the ingestion causing local gastric irritation, ulceration, and hematemesis. A neurological assessment needs to be done to find out the level of consciousness of an individual along with any signs of seizures. Renal involvement could be assessed by the patient's acidotic status along with decreased urine output, swelling involving the periorbital region, lower limb, or generalized edema.

TABLE 3: Hydrocarbons with additives and systemic toxicity.

Hydrocarbon	*Toxicity*
Camphor	Neurotoxicity and convulsions
Halogenated hydrocarbon	Arrhythmias and liver failure
Aromatic hydrocarbon	Bone marrow depression and leukemia
Metals	Neurotoxicity
Pesticides	Convulsions, cholinergic crises, and respiratory depression

Interpretation of the Findings

History suggestive of accidental consumption of hydrocarbons or chronic abuse coupled with the smell of hydrocarbon helps to find out the signs and symptoms that are consistent with the poisoning, and a physical examination helps to arrive at a diagnosis of hydrocarbon ingestion or inhalation. Certain symptoms can occur due to concomitant toxicity with other substances apart from hydrocarbon toxicity. CNS depressants effect can be due to the use of sedatives or alcohol consumption; similarly, pneumonitis may be due to other poisons such as organophosphorus and paraquat. Pain over the right upper quadrant could also be due to acute fulminant hepatitis along with an enlarged liver. Fever and leukocytosis are common and may not reflect infection.

INVESTIGATION

The diagnosis of hydrocarbon poisoning could be done with the history, characteristic smell, symptoms, and signs consistent with the history. Few investigations could directly give a clue to the offending hydrocarbon poisoning—urine for hippuric acid and toluene, urine for phenol and S-phenylmercapturic acid (S-PMA) for benzene, and carbon monoxide levels for methylene chloride. Certain investigations which should be carried out would be complete blood count (CBC), renal profile, and liver function test. ABG analysis should be done which would help to determine the involvement of various organs due to poisoning and to find out any other associated poisoning. An X-ray of chest is done to check for signs of aspiration (**Fig. 1**), such as pneumatocele, pleural effusion, pneumothorax, and pneumonia. For coexisting infections, sputum cultures may be of help to rule out other bacterial pneumonia.

For chronic abusers (inhalant hydrocarbons), MRI could help to see the involvement of the brain in the form of atrophic changes and hypointensity in T2-weighted images involving the thalamus and basal ganglia.

TREATMENT

Management of a patient of suspected hydrocarbon poisoning would depend upon the ingested or inhaled poison with associated organ involvement and radiological finding encountered. There is no specific antidote available for hydrocarbon poisoning. The patient should be taken to the bed and connected to the monitor; start oxygen if the SpO_2 is <94% and get IV line secured. Begin with an assessment of

FIG. 1: Aspiration pneumonia due to kerosene.

Courtesy: Department of Emergency, Apollo Hospitals, Bilaspur, Chhattisgarh, India.

the airway and the need for airway management including the placement of advanced airway. Any oral or oropharyngeal swelling and hoarseness of voice would warrant an early definitive airway. Assessment of breathing should include the rate, effort, respiratory distress, development of cyanosis, low SpO_2, noisy breathing, audible wheezes and finding consistent with pneumothorax, and consolidation. This would require oxygenation, ventilation, nebulization with beta-agonists, intercostal drain (ICD) placement for pneumothorax and prevention of secondary infection with the use of appropriate antibiotics.

Poisoning due to ingestion of hydrocarbons with no symptoms should not be lavaged and activated charcoal use should be avoided as this could increase the risk of aspiration and pneumonitis. In case of hydrocarbons with inherent toxicity [CHAMP (*C*amphor, *H*alogenated hydrocarbons, *A*romatic hydrocarbons, *M*etals, *P*esticides)] or mixed with other substances, gastric lavage may be undertaken by securing the airway by endotracheal intubation. Activated charcoal may be used in such cases if the substance gets adsorbed. A thorough decontamination should be undertaken (removing all the clothes and giving a full bath to remove the skin contaminants).

Patients who are symptomatic and have X-ray changes suggestive of aspiration should be hospitalized. Early use of surfactant in aspiration could help in improving the oxygenation and prevent the development of pneumonitis in cases where the oxygen index is high; PaO_2/FiO_2 ratios are low with low lung compliance. Use of corticosteroids is not of much benefit in cases of hydrocarbon pneumonitis.

Management of pneumonitis, along with respiratory distress, would require mechanical ventilation. There occurs a large V/Q mismatch leading to the use of high positive end-expiratory pressure (PEEP) for ventilating these cases. Risk for barotraumas due to high PEEP can be managed with high-frequency jet ventilation (HFJV) and extracorporeal membrane oxygenation (ECMO), this being the last resort if all methods fail though it carries a poor outcome.

Cardiac arrhythmias occurring due to hydrocarbon poisoning could be managed using advanced cardiac life support (ACLS) or pediatric advanced life support (PALS) protocols. Avoid using catecholamine as it can cause worsening of arrhythmias [use short-acting beta-blockers (esmolol, metoprolol) for cardiac dysrhythmias]. Epinephrine can cause arrhythmias in acute poisoning and should be avoided (use vasopressin).

N-acetylcysteine (NAC) for fulminant hepatic failure due to carbon tetrachloride and hyperbaric oxygen therapy for methylene chloride or carbon tetrachloride poisoning can be used.

Skin involvement may present as burn which needs to be washed with warm water, decontaminated and managed as per the standard burn protocol. Skin rash occurring due to chronic exposure, over the mouth and nose, needs to be kept clean, prevented from secondary infection, and re-exposure needs to be stopped.

Supportive care, prevention of organ failure, and treating secondary infection remain the mainstay of treatment. Management of hydrocarbons toxicity is summarized in **Flowchart 1**.

DISPOSITION

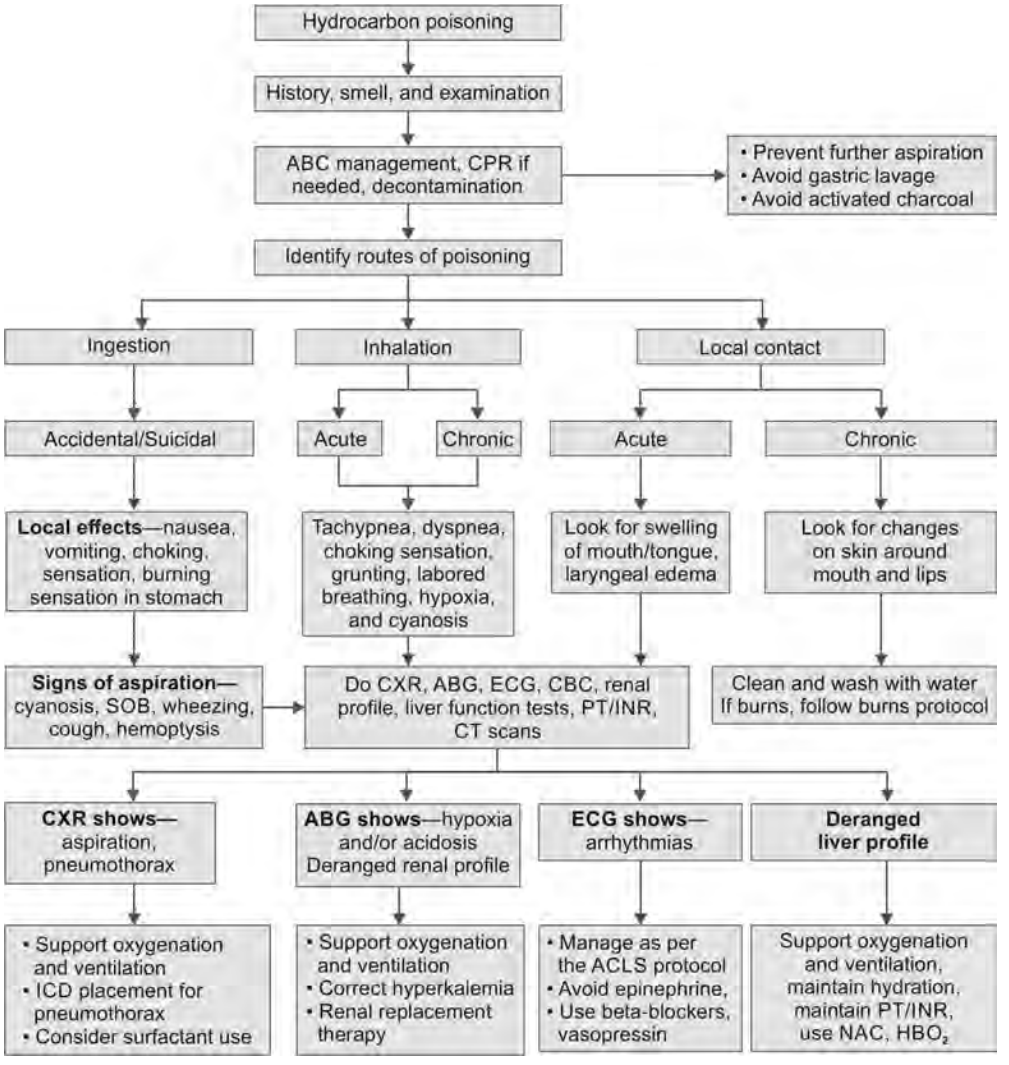
Patients needing ventilation support, high FiO_2 and PEEP, use of vasopressors for maintaining blood pressure, altered sensorium, and multiorgan involvement should be managed in intensive care unit (ICU), and those with minimal symptoms of respiratory involvement, i.e., conscious patients, can be managed in wards.

Patients with hydrocarbon ingestion/inhalation with almost no symptoms along with no respiratory or CNS involvement should be in observation for 6 hours followed by X-ray. If the patient remains stable and symptom-free, then he/she can be discharged home. In case symptom appears, the patient would need hospitalization.

SUMMARY

Hydrocarbons are organic compounds of carbon and hydrogen occurring in liquid and gaseous states.

- Toxic effects of hydrocarbons are attributed to their viscosity, volatility, surface tension, and hydrogen side chain.
- Hydrocarbon toxicity occurs due to aspiration, inhalation, and by dermal contact.
- Aspiration pneumonitis, cardiac arrhythmias, seizures, hepatic failure, renal failure, and bone marrow depression are complications of various hydrocarbons.
- Sniffing death syndrome is a dreaded complication of hydrocarbon inhalation abuse.
- There is no antidote for hydrocarbon poisoning as of date.
- Symptomatic care along with close observation and monitoring, organ support, and preventing secondary infection are the cornerstones of management.
- Giving gastric lavage and use of activated charcoal are contraindicated except in selective cases.
- Patients with aspiration would require ICU care with supplemented oxygenation and ventilation though the symptoms of aspiration can be delayed.
- Cardiac arrhythmias need to be managed as per ACLS guidelines with a caution to avoid use of catecholamines.
- Patients of hydrocarbon aspiration/inhalation can be discharged after 6 hours if they remain symptom-free and chest X-ray is normal.


Hydrocarbon poisoning
History, smell, and examination
ABC management, CPR if needed, decontamination
• Prevent further aspiration
• Avoid gastric lavage
• Avoid activated charcoal
Identify routes of poisoning
Ingestion
Inhalation
Local contact
Accidental/Suicidal
Acute
Chronic
Acute
Chronic
Local effects—nausea, vomiting, choking, sensation, burning sensation in stomach
Tachypnea, dyspnea, choking sensation, grunting, labored breathing, hypoxia, and cyanosis
Look for swelling of mouth/tongue, laryngeal edema
Look for changes on skin around mouth and lips
Signs of aspiration—cyanosis, SOB, wheezing, cough, hemoptysis
Do CXR, ABG, ECG, CBC, renal profile, liver function tests, PT/INR, CT scans
Clean and wash with water If burns, follow burns protocol
CXR shows—aspiration, pneumothorax
ABG shows—hypoxia and/or acidosis Deranged renal profile
ECG shows—arrhythmias
Deranged liver profile
• Support oxygenation and ventilation
• ICD placement for pneumothorax
• Consider surfactant use
• Support oxygenation and ventilation
• Correct hyperkalemia
• Renal replacement therapy
• Manage as per the ACLS protocol
• Avoid epinephrine,
• Use beta-blockers, vasopressin
Support oxygenation and ventilation, maintain hydration, maintain PT/INR, use NAC, HBO2

(ABC: airway, breathing, circulation; ABG: arterial blood gas; ACLS: advanced cardiac life support; CBC: complete blood count; CPR: cardiopulmonary resuscitation; CT: computed tomography; CXR: chest X-ray; ECG: electrocardiogram; HBO_2: hyperbaric oxygen; ICD: Intercostal drain; INR: international normalized ratio; NAC: N-acetylcysteine; PT: prothrombin time; SOB: shortness of breath)

FLOWCHART 1: Summary assessment, evaluation, and management of hydrocarbon poisoning.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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ONLINE REFERENCES

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CHAPTER

Caustic Ingestion

Narendra Nath Jena, Subbulakshmi Dhanabal

INTRODUCTION

Caustic ingestion is a grave public health problem. It is more common in the developing countries, but still seen in developed countries. It is a medical emergency and shows diverse clinical presentations. The ingestion of caustic substances has devastating effects on the upper gastrointestinal (GI) and respiratory tracts and the caustic injury is associated with numerous life-threatening complications. Caustics, also known as corrosive, are chemical and known to cause injury when they come in contact with tissue. Strong acids, with pH < 3 and strong alkali with pH > 11, are more dangerous to human exposure. Caustics are used both in household and in industrial products as hydrochloric/sulfuric acid, sodium/potassium hydroxide, and others. Eyes, face, and extremities are most affected while they can cause mortality if ingested. On exposure to caustic, immediate water irrigation is done followed by pain management, fluid, and electrolyte therapy. Special attention is required for GI exposure of caustic as this is associated with a high rate of morbidity and mortality.

PATHOPHYSIOLOGY

The degree of tissue injury is determined by several factors (**Fig. 1**): pH, concentration, duration of contact, volume, and titratable acid or alkaline reserve. Significant injuries are caused with acid at a pH < 3 and alkalis at a pH > 11. Litmus paper can be used to determine the pH in the emergency department. Solid or granular caustics often injure the oropharynx and proximal esophagus, whereas liquid alkali ingestions are characterized by more extensive esophageal and gastric injuries. Esophageal mucosal burns from caustic ingestions are classified by a visual endoscopic grading system, which correlates with the risk of future complications. Following the initial mucosal injury, tissue remodeling occurs over roughly 2 months. In mild cases, normal esophageal function is restored, but in severe cases, dense scar tissue forms, resulting in stricture formation. Esophageal strictures are a source of significant morbidity and may require long-term treatments with dilations, stenting, or surgery. Early phases of remodeling, particularly 2–14 days after exposure, are associated with increased tissue friability and a higher risk of perforation, both spontaneous and iatrogenic. *Alkali injury*: Alkali injuries induce a deep tissue injury called *liquefaction necrosis.* This process includes protein dissolution, collagen destruction, fat saponification, cell membrane emulsification, submucosal vascular thrombosis, and cell death.

Acid injury: Acid ingestion causes *coagulation necrosis*. In this process, hydration (H^+) ions desiccate epithelial cells producing an eschar. This process leads to edema, erythema, mucosal sloughing, ulceration, and necrosis of tissues. Both acids and alkalis cause fibrosis and stricture formation.

Esophageal injury mechanism by caustic ingestion (**Table 1**) is different and complex; it initially starts with lipid peroxidation and in later stage, stricture formation develops. A high concentration of malondialdehyde is found 24 hours postexposure, which is the end product of lipid peroxidation and glutathione. A high concentration of malondialdehyde also indicates the presence of reactive oxygen species and endogenous free radicals' scavengers in the esophageal tissues exposed to sodium hydroxide. Also, low glutathione in tissues exposed confirm the presence of reactive oxygen species and damage of free radicals.

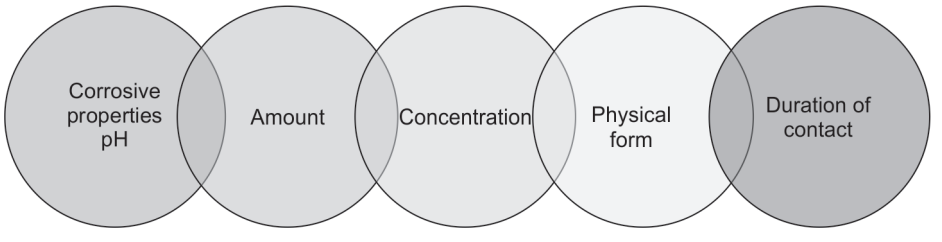

FIG. 1: Factors affecting the injury by caustic.

ETIOLOGY

Many chemicals used in industry have caustic potential. Household caustics are often less concentrated forms of industrial-strength cleansers (**Table 2**).

TABLE 1: Pathophysiology of esophageal injury.

Within minutes of caustic ingestion	Esophageal injury begins within minutes—eosinophilic necrosis swelling and hemorrhagic congestion
4–7 days of caustic ingestions	During this period, inflammation, mucosal sloughing, bacterial invasion, and appearance of granulation occur. Ulcer gets covered by the fibrinous layer and perforation may occur if it penetrates the mucosal plane
4th day of caustic ingestion	Fibroblast at the injury site
5th day of caustic ingestion	Esophageal mold consists of dead cells and secretion
10th day of caustic ingestion	Esophageal repair begins
1st month from caustic ingestion	Esophageal ulcer begins to epithelialize

TABLE 2: Caustic compounds.

Alkalis: Caustic compounds	*Acids: Caustic compounds*
Properties: pH > 7, tasteless, odorless, causes liquefaction necrosis, esophageal injuries are common while duodenal injuries are less common	*Properties:* pH < 7, pungent odor and noxious taste, coagulation necrosis, less esophageal injuries, more gastric injury
Sodium hydroxide (industrial chemicals, drain openers, oven cleaners)	*Sulfuric acid* (automobile batteries, drain openers, explosives, fertilizers)
Potassium hydroxide (drain openers, batteries)	*Acetic acid* (printing and photography, disinfectants, hair perm neutralizer, pickling solution)
Calcium hydroxide (cement, hair relaxers, perm products)	*Hydrochloric acid* (cleaning agents, metal cleaning, chemical production, swimming pool products)
Ammonium hydroxide (hair relaxers and perm products, dermal peeling/exfoliation, toilet bowl cleaners, glass cleaners, fertilizers)	*Hydrofluoric acid* (rust remover, petroleum industry, glass and microchip etching, jewelry cleaners)
Lithium hydroxide (photographic developer, batteries)	*Formic acid* (model glue, leather and textile manufacturing, tissue preservation)
Sodium tripolyphosphate (detergents)	*Chromic acid* (metal plating, photography)
Sodium hypochlorite (bleach)	*Nitric acid* (fertilizer, engraving, electroplating)
	Phosphoric acid (rust proofing, metal cleaners, disinfectants)

CLINICAL FEATURES

Clinical presentation varies and depends on the type/quantity of the agent ingested, timing of ingestion, and presence of food in the stomach. Burns to the lips, mouth, and oropharynx may be seen, but this does not necessarily correlate with the degree of the injury to the esophagus or stomach. The initial symptoms of caustic ingestion include drooling and dysphagia. In severe cases, pain, vomiting, and sometimes bleeding develop immediately in the mouth, throat, chest, or abdomen. Airway burns may cause coughing, tachypnea, or stridor (**Table 3**). Swollen, erythematous tissue may be visible intraorally; however, caustic liquids may cause no intraoral burns despite serious injury farther down the GI tract. The presence or absence of oropharyngeal burns in children does not predict the presence of esophageal or gastric burns. Esophageal perforation may result in mediastinitis, with severe chest pain, tachycardia, fever, tachypnea, and shock. Gastric perforation may result in peritonitis. Esophageal or gastric perforation may occur within hours, after weeks, or any time in between. Esophageal strictures can develop over weeks, even if initial symptoms had been mild and treatment had been adequate.

EVALUATION

History: The key priority is rapid airway assessment and stabilization. Following that, obtain a directed history to determine the type, amount, and timing of the ingested caustic and the presence of co-ingestants. Determine if the ingestion was intentional or unintentional. *Physical examination:* Look for signs of respiratory distress or circulatory shock. With ingestions, look for signs of oropharyngeal injury (mucosal burns, drooling), respiratory injury (dysphonia, coughing, stridor, wheezing), and gastric injury (vomiting, epigastric tenderness). Streaks of caustic burns on the face or chest are called "dribble burns."

Assess for hemodynamic instability. Causes of shock include GI bleeding, complications of GI perforation, volume depletion, and toxicity from co-ingestants. Examine for peritoneal signs due to hollow viscous perforation. Consider mediastinitis in patients complaining of chest discomfort, and palpate the chest wall and neck for signs of subcutaneous emphysema. Inspect the eyes for ocular burns and the skin for splash and dribble burns.

TABLE 3: Clinical presentation.

Gastrointestinal tract	Drooling; dysphagia; odynophagia; severe pain of lips, mouth, throat, chest, abdomen; vomiting; hematemesis
Respiratory tract	Hoarseness, stridor, epiglottitis, laryngeal edema and ulceration, pneumonitis, impaired gas exchange
Eye	Pain, irritation, clouding of cornea, decreased vision
Skin	Dribble marks on the face, chest, and legs; first, second, or third-degree burns

INVESTIGATIONS

Intentional ingestions are associated with higher grades of GI tract injury, with or without clinically obvious signs. Laboratory evaluation should include a venous or arterial blood gas, electrolyte panel, hepatic profile, complete blood count, lactate, and blood type and screen. Strong acid ingestions may be associated with both severe anion gap (e.g., sulfuric acid) and nongap acidoses (e.g., hydrochloric acid). In suicidal patients, obtain acetaminophen and salicylate levels to screen for potential co-ingestants. An ECG is indicated following a hydrofluoric acid exposure to check for QT interval prolongation from hypocalcemia. Esophagogastroduodenoscopy should be performed in the first 12–24 hours postingestion, with great care to avoid iatrogenic perforation. The grade and extent of the lesions (**Table 4**) of the upper GI tract can be determined and classified according to Zargar's modified endoscopic classification of burns due to caustic ingestion. Severe hypopharyngeal burns are an absolute contraindication for esophagogastroduodenoscopy.

MANAGEMENT

Initial Management

If only a small amount is ingested, observe and discharge the patient from the ED if accepting liquid or semi-solid food orally, asymptomatic, and oral examination is normal. In major ingestion, pay special attention to the airway/oxygenation. Keep the patient nil per oral. Intravenous fluids and nutritional support should be started. Proton-pump inhibitors (reduce exposure of the injured esophagus to gastric acid, which may result in decreased stricture formation), antibiotics (if there is evidence of perforation), and pain relief medication should be added. Emergency surgical intervention is indicated in case of perforation or peritonitis or if uncontrolled massive hematemesis occurs.

Activated charcoal is *relatively contraindicated* in caustic ingestions because of poor adsorption and endoscopic interference. Other measures which should not be included in initial management are emesis, nasogastric tube insertion, and lavage. Do not induce emesis as this increases the risk of mucosal injury and perforation. Do not try to insert nasogastric tube/take lavage as this may cause esophageal perforation and increase the risk of aspiration. Do not try to neutralize the substance (risk of heat production resulting from this exothermic reaction).

TABLE 4: Endoscopic grading according to Zargar classification for caustic injuries.

Grade	*Description*
Grade 1	Edema and hyperemia of the mucosa
Grade 2A	Superficial localized ulcerations, exudates, whitish membranes, blisters, erosions, hemorrhages, and friability
Grade 2B	Circumferential and deep ulcerations
Grade 3A	Multiple and deep ulcerations and small scattered areas of necrosis
Grade 3B	Extensive necrosis
Grade 4	Perforation

Nutrition

The endoscopic grade of lesions needs to be assessed for planning nutritional support in patients with caustic ingestion. Patients with grade 1/2A lesions on endoscopy can tolerate oral feeds, while those with grade 2B/3A lesions will need nasoenteral feeding. Patients with grade 3B lesions require gastrostomy for enteral feeding and rarely need total parenteral nutrition (TPN).

Acute Presentation

Within 48–72 hours of corrosive ingestion: Upper GI endoscopy should be performed on day 1–2 (ideally between 12 and 24 h of ingestion). If endoscopy reveals only mild lesions, then the patient can be discharged and clinical follow-up should be done at 1 month. If severe lesions are found on endoscopy, then surgical gastrostomy is indicated, which should be followed by repeat endoscopy and dilatation after 3 weeks.

Delayed Admission

Within 72 hours to 3 weeks of corrosive ingestion: No endoscopy is indicated here. Gastrostomy should be done if there is severe dysphagia. Endoscopy and dilatation of stricture (if present) should be done 3 weeks after ingestion.

Late Admission

More than 3 weeks of ingestion requires endoscopy and dilatation of stricture. If the procedure is successful, then a follow-up endoscopy should be done at 1 month. If the procedure is unsuccessful, then surgical gastrostomy is performed, which is followed by retrograde dilatation of stricture after 10 days of operation.

COMPLICATIONS

Aspiration of corrosive substances into the respiratory tree may cause endotracheal or bronchial necrosis with mediastinitis. Acute kidney injury, disseminated intravascular coagulation, acid–base disturbances, and pneumonia may also occur. Esophageal stricture formation is the most feared long-term complication; stenosis gastric antrum or pylorus may also occur and so may fistula formation. Stricture formation begins weeks to months after injury and is the most important consequence of corrosive poisoning. The procedures used for prevention and treatment of strictures are as follows:

- *Dilatation therapy*: This is done 3–6 weeks after injury; progressively larger bougies are passed over endoscopically placed guidewires for dilatation
- *Surgery*: Esophageal strictures resistant to dilatation therapy may require surgery that includes resection of stricture surgically and esophageal bypass surgery.

DISPOSITION AND FOLLOW-UP

Asymptomatic patients, with low-risk ingestions and no signs of drooling, stridor, or vomiting and who tolerate food or drink, may be discharged from the ED after a period of observation. Admit all patients with symptomatic caustic ingestions.

Patients with grade 1 injuries can be discharged from the hospital after endoscopy, provided they can tolerate oral fluids and food. Grade 2A injuries warrant hospitalization to ensure that symptoms and injury do not progress. Grade 2B and 3 injuries are significant, require enteral or parenteral nutrition, and have an early risk for bleeding or perforation; admit these patients to an intensive care unit. Contact the regional poison control center for data collection purposes and assistance with management.

SUMMARY

Caustic substance ingestion associated with great potential for morbidity and mortality. Close monitoring of hemodynamics, maintaining the patient's airway, aggressive supportive care, remains paramount. Currently, literature do not support the use of parenteral corticosteroids or systemic antibiotics without concomitant signs of infection following caustic ingestion. Early consultation with a gastroenterologist, otolaryngologist, or surgeon should be taken, because the patient may require esophagogastroduodenoscopy (EGD) or surgical intervention. Patients exposed to hydrofluoric acid by any route require decontamination as well as specialized treatments, including topical, regional, and systemic treatments to reduce burns, pain, and systemic complications. These patients may also require early consultation with a surgeon or interventional radiologist, should there be a need for surgical debridement or intra-arterial therapies.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Inhaled Toxins

Subramanian Senthilkumaran, Ponniah Thirumalaikolundusubramanian

INTRODUCTION

Inhalation injury is a clinical syndrome that occurs when the respiratory system is exposed to a wide range of chemicals in different forms, namely smoke, gases, vapors, or fumes. Moreover, liquids and solids can also be inhaled in the form of mists, aerosols, or dust. These exposures happen mostly in the setting of industrial chemical accidents and residential fires. Inhaled constituents may directly injure the respiratory system at various levels, leading to a wide range of damage to the airways and/or parenchyma resulting in nasal mucositis, tracheitis, and bronchitis to pulmonary edema. These may also result in systemic toxicity when absorbed. The severity and pathogenesis of inhalational injury depend upon the nature of the chemical and duration of exposure as well as on the quantity and intensity of exposure to the toxin/chemical.

ETIOLOGY

Inhalation injury characteristically results from exposure to harmful substances which can be broadly classified into asphyxiants, irritants, and systemic toxins. Occupational exposures occur due to working in poorly ventilated areas or entering into work without proper personal protective equipment (PPE), and vary significantly based on the exposed chemicals. Common causative factors in residential fires are heat, inert gases, and chemical products of combustion such as carbon monoxide (CO), hydrogen cyanide, sulfur dioxide, and particulate matter. In few cases of acute inhalational injury, more than one substance or mechanism may be involved.

PATHOGENESIS

The pathophysiology of inhalation injury reveals the heterogeneity of inhalation exposures. Major categories of injury include direct thermal injury to the airway, asphyxiation, systemic toxic effects, etc. Inhalation injury may affect the respiratory system at various levels. Anatomically, the injuries are classified into (1) thermal injury limited to upper airway except in the circumstance of steam jet exposure, (2) local chemical irritation throughout the respiratory tract, and (3) systemic toxicity as may occur with inhalation of CO or cyanide.

The location and severity of injury depend on various factors including the characteristics of the toxic agent, the quantity and diameter of the particles in the fumes, the duration of the exposure, the solubility of the gases, environment, and host factors (**Table 1**).

Upper Airway Injury

Thermal damage is usually limited to the oropharyngeal region, due to the efficient heat exchange. Poor conductivity of air and reflex closure of the larynx help to protect the lower lung from direct thermal injury. The immediate injury result in massive edema of the tongue, epiglottis aryepiglottic fold, airway compromise leading to rapid clinical deterioration and these are further worsened over a matter of hours as in cases of combined burn and inhalation injury, which promotes early edema formation in the upper airway.

In addition to the acute insult, damage to ciliary function impairs physiological clearance of the airway, leading to an enhanced risk of bacterial infection for several weeks. Additionally, the increased production of copious secretions causes distal airway obstruction, atelectasis, and impaired gas exchange.

Tracheobronchial Injury

Frequently, the chemicals in smoke cause injury to the tracheobronchial tree with the exception of inhalation of

TABLE 1: Risk factors.

Inhaled toxin-related	*Host factors (individual related)*	*Others*
Concentration	Exertional state of the victim	Ventilation of the room
Quantity	Extremes of age	Environmental status
Duration of exposure	Underlying lung condition(s)	
Particle size	Debilitating illness(s)	
Water solubility	History of smoking	

steam. Nevertheless, toxic inhalation of noxious gases such as chlorine, liquids such as acid or alkali, and smoke from fire is associated with a similar process.

The tracheobronchial region is abundantly innervated by vasomotor and sensory nerve endings. So, neuropeptides are often released because smoke inhalation stimulates these nerves. These neuropeptides induce reflex bronchoconstriction and release nitric oxide synthase to generate reactive oxygen species. These neuropeptides function as tachykinins, inducing an inflammatory response with the downstream effects of bronchoconstriction, increased vascular permeability, and vasodilation. These potentiate local cellular damage and loss of hypoxic pulmonary vasoconstriction, which increases several fold of bronchial blood flow. In addition, the increased bronchial blood flow activates the polymorphonuclear leukocytes and release cytokines to the lung, increasing the host inflammatory response. Moreover, the damage of an intact bronchial epithelium and the effects of nitric oxide synthase result in a loss of plasma proteins and fluid leak from the intravascular space into the alveoli and bronchioles. This transvascular shift of protein results in inflammatory exudate and cast formation within the airways, leading to alveolar collapse. These progressions contribute to ventilation–perfusion mismatch, a major mechanism for hypoxemia following the inhalation injury.

Parenchymal Injury

The cascade of inflammatory mediators following inhalation injury results in the interaction of irritant substances with lung parenchyma, leading to both hyperinflation and atelectasis. The debris from mucosal sloughing, intrapulmonary hemorrhage, inflammatory exudate, and increased transvascular fluid flux results in mechanical obstruction of small airways causing hyperinflation and air trapping. The alveolar collapse occurs due to impaired surfactant production and activity, leading to segmental atelectasis and, therefore, impaired oxygenation. Besides, a severe imbalance in alveolar hemostasis and decreased fibrinolytic activity, with massive fibrin deposition in the airways, causes decreased lung compliance, loss of hypoxic pulmonary vasoconstriction, increased ventilation–perfusion mismatch, and increase in dead space ventilation. The risk factors that determine/influence inhalation injury are given in **Table 1**.

CLINICAL FEATURES

The clinical symptoms due to highly soluble substances cause persistent coughing and severe burning in the eyes, nose, throat, and large airways within minutes of exposure, which result in lacrimation, rhinitis, epistaxis, and pharyngitis as well as retching and shortness of breath with wheezing. Physical findings including facial injury, singed nasal hairs, soot in the proximal airways, carbonaceous sputum production, hoarseness of voice, and stridor which indicate the diagnosis of upper airway injury.

Signs of lower respiratory tract injury may include tachypnea, decreased breath sounds, rales, rhonchi, or use of accessory respiratory muscles. Respiratory failure may occur with 12–48 hours after smoke exposure. A faster time is associated with more severe injury. CO poisoning should be assumed in any patient who presents after smoke inhalation until excluded by a normal carboxyhemoglobin level as measured by CO-oximetry. Generalized symptoms such as headache, giddiness, nausea, or vomiting may develop in few cases.

INVESTIGATION

Complete blood count, electrolytes, blood urea nitrogen, creatinine, lactate level, and toxicology screen are required. An arterial blood gas analysis with CO-oximetric measurement for oxyhemoglobin, carboxyhemoglobin, methemoglobin, and cyanide levels, as indicated, has to be carried out. Chest radiography is done as a part of the initial evaluation, although it may have a low sensitivity for inhalation injury. The presence of lung opacities on initial chest films has been implicated as a marker of severe injury with a poor prognosis. A CT scan of the thorax may reveal ground-glass opacities in peribronchial distribution, within few hours of inhalation injury.

DIAGNOSIS

The diagnosis of inhalation injury may be assumed based upon clinical findings in the setting of smoke exposure, but a definitive diagnosis relies upon direct examination of the airways. The fiberoptic bronchoscopy allows assessing the patency of the airway. Clinical signs of inhalation injury include mucosal erythema and edema, blistering, ulceration, bronchorrhea, fibrin casts, or evidence of charring. Bronchoscopic criteria, used to grade inhalation injury, are depicted in **Table 2**. The grading and findings correlate well with mortality as well as gas exchange.

MANAGEMENT

Prehospital Care

- Immediate evacuation of a victim from the site of fire/toxin to limit the time of exposure.

TABLE 2: Bronchoscopy criteria used to grade inhalation injury and findings.

Grading scale	*Bronchoscopy findings*
0 (no injury)	Absence of carbonaceous deposits, erythema, edema, bronchorrhea, or obstruction
1 (mild injury)	Minor or patchy areas of erythema or carbonaceous deposits in the proximal or distal bronchi
2 (moderate injury)	A moderate degree of erythema, carbonaceous deposits, bronchorrhea, or bronchial obstruction
3 (severe injury)	Severe inflammation with friability, copious carbonaceous deposits, bronchorrhea, or obstruction
4 (massive injury)	Evidence of mucosal sloughing, necrosis, and endoluminal obliteration

- Removal of all clothing and jewelry as soon as possible as they may be contaminated by toxins [(such as hydrogen cyanide (HCN)] or may retain heat.
- Decontamination is done using full isolation precautions.
- *Clinical assessment*:
  - Expeditious assessment of the patient's airway, breathing, and circulation.
  - Assess for any life-threatening injuries which may take precedence.
  - Bedside assessment of chest for adequacy of breathing in a nonintubated patient by respiratory rate, chest wall motion, and auscultation of air movement, and all these shall be frequently re-evaluated.
- Administration of humidified high-flow oxygen to maintain oxygen saturation >90%.

Airway

- Securing the airway is pivotal in patients with inhalation injury.
- It is better to intubate early when swelling is least and the patient is still physiologically intact.
- The criteria for early intubation are based on the clinical signs such as deep burns to the face or neck, blisters or edema of the oropharynx, stridor, use of accessory muscles, respiratory distress, sub- and suprasternal retractions, or hypoventilation.
- Intubation in victims with inhalation injury is potentially difficult and has its own risk, and hence prefers to use awake fiberoptic intubation in order to preserve the respiratory drive and spontaneous ventilation.
- Usage of video laryngoscope for intubation is an emerging and promising technique.
- Mask ventilation is an alternative in situations where one "can't ventilate or can't intubate," as in nonburn patients with injury in supraglottic airways or in those with difficulties for cricothyrotomy and tracheostomy
- Although early tracheostomy provides comfort and security to patients, there are no significant differences in the length of stay, incidence of pneumonia, survival, or duration of ventilator use, when compared with late tracheostomy.
- In case of anterior neck burns, tracheostomy shall be delayed until 5–7 days after skin grafting.

Fluid Resuscitation

- The goal of fluid resuscitation is to maintain an adequate urine output.
- The fluid requirements are not predicted by the depth and size of their burns.
- The formula of fluid resuscitation should be used only as a guide and titrated to clinical endpoints.
- Ringer lactate is the fluid of choice.
- Due to an increase in insensible loss of fluid through the injured lung in victims of smoke inhalation injury, these cases require 25% higher fluid requirement.
- As aggressive resuscitation may increase pulmonary microvascular hydrostatic pressure and result in edema formation. Hence, there is a need for close monitoring of fluid balance in order to ensure adequate resuscitation and avoidance of complications.

Nutrition

- Patients with inhalation injury may also demonstrate marked hypermetabolism.
- Enteral nutrition formulas with a low respiratory quotient will help to limit carbon dioxide production, improving the patient's ability to keep up with respiratory demands.

Pulmonary Care

- It is aimed to relieve bronchospasm and reduce pulmonary secretions by pulmonary toileting so as to prevent the airway obstruction and atelectasis leading to pneumonia.
- Aerosolized bronchodilators are administered to relax the bronchial muscle, stimulate mucociliary clearance, decrease airflow resistance, and improve dynamic compliance.
- Nebulization of levosalbutamol to relieve bronchospasm and racemic epinephrine for stridor
- Tiotropium, a muscarinic receptor antagonist, is administered at 4–6 hours' interval to improve PaO_2/FiO_2 ratio as well as decrease the peak airway pressure after smoke inhalation injury.
- A combination of aerosolized mucolytic agents, such as N-acetylcysteine alternating with aerosolized heparin, is done for the airway clearance along with therapeutic coughing, chest physiotherapy, deep breathing exercise, and postural drainage.
- Prophylactic antibiotics and corticosteroids are not indicated following smoke inhalation.

Mechanical Ventilation

- The goal of mechanical ventilation in smoke inhalation injury is to keep the alveoli patent, oxygenate the lungs, and prevent barotrauma.
- The optimal ventilator strategy for patients with burns and inhalation injury is not well defined.
- Increased production of carbon dioxide requires high minute ventilation to maintain a normal pCO_2 and may require ventilatory support to achieve.
- The lungs are ventilated using a tidal volume of 6–8 mL/kg with a respiratory rate of 16–18 breaths/min and peak airway pressure <35 mm Hg should be maintained.
- FiO_2 is adjusted to maintain PaO_2 between 80 and 100 mm Hg.
- Optimal positive end-expiratory pressure (PEEP) is administered to maintain the desired airway pressure below which the alveoli collapse.
- Even simple prone positioning has also been found to improve oxygenation.
- The newer modes of ventilation such as high-frequency percussive ventilation, high-frequency oscillatory ventilation, pressure control inverse ratio ventilation, and airway pressure release ventilation have proven to be beneficial in managing patients with smoke inhalation injury.

Future Therapies

- The use of extracorporeal membrane oxygenation (ECMO) is beneficial for the victims who develop severe respiratory failure after smoke inhalation injury.

- Newer agents, such as perfluorohexane and porcine pulmonary surfactant, are being investigated for their beneficial role in attenuating the release of inflammatory mediators in the airway and lungs.

Special Population

- In pediatric patients, airway compromise is the most common cause of severe morbidity and mortality, likely due to the small size of the airway. The threshold for intubation needs to be lower in pediatric patients due to the potential for rapid development of airway edema.
- In older adults, mortality from burns increases to 6-fold due to lower physiological reserves, decrease in lung mechanics, reduction in lean body mass, and comorbidities. Additionally, elderly burn patients are more likely to develop complications such as pneumonia and urinary tract infections while on treatment.
- Patients with inhalation injury due to agents other than smoke are typically managed in the same fashion as for smoke inhalation, with an exception of monitoring for CO poisoning.

ASPHYXIANTS

Asphyxiants are gases that deprive body tissues of oxygen and it may be gases, liquids, or solids, or their metabolites. They are broadly classified into two categories: (1) Simple, and (2) Systemic. Simple asphyxiants such as carbon dioxide, nitrogen, and propane, when present in high concentrations in air, especially within a confined space, merely displace oxygen from ambient air and reduce fraction of inspired oxygen and subsequent hypoxemia whereas systemic asphyxiants such as CO, cyanide, and hydrogen sulfide interfere with oxygen transport system or with mitochondrial oxidative phosphorylation and thereby cause tissue hypoxia. However, any gas in high concentration can act as an asphyxiant. Even though methane, ethane, argon, and helium are more innocent at low concentrations, at high levels they can displace oxygen or block the reaction of cytochrome oxidase or hemoglobin, impairing cellular respiration and oxygen transport.

Mild symptoms of asphyxia include headache, dizziness, nausea, and vomiting. Severe symptoms range from dyspnea, altered mental status, cardiac dysrhythmia, ischemia, syncope, seizure, coma to even death. Treatment of asphyxiant poisoning is aggressive supportive care, with control of the airway and ventilation and maintenance of cardiac output. Supportive care is often enhanced by the administration of specific antidotes.

CARBON MONOXIDE POISONING

- CO is a colorless, nonirritant, and odorless gas produced by incomplete combustion of carbonaceous material such as wood, petrol, coal, natural gas, and kerosene.
- The common sources of CO poisoning are car exhaust, clogged chimneys, charcoal burners, poorly maintained and faulty heaters, fires, burning of biomass fuels, gas burners, and industrial emissions.
- Inhalation is the only exogenous exposure route for CO poisoning.
- CO has approximately 210 times more affinity for hemoglobin than oxygen. Binding thus reduces hemoglobin oxygen-carrying capacity and delivery to the tissues. This can result in tissue hypoxia and ischemic injury.
- CO also binds cytochromes, causes endothelial oxidative injury and lipid peroxidation, and triggers inflammatory cascades.
- Clinical symptoms and signs correlate well with measured carboxyhemoglobin percentage (**Table 3**).
- Noncardiogenic pulmonary edema, lactic acidosis, rhabdomyolysis, hyperglycemia, disseminated intravascular coagulation, bullae, and alopecia are other clinical features seen with CO exposure.
- Pre-existing cerebral or cardiovascular disease, anemia, and volume depletion or cardiac failure increase toxicity.
- The diagnosis of acute CO poisoning should be confirmed by an elevated level of carboxyhemoglobin either in arterial or in venous blood.
- Elevation of the blood lactate level is an indication of severity.
- Obtaining an electrocardiogram and cardiac biomarkers in patients with moderate-to-severe CO poisoning is recommended.
- The administration of 100% oxygen will displace CO from hemoglobin and decrease the effective half-life from 4 hours to 40 minutes. The half-life is initially even shorter as hyperventilation and increased cardiac output also increase the rate of elimination.
- CO-poisoned patients should receive a high flow of oxygen for 8 hours, and in case pregnant, it should be for 24 hours.
- Hyperbaric oxygen (HBO) is a therapeutic option for CO-poisoned patients; however, its use cannot be mandated.
- The indications in patients for HBO therapy recommended by the Undersea and Hyperbaric Medical Society are given in **Box 1**.

TABLE 3: Concentrations of carboxyhemoglobin and clinical features.

<10%	Nil (commonly found in smokers)
10–20%	Nil or vague nondescript symptoms
30–40%	Headache, tachycardia, confusion, weakness, nausea, vomiting, collapse
50–60%	Coma, convulsions, Cheyne–Stokes breathing, arrhythmias, ECG changes
0–80%	Circulatory and ventilatory failure, cardiac arrest, death

BOX 1: Indication for hyperbaric oxygen therapy.

- Transient or prolonged loss of consciousness
- Abnormal neurologic signs
- Cardiovascular dysfunction
- Severe acidosis
- Age over 36 years
- CO exposure of ≥24 h
- Carboxyhemoglobin level ≥25%
- Pregnant patients with evidence of fetal distress

CYANIDE POISONING

- Cyanide is one of the most rapidly lethal agents that is found in liquid and gaseous forms. It can lead to death in a few minutes to a few hours.
- Cyanide poisoning may result from a variety of exposures including structural fires consisting of the combustion of wool, silk, synthetic rubber, and polyurethane, which contain carbon and nitrogen to convert into cyanide. Industrial exposures include metal extraction and refining, electroplating, photography, fumigation, medical exposures, and certain foods such as apricot, peach, apple, cherry, and plum as amygdalin, a cyanogenic glycoside.
- Smoking is the most common form of cyanide exposure and may lead to "tobacco amblyopia."
- Intravenous and inhalation of cyanide fumes produce a faster onset of signs and symptoms than exposure via the oral or transdermal route due to fast diffusion into the bloodstream.
- Cyanide mainly inhibits oxidative phosphorylation by blocking the reduction of oxygen to water. This results in cessation of cellular respiration and further results in tissue hypoxia and the depletion of adenosine triphosphate (ATP), thus leading to the production of a severe lactic acidosis.
- At higher concentration of cyanide levels, pulmonary edema is documented and it is believed to be secondary to left ventricular failure and increased pulmonary wedge pressure due to vasogenic response of pulmonary-arteriolar and/or coronary artery.
- Clinical features vary from mild vertigo, headache, dizziness, confusion to seizures, coma, cardiac arrhythmia, apnea, and cardiac arrest.
- Hypotension and bradycardia are pathognomonic for cyanide poisoning.
- Mouth-to-mouth rescue breathing is contraindicated in cyanide poisoning due to the risk of contamination and toxicity to the provider.
- Decontamination is an important part in the management of cyanide exposure through topical and inhalation routes.
- Administer high flow of medical oxygen at the maximum rate.
- The *Cyanide Antidote Kit* contains amyl nitrite, sodium nitrite, and sodium thiosulfate.
- Amyl nitrite is a nitrite-based cyanide antidote which oxidizes hemoglobin to methemoglobin, which complexes with cyanide to form nontoxic cyanmethemoglobin.
- Amyl nitrite, one ampoule (0.3 mL), is inhaled before securing an intravenous access. To be more effective, amyl nitrite must be used in association with oxygen by breaking the ampoule within the oxygen mask.
- Intravenous sodium nitrite of 300 mg given over 2–4 minutes, which forms methemoglobin and attracts cyanide away from inhibited cytochrome oxidase, forms cyanmethemoglobin which allows the resumption of cellular respiration. This antidote should be administered in combination with sodium thiosulfate at the dose of 12.5 g in 50 mL, intravenously over 30 minutes in adults which enhances the activity of rhodanese by donating a sulfur group, thereby increasing the amount of less toxic metabolite thiocyanate, which is renally eliminated.
- Sodium thiosulfate acts more slowly compared to other antidotes because it penetrates the cell and mitochondrial membranes poorly.
- Hydroxocobalamin is a safe and effective antidote given at a dose of 5 g infused over 15 minutes and it detoxifies cyanide into nontoxic cyanocobalamin, which is excreted in the urine.
- It is known to cause a reddish discoloration of the body fluids.

SUMMARY

- About one third of patients with burn injuries have a concomitant inhalation injury.
- CO poisoning should be presumed in any patient who presents following smoke inhalation until it is excluded by a normal carboxyhemoglobin level on CO-oximetry.
- Early intubation is justified for any patient with suspected inhalation injury and signs of respiratory distress.
- Early use of bronchoscopy helps to confirm the diagnosis and grading of inhalation injury.
- The inpatient management of patients with inhalation injury treatment is mainly supportive and consists of monitoring the patient for subsequent development of airway compromise.
- Clearing the airways with a combination of inhaled N-acetylcysteine and heparin is an essential component in the management of patients with inhalation injury.
- CO poisoning is often overlooked.
- Pulse oximetry is often falsely reassuring with normal saturations.
- The fetus is particularly susceptible to the effects of CO intoxication.
- Fetal monitoring in the form of a cardiotocography (CTG) and an obstetric consultation is mandatory for the pregnant victims.
- In case of industrial fire, cyanide toxicity is also suspected.
- Patients with cyanide poisoning will not be cyanotic but will have a cherry-red color due to excess oxygen in the bloodstream.

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CHAPTER

Iron and Heavy Metals

Sameer Thapa, Anup Raj Upreti

INTRODUCTION

The accumulation of heavy metals above average level that may modulate numerous enzymatic systems resulting in serious consequences in the body is termed as heavy metal poisoning. The sign and symptoms may vary depending upon the nature and quantity of the heavy metals ingested or exposed. The most common heavy metals associated with poisoning are iron, lead, mercury, and arsenic.

IRON

Sources of Iron

Prenatal vitamins, pediatrics multivitamins tablets containing iron.

Absorption

Iron absorbs as elemental iron. The fraction of elemental iron may vary depending upon its preparation: iron has direct corrosive injury on gastrointestinal (GI) mucosa resulting in hemorrhagic necrosis, perforation, and peritonitis. Unbound (free) iron causes:

- Cell membrane toxicity by hydroxyl free radicals-mediated lipid peroxidation
- Increases capillary permeability and both arteriolar and venodilator causing hypotension and venous pooling
- Inhibition of oxidative phosphorylation causing metabolic (lactic) acidosis
- Direct myocardial toxicity and decreases cardiac output
- Oxidative and free radical injury leading to hepatic damage

Clinical Features of Iron Toxicity

- *Asymptomatic:*<20 mg/kg
- *GI symptoms only*: 20–60 mg/kg
- *Severe systemic toxicity*: 60–120 mg/kg
- Potential lethal > 120 mg/kg

Stages of iron toxicity are as follows:

- *Stage I (0–6 hours)*: Direct corrosive effects of iron in the gut causes vomiting, abdominal pain, diarrhea, hematemesis, hematochezia, and fluid loss may result in hypovolemic shock.
- *Stage II (6–24 hours)*: Latent period of apparent improvement contributing to false sense of recovery. During this time iron shifts intracellularly from the circulation.
- *Stage III (12–48 hours)*: Intracellular iron disrupts cellular metabolism with resultant vasodilator shock and third space loss, high anion gap metabolic acidosis (HAGMA), hepatorenal failure and coagulopathy.
- *Stage IV (2–5 days)*: Acute hepatic failure, convulsion, and coma. It resulted from direct action of iron on mitochondria and has a high mortality.
- *Stage V (2–6 weeks)*: Delayed sequelae of iron poisoning, scarring from the initial corrosive injury of GI mucosa characterized by pyloric or proximal bowel stricture resulting which is sometimes associated with obstruction.

Treatment of Iron Toxicity

- *Resuscitation:* Assess airway, breathing, and circulation. Consider nasogastric tube.
- *Treat hypovolemia:* IV crystalloid 10–20 mL/kg boluses to prevent shock from GI losses, vasodilation, and third spacing and replace blood if needed treat coagulopathy with fresh frozen plasma (FFP) and vitamin K. Treat coma, seizure, and metabolic acidosis if they occur.
- *Decontamination*: Whole bowel irrigation with polyethylene glycol–electrolyte lavage solution (PEG-ELS) for significant ingestions (>20 mg/kg of elemental iron, iron tablets identified in X-ray abdomen).
- *Route*: Orally or nasogastric tube.
  - Dose: 2 L/h by continuous infusion (children 25 mL/kg/h) continued until the rectal effluent is clear and there is no radiographic evidence of pill fragments.
  - Injection metoclopramide 10 mg IV in adults (0.1 mg/kg in pediatrics to reduce nausea and increase gastric emptying).
- *Antidote*: Deferoxamine chelation therapy is indicated in the presence systemic toxicity or serum iron level above 500 µg/dL. It chelates iron to form the water-soluble compound ferrioxamine. And also limit the entrance of iron into the cell and chelate intracellular iron. Continue

cardiac monitoring, reconstitute 500 mg of powder with 5 mL of sterile water, and dilute in 100 mL of 0.9% saline or 5% dextrose. IV infusion at 15 mg/kg/h for up to 24 hours reduced if hypotension occurs, may be titrated up to 35 mg/kg/h in severe toxicity. Pregnancy is not a contraindication to deferoxamine. The infusion can be stopped when the patient is clinically stable and the serum iron level is <350 μg/dL. Adverse effects include hypersensitivity, hypotension, (with rapid or high dose IV administration), toxic retinopathy, *Yersinia* sepsis (the ferrioxamine complex is a siderophore that promotes growth).

- *Early exchange transfusions:* Serum iron levels exceeding 1,000 μg/dL.
- *Disposition*: Asymptomatic, ingested <20 mg/kg of elemental iron, normal abdominal radiograph should be observed for 6 hours and can be discharged if he or she remains asymptomatic after 6 hours of observation. The patient who has ingested >20 mg/kg of elemental iron or has pills visible on an abdominal radiograph should receive whole-bowel irrigation. Psychiatric assessment should be performed in adults before discharge from hospital.

LEAD

Sources of Lead

Battery burning, refinery, smelter, fuel combustion, automobile exhaust, and brass making; glassmaking; stripping old paint, and contaminated herbal medications; ingestion of paint chips, lead-laden floor dust, and lead foreign bodies: Lead found in inorganic, organic and leaded gasoline.

Absorption

Lead absorb by inhalation, ingestion and through cutaneous route. Lead binds to sulfhydryl groups, phosphate or carboxyl ligands resulting in inactivation or alteration of enzymes and exerts toxic-most effects in the hematopoietic, neurologic, renal, and reproductive systems. Lead toxicity causes injury to astrocytes, resulting disruption of the blood-brain barrier causes cerebral edema, and seizures, segmental demyelination, and motor axonal degeneration. It interferes with porphyrin metabolism, which contributes to lead-induced anemia. Lead toxicity may cause spontaneous abortion, premature membrane rupture, depressed sperm counts, abnormal or nonmotile sperm, and sterility. Chronic lead toxicity can depress free thyroxine levels without producing clinical hypothyroidism.

Clinical Features of Lead Toxicity

Central Nervous System

- *Acute*: Ataxia, altered mental status, encephalopathy, convulsion, coma, and papilledema.
- *Optic neuritis chronic*: Headache, sleep disturbances, fatigue, irritability, depression, mood swing, and behavior changes memory deficit.
- *Peripheral nervous system*: Wrist drop or foot drop, decreased or absent DTR, paresthesia, and intact sensory function.
- *Gastrointestinal*: Cramping abdominal pain, nausea, vomiting, metallic taste constipation, and diarrhea. *Renal acute*: Fanconi syndrome, renal tubular acidosis
- *Chronic*: Acute kidney impairment, hypertension, and gout.
- *Reproductive*: Impotence, decreased libido, decreased sperm count, and erectile dysfunction.
- *Others*: Myalgia, fatigue, irritability, insomnia, tremor, arthralgia, muscular exhaustibility, anorexia, and bluish black lead line on gums (Burton's line) (**Table 1**).

Treatment of Lead Toxicity

- *Resuscitation*: Assess airway, breathing, and circulation. Provide adequate hydration to maintain urine flow but avoid overhydration which may aggravate cerebral edema.
- *Acute lead encephalopathy*: Aggressive control of ICP *controlled hyperventilation*: $PaCO_2$ 25–30 mm Hg intubation and neurosurgical consultation for invasive monitoring of intracranial pressure.
- *Diuretics*: Mannitol 20%, 1 g/kg IV infusion over 20 minutes
- *Dexamethasone*: 16 mg/kg in divided doses
- *Seizure control*: Treat seizures if they occur. With IV diazepam adult: Up to 10 mg IV slowly, repeat if necessary. Child: 0.1–0.3 mg/kg slowly. Seizure from lead encephalopathy may be resistant to anticonvulsant therapy.
- *Foley's catheterization*: To monitor urinary specific gravity, sediment, and lead level. *Decontamination* with whole-bowel irrigation should be considered.
- *Chelation therapy*: Chelation therapy doses are based on blood lead level, weight, and age.
  - Blood lead level (*BLL) >70 μg/dL or with lead encephalopathy:* dimercaprol or BAL: 75 mg/m^2 deep IM injection q 4 hours for 5 days for children or 4 mg/kg every 4 hours for adults. Contraindicated in patients allergic to peanuts. Followed by ethylenediaminetetraacetic acid ($CaNa_2EDTA$) 1,500 mg/m^2/day (approximately 50–75 mg/kg/day). Start 4 h after BAL.

TABLE 1: Features of lead toxicity.

Level (μg/dL)	*Adults symptoms*	*Children symptoms*
10	None	Decreased IQ, hearing and growth
20	Increased protoporphyrin, no symptoms	Decreased nerve conduction velocity Increased protoporphyrin
30	Increased blood pressure Decreased hearing	Decreased vitamin D metabolism
40	Peripheral neuropathies Nephropathy infertility (men)	Decreased hemoglobin synthesis
50	Decreased hemoglobin synthesis	Lead colic
70	Anemia	Anemia, encephalopathy, nephropathy
100	Encephalopathy	Death

- *Blood lead level BLL of >69 μg/dL with* less severity: $CaNa_2EDTA$ 50 mg/kg/day or 1,000 mg/m^2/day, given in two to four divided doses for up to 5 days.
- *Blood lead levels of 45–69 μg/dL in patients without vomiting or central nervous system (CNS)*: oral succimer [2,3-dimercaptosuccinic acid (DMSA)]. The initial dose of DMSA is 10 mg/kg every 8 hours for 5 days, then 10 mg/kg every 12 hours for 14 days.
- *Blood lead level <45 μg/dL*: No need for chelation

Disposition

Acute lead exposure with CNS symptoms and children with a BLL of 69 μg/dL or higher: Hospitalize and start chelation therapy. Asymptomatic children and adults—repeat BLL after 2 weeks to ensure decreasing levels. Ingested a single lead foreign body passes harmlessly.

MERCURY

Source of Mercury

Elemental salts battery and thermometer manufacture; dentistry; jewelry and lamp manufacture; photography; mercury mining; manufacture of scientific instruments; fur processing; tannery work; chemical laboratories; and manufacture of explosives, fireworks, disinfectants, button batteries, inks, and vinyl chloride. Contaminated seafood; embalming; manufacture of fungicides, bactericides, handling of insecticides; and pesticides and coated seeds.

Mercury Absorption

Mercury absorb by inhalation, ingestion and through cutaneous route.

Form: Inorganic mercuric salts

Elemental (metallic) mercury: Liquid, vapor organic (alkyl) mercury. Mercury binds to sulfhydryl (SH) groups resulting in enzyme inhibition and cellular toxicity.

Mercury causes: Renal tubular damage by immune reaction and direct damage, direct corrosive effect on GI tract and hemorrhage. Mercury causes contact dermatitis by an immune reaction, and also causes hypertension and tachycardia by inhibiting catechol-o-methyltransferase. Mercury is a direct pulmonary irritant. Atrophy of the cerebellum, postcentral gyri, and calcarine areas of the brain causing ataxia and sensory and visual field disturbances.

Clinical Features of Mercury Toxicity

Risk assessment: Severity of toxicity is determined by mercury form and route of exposure. Air-borne exposure of volatile elemental mercury>10 mg/m^3 is considered life-threatening.

Inorganic mercuric salts: Fatal oral dose of mercuric chloride: 1–4 g

Organic mercury: Fatal oral dose of methylmercury: 10–60 mg/kg

Acute inhalation of metallic mercury: Chest tightness, respiratory distress ARDS, burning in mouth and throat, nausea, vomiting, bloody diarrhea, and renal tubular necrosis

Acute aspiration of liquid metallic mercury: Tracheobronchial hemorrhage and ARDS

Acute Ingestion of inorganic mercury salts: Hemorrhagic gastroenteritis, abdominal pain, intestinal necrosis, shock, and acute tubular necrosis (ATN).

Chronic inhalation of metallic mercury: Metal fume fever, renal dysfunction, skin changes, and neuropsychiatry disturbance (fatigue, insomnia, anorexia, and memory loss).

Chronic inhalation of inorganic mercury: Neurasthenia, erethism, and acrodynia.

Organomercury exposure: Ataxia, tremor, hyperreflexia, spasticity, hearing loss, dysarthria, and visual field defect. Swallowing of liquid metallic mercury does not produce adverse effects unless the tract contains fistulas or delay gut motility because of poor GI absorption.

Treatment of Mercury Toxicity

Resuscitation: Assess airway, breathing, and circulation. For acute inhalation, remove patient from the source, manage acute pneumonitis and pulmonary edema if necessary. Suction and postural drainage are indicated in cases of acute aspiration of metallic mercury. Anticipate gastroenteritis and treat shock aggressively with IV fluids.

Chelation therapy: BAL is contraindicated for patients poisoned with organic mercury compounds. BAL is used for clinically significant acute inorganic mercury intoxication. BAL: 5 mg/kg IM stat, then 2.5 mg/kg IM every 8–12 h for 1 day and then 2.5 mg/kg IM every 12–24 hours until clinical improvement occurs days. Others: DMPS, DMSA, and D-penicillamine.

Disposition

Acute intoxication and features of neurotoxicity require decontamination and admission for supportive treatment. Self-inject metallic mercury needs admission for surgical debridement. Asymptomatic and fish eaters should abstain from eating locally caught fish and can be observed closely with monthly urine testing as outpatients.

ARSENIC

Sources of Arsenic

Homeopathic medicines, insecticides; rodenticides; herbicides; coal combustion and uranium mining; wood preservatives; veterinary medicines; and semiconductor industry.

Absorption

Arsenic absorb by ingestion, inhalation and through cutaneous route. Arsenic available as elemental arsenic which is poor water soluble and also non toxic. Inorganic trivalent arsenite is more toxic. Arsine is a organic and gaseous form. Arsenic binds to sulfhydryl groups, inhibiting the enzymes such as lactate dehydrogenase and glyceraldehyde-3-phosphate dehydrogenase which involves in glycolysis. In chronic exposures, arsenic redistributes to the liver, kidneys, lungs, nervous system, spleen, hair, and nails, however, it does not easily cross blood-brain barrier. Arsenic crosses the

placenta and has produced teratogenicity in humans. The chemical warfare agent's lewisite (dichlorvos 2-chlorovinyl arsine) causes severe irritation and necrosis of eyes, skin, and airways.

Clinical Features of Arsenic Toxicity

Arsenic risk assessment: Ingestion of <0.05 mg/kg may cause mild GI symptoms. Ingestion of >1 mg/kg is potentially fatal. Chronic intoxication usually takes 10+ years to occur from artesian water. *Children:* Any ingestion of arsenic insecticide should be considered as potentially fat.

Acute exposure to arsine gas: Hemolysis associated with renal tubular injury

Gastrointestinal: Hypersalivation and metallic or garlic taste, nausea, vomiting, abdominal pain, watery diarrhea, hematemesis and hematochezia, and pancreatitis

Cardiovascular: Hypotension, tachycardia, arrhythmias, and prolonged QT interval

Neurological: Headache, drowsiness, delirium, coma, encephalopathy, and seizures. Peripheral neuropathy

Skin: Cutaneous lesions (hyperkeratosis of palms and soles and hyperpigmentation), nail changes (Mee's lines), painful sensorimotor neuropathy, and malignancies of the skin of bladder

Others: Hepatitis, rhabdomyolysis, hemolytic anemia, pancytopenia, unilateral facial nerve palsy, pancreatitis, pericarditis, pleuritis, and fetal demise

Treatment of Arsenic Toxicity

Resuscitation: Assess airway, breathing, and circulation.

Treat hypovolemia: IV crystalloid 10–20 mL/kg, if response is not adequate, start noradrenaline [dose—0.15 mg/kg in 50 mL D5W at 1–10 mL/h (0.05–0.5 μg/kg/min)]. Correct any electrolyte abnormality—potassium, calcium, and magnesium. Avoid drugs that prolong QT interval. Continuous cardiac monitoring—treat coma and arrhythmia if occur, prolonged QT, Torsades de pointes, ventricular tachycardia, and ventricular fibrillation.

Treat seizures: Rule out dysrhythmia, managed with benzodiazepine; lorazepam 0.1 mg/kg max 4 mg; diazepam 0.15 mg/kg max 10 mg; and midazolam 0.2 mg/kg max 10 mg.

Decontamination: Whole bowel irrigation with PEG if the patient is cooperative and recent ingestion (<1 hour) or radiopaque material is visualized on an abdominal radiograph. It requires one nurse—probably for the next 6 hours, administer PEG solution at 2 L/h by continuous infusion (children 25 mL/kg/h). Given metoclopramide (avoid phenothiazine) to reduce nausea and increase gastric emptying.

Hemodialysis removes arsenic in the setting of acute renal failure.

Exchange transfusions or plasma exchange can be considered early after an arsine exposure.

Chelation therapy: Chelation is indicated when there is history of exposure in a symptomatic patient. *Drug of choice*—capsule succimer 10 mg/kg q8h × 5 days, then q12 h for 14 days. If oral administration is not possible, then *dimercaprol* 3 mg/kg IM every 4 hours for 48 hours, then twice daily for 7–10 days.

Disposition

Chronic intoxication can be managed as an outpatient, patients who are asymptomatic at 12 hours postpotential ingestion are not poisoned and may be medically cleared. Those who are symptomatic require aggressive supportive care and chelation until symptoms resolve. Follow-up bloods will be required to monitor ongoing complications if they survive the acute phase. Also warn patients on discharge about ascending neuropathy.

INVESTIGATIONS

History, physical examination along with important laboratory and radiological investigations are important for diagnosing toxicity due to heavy metal poisoning (**Table 2**).

OTHER METAL POISONING

Thallium Poisoning

Thallium poisoning presents with extreme drowsiness (somnolence), nausea, vomiting, abdominal pain, and bloody vomiting (hematemesis). Other important features are loss of hair especially scalp hair (alopecia); rapidly progressive and painful sensory polyneuropathy; motor neuropathy; cranial nerve palsies; seizures; impaired ability to coordinate voluntary movements (cerebellar ataxia); and/or mental retardation. Some patients may have eye symptoms including optic nerve atrophy, inflammation of the optic nerve (retrobulbar neuritis), and impaired functioning of the muscles of the eyes (ophthalmoplegia). In some cases, progression of thallium poisoning to renal and cardiac failure, confusion, psychosis, organic brain syndrome, and/or coma also noted.

Chromium Poisoning

Chromium is used in the manufacturing unit of cars, glass, pottery, and linoleum. Lung and respiratory tract cancer as well as kidney diseases manifest due to exposure of too much chromium in workers of these manufacturing units. Clinical features of overexposure to chromium are GI symptoms, such as diarrhea and vomiting, often with blood, severe dehydration electrolyte disorders, acidosis, and shock.

Cadmium Poisoning

Cadmium is used in the manufacturing units of electroplating, batteries, vapor lamps.

Characteristics of the cadmium exposure are as follows: symptoms develop 2–4 hours after exposure. Overexposure of cadmium causes fatigue, headaches, nausea, vomiting, abdominal cramps, diarrhea, and fever. Patient may present with breathlessness due to development of pulmonary edema and in later stage emphysema. Increased salivation; yellowing of the teeth; tachycardia, anemia, cyanosis, due to insufficient oxygen supply to these tissues; and anosmia, renal tubular dysfunction leads to proteinuria, and osteomalacia.

TABLE 2: Recommended work-up for heavy metal poisoning.

Arsenic	*Iron*	*Lead*	*Mercury*
• CBC: Anemia, leukocytosis or leukopenia, and RBC basophilic stippling • Renal function tests: Proteinuria, hematuria, and pyuria • LFT: The alanine transaminase, aspartate transaminase, and bilirubin levels may be elevated • Urine level: 24-hour urinary excretion of arsenic >100 µg • Blood level: Blood arsenic level is useful if the patient is anuric. Level > 70 µg/L suggests poisoning • X-ray abdominal: Radiopaque intestinal metallic flakes • Hair and nail level: Hair and nail specimens can confirm the diagnosis • Echo: Cardiomyopathy is suspected • In cases of chronic arsenic poisoning, 12-lead ECG: Prolonged QTc interval	• Serum iron level: (3–5 h postingestion) <350 µg/dL associate with minimal toxicity, 350–500 associates with moderate toxicity and >500 µg/dL predicts severe systemic toxicity • Radiography: X-rays chest and abdominal (can confirm and monitor ingestion but some preparations are not radio-opaque—this is not a rule out test) • Biochemistry: CBC, LFTs, electrolytes, serum glucose level, RFT, ABG, and coagulation studies	• Blood lead level: BLL = 10 µg/dL or higher considered toxic • CBC: Low Hb • PBS: Normochromic or hypochromic and microcytic RBC, basophilic stippling • RFT • LFT • Radiograph: X-ray abdomen and pelvis, plain radiographs of the wrist and knees: horizontal metaphyseal "lead bands" or "lead lines" • CT head: To rule out cerebral edema due to acute lead encephalopathy. In cases of altered mental status, seizures, or coma	• Blood mercury level >10 µg/L require further investigations for possible exposure • Radiograph: History of injection or ingestion of metallic mercury • Others: ABG, electrolytes, glucose, LFT, and RFT

(ABG: arterial blood gas; CBC: complete blood count; ECG: electrocardiogram; LFT: liver function test; PBS: peripheral blood smear; RFT: renal function test)

SUMMARY

Accumulation of heavy metals, in toxic amounts, in the soft tissues of the body gives rise to features of heavy metal poisoning. Severity of the clinical features varies according to the amount of metal accumulated. Few heavy metals (zinc, copper, chromium, iron, and manganese) are essential for body in very small amount but serious damage may occur, if they present in concentrations sufficient to cause poisoning. Lead, mercury, arsenic, and cadmium most commonly associated with poisoning of humans. Humans exposed to toxic doses of heavy metals because of industrial exposure, air or water pollution, foods, medicines, improperly coated food containers, or the ingestion of lead-based paints. This is very important for the emergency physician to be aware about the heavy metal toxicity, their features and management.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Dyshemoglobinemias

Gireesh Kumar KP

INTRODUCTION

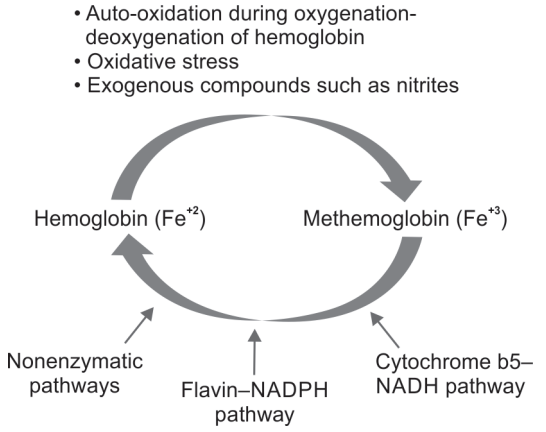
Dyshemoglobinemias are clinical disorders in which the hemoglobin is functionally altered and loses the ability of carrying oxygen properly. The most clinically relevant dyshemoglobinemias are methemoglobinemia, sulfhemoglobinemia, and carboxyhemoglobin (CO-Hb).

METHEMOGLOBINEMIA

Clinically significant methemoglobinemia (congenital or acquired) develops when red blood cells (RBCs) contain methemoglobin at levels higher than 1%. is an altered state of hemoglobin in which the ferrous (Fe^{++}) irons of heme are oxidized to the ferric (Fe^{+++}) state [i.e., hemoglobin with its iron in the ferric (oxidized; Fe^{+++}) state (**Fig. 1**)], which cannot reversibly bind oxygen and, oxygen dissociation curve is left-shifted, making it more difficult to release O_2 (**Fig. 2**).

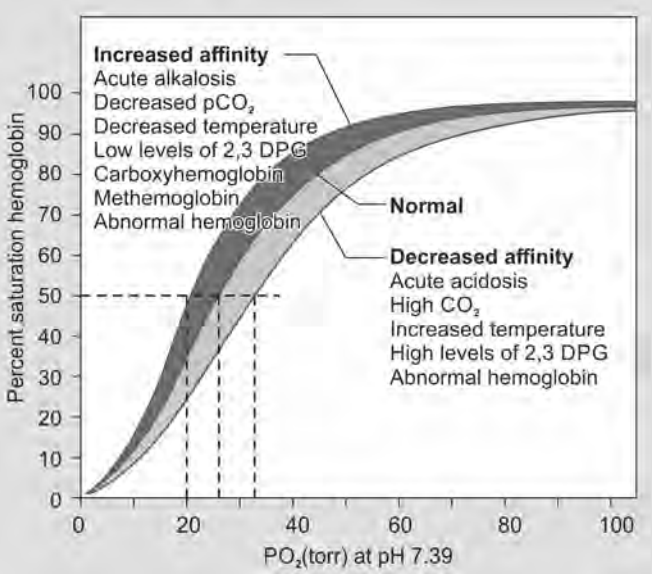
The effect is that patients with acutely increased concentrations of methemoglobin have a functional anemia (i.e., the amount of functional hemoglobin which can carry oxygen is less than the measured level of total hemoglobin). The methemoglobin-containing hemoglobin cannot deliver oxygen to tissues and the remaining oxyhemoglobin has very high oxygen affinity, resulting in impaired oxygen delivery to the tissues, which leads to severe tissue hypoxia.

Normal concentration of methemoglobin in body <1% of total hemoglobin: Auto-oxidation of hemoglobin to methemoglobin occurs spontaneously at a slow rate, each day converting 0.5–3% of the available hemoglobin to methemoglobin. This auto-oxidation, along with the subsequent reduction of methemoglobin, acts to maintain a steady-state level of methemoglobin). When the level is >10% (or 1.5 g/dL absolute concentration of methemoglobin), central cyanosis occurs. There are two types of methemoglobinemia: (1) Congenital; and (2) Acquired.



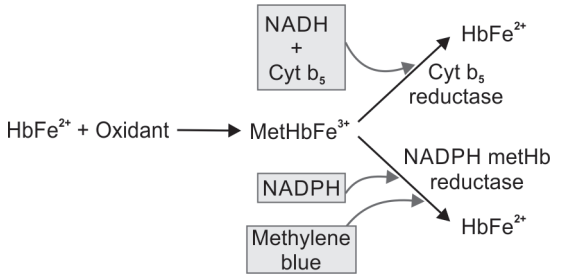
(NADH: nicotinamide adenine dinucleotide; NADPH: nicotinamide adenine dinucleotide phosphate)

FIG. 1: Pathophysiology methemoglobinemia [ferrous (Fe^{++}) irons of heme are oxidized to the ferric (Fe^{+++}) state].



(DPG: diphosphoglycerate)

FIG. 2: Left shift of curve reduces the amount of oxygen delivered to tissues.



(NADH: nicotinamide adenine dinucleotide; NADPH: nicotinamide adenine dinucleotide phosphate)

FIG. 3: Congenital methemoglobinemia (enzymatic reduction of methemoglobin back to normal hemoglobin).

Congenital Methemoglobinemia

There is diminished enzymatic reduction of methemoglobin back to normal hemoglobin [also known as ferrohemoglobin; i.e., hemoglobin with its iron in the ferrous [reduced; Fe^{++}] state] or a mutant globin which facilitates spontaneous oxidation of ferrous iron to ferric state (**Fig. 3**). Patients have lifelong cyanosis but are generally asymptomatic.

Type I disease: Most of the cases are type I, in which the functional deficiency of cytochrome b5 reductase is limited to erythrocytes. Methemoglobinemia and the resulting cyanosis (and possibly polycythemia) are the only clinical features.

Type II disease: In type II cytochrome b5 reductase deficiency, which represents 10–15% of cases of enzymopenic congenital methemoglobinemia, cytochrome b5R is deficient in all cells. They can have cyanosis with severe developmental abnormalities; most affected infants die in the first year of life.

Acquired Methemoglobinemia

Acquired methemoglobinemia occurs due to the ingestion of some drugs or agents that cause an increase in the production of methemoglobin. It can be a severe problem or even a fatal illness. Methemoglobinemia can be caused by nitrites, nitroprusside, nitroglycerin, chlorates, sulfonamides, aniline dyes, nitrobenzene, antimalarials, dapsone, metoclopramide, and phenazopyridine (**Box 1**). Dapsone and topical anesthetic agents (e.g., lidocaine, benzocaine, prilocaine) are the most common precipitating agents of acquired methemoglobinemia. Drugs with oxidant properties (e.g., benzocaine, lidocaine, dapsone) are commonly added to heroin, cocaine, and other illicit drugs which can also cause unexplained acquired methemoglobinemia in drug abusers. Dapsone is used commonly for the treatment of leprosy, malaria, and a variety of blistering skin diseases, including dermatitis herpetiformis.

Methylene blue (MB) is itself an oxidant at doses >7 mg/kg and thus may cause methemoglobinemia in susceptible patients. While MB is a recognized treatment for methemoglobinemia, it may worsen the clinical status of persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency because it can trigger acute hemolysis that can further reduce oxygen delivery to the tissues. In high doses, MB can paradoxically increase methemoglobinemia.

Methemoglobin is produced by oxidation of the heme iron moieties to the ferric state, leading to a characteristic bluish-brown muddy color of skin and mucous membranes resembling cyanosis. Methemoglobin has such high oxygen affinity that virtually no oxygen is delivered to tissues. Methemoglobinemia can cause symptoms of cerebral ischemia at levels >15%; levels >60% are usually lethal.

BOX 1: Medications and chemicals that can cause acquired methemoglobinemia.

- Dapsone
- Clofazimine, chloroquine, primaquine
- Amino salicylic acid (also called p-amino salicylic acid or 4-aminosalicylic acid)
- Local anesthetics, topical creams, and sprays such as benzocaine (in teething rings and ointments), lidocaine, prilocaine
- Quinones, sulfonamides
- Menadione, metoclopramide
- Methylene blue
- Nitroglycerin, phenacetin, phenazopyridine
- Rasburicase

Chemicals and environmental substances:

- Naphthalene (used in mothballs)
- Nitrates and nitrites (e.g., amyl nitrite, farryl nitrite, sodium nitrite, nitrate- and nitrite-containing foods, nitric oxide, well water)
- Paraquat (used in herbicides)
- Resorcinol (used in resin melting and wood extraction)
- Antifreeze, benzene derivatives (used as solvents)
- Acetanilide (used in varnishes, rubber, and dyes)
- Anilines and aniline dyes such as diaper and laundry marking inks, leather dyes, red wax crayons
- Chlorates and chromates (components used in chemical/industrial synthesis)
- Hydrogen peroxide (used as a disinfectant and cleaner)
- Naphthoquinone (used in chemical synthesis)
- Nitrobenzene (used as a solvent)

Inherited disorders (extremely rare):

- Cytochrome b5-reductase deficiency
- Hemoglobin M disease

Clinical Features

Headache, fatigue, lethargy, dyspnea, tachycardia, dizziness, and hypotension due to the vasodilating properties of nitrates as well as tissue hypoxia. Seizures also may occur.

Cyanosis is clinically detected when the absolute concentration of methemoglobin reaches >1.5 g/dL, equivalent to methemoglobin percentage of around 15% at normal hemoglobin concentrations (hypoxic cyanosis occurs when the concentration of unsaturated hemoglobin exceeds 4 g/dL). Levels of methemoglobin >30–40 % are considered "life-threatening" and may be fatal. Acquired methemoglobinemia can become symptomatic when methemoglobin level is >10% of the total hemoglobin. Levels of methemoglobin > 30–40% are considered "life-threatening" and are associated with severe hypoxia and may lead to death.

Diagnosis

The diagnosis is suggested in patients with a normal oxygen tension [by arterial blood gas (ABGs)] and generalized cyanosis (corresponding to a methemoglobin level of 15% or more) that does not respond to oxygen. Pulse oximetry is not accurate and not reliable in patients with high methemoglobin levels. However, an abnormal saturation value in a cyanotic and relatively asymptomatic patient may suggest the presence of an elevated methemoglobin fraction. Clinical cyanosis and normal arterial oxygen tension by arterial blood gas are highly suggestive of methemoglobinemia.

Methemoglobin and Routine Pulse Oximeter

Methemoglobin absorbs at both 660 and 940 nm. Methemoglobinemia should be considered in patients with cyanosis and normal PaO_2. The level of methemoglobin increases up to 20% and SaO_2 drops by about one half of the methemoglobin percentage. At higher methemoglobin levels, SaO_2 falls to 85% regardless of the actual percentage of oxyhemoglobin, thus leading to over- or underestimation of the true SaO_2.

Inaccuracy of routine pulse oximetry and blood gas analysis: Routine pulse oximetry is mostly inaccurate for monitoring oxygen saturation in the presence of methemoglobinemia and should not be depended upon to make the diagnosis of this disorder.

The diagnosis of methemoglobinemia is confirmed by direct measurement of methemoglobin by a multiple wavelength co-oximeter. Measurement of greater numbers of wavelengths enables the instrument of CO-Hb, methemoglobin, other hemoglobin moieties, and "background" light-absorbing species. Optimally, methemoglobin can be detected by the co-oximeter and confirmed by the specific Evelyn–Malloy method. This type of assay involves the addition of cyanide, which binds to the positively charged methemoglobin, and eliminating the peak at 630–635 nm in direct proportion to the methemoglobin concentration.

The characteristic muddy appearance of freshly drawn blood can be a critical clue: The most important finding is the development of cyanosis in the presence of a normal arterial pO_2 and/or the presence of "chocolate brown blood." Symptoms of methemoglobinemia are proportional to the methemoglobin level in the blood and include skin color changes and blood color changes at levels up to 15%. As methemoglobin levels rise >15%, neurologic and cardiac symptoms arise as a consequence of severe tissue hypoxia. Levels >70% are usually fatal (**Table 1**).

The best diagnostic test is methemoglobin assay. The standard method of assaying methemoglobin uses a microprocessor-controlled, fixed wavelength co-oximeter. This device interprets all readings in the 630-nm range as methemoglobin; thus, false positives may occur in the presence of other pigments, including sulfhemoglobin, MB, and certain drugs. Sulfhemoglobin, in concentrations >0.5 g/dL, also causes "cyanosis" with a normal PaO_2 and may be erroneously documented as methemoglobin. Sulfhemoglobin can be distinguished from methemoglobin by virtue of its peak absorption at 620 nm which, unlike methemoglobin, is not abolished by the addition of cyanide.

- *Blood investigations to rule out hemolysis*: Complete blood count, reticulocyte counts, lactate dehydrogenase (LDH), indirect bilirubin, peripheral blood smear, haptoglobin.

TABLE 1: Toxicity in acute acquired methemoglobinemia.

Methemoglobin level percent	*Symptoms**
0–3	Normal range for adults
3–12	Minimal level associated with clinical cyanosis, slight discoloration (e.g., pale, gray, blue) of the skin
3–20	Cyanosis present, usually not symptomatic unless pre-existing condition present
20–50	Mild-to-moderate hypoxemia symptoms†
50–70	Severe, life-threatening hypoxemia symptoms‡
>70	Fully cyanosis and usually fatal

*Conditions such as anemia, heart, and lung disease may exacerbate toxicity.
†Headache, lightheadedness, fatigue, tachycardia, dyspnea, and lethargy.
‡Abnormal cardiac rhythms, respiratory depression, altered sensorium, coma, shock, and seizures.

- *Laboratory tests for end-organ damage*: Liver function tests (LFT), electrolyte levels, blood urea nitrogen (BUN), creatinine.
- Blood levels of nitrites and other offending drugs
- ABG
- Chest X-ray to exclude pulmonary or cardiac disease
- Potassium cyanide test can be done to distinguish methemoglobin from sulfhemoglobin.

Treatment

Take care of airway, breathing, and circulation and intervene if needed. Administration of supplemental oxygen to be started for all patients with cyanosis.

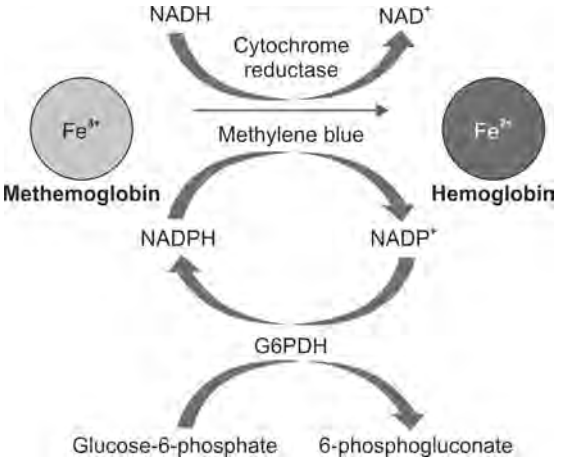
Cytochrome b5 Reductase Deficiency

Treatment of cyanosis in individuals with type I and II cytochrome b5 reductase deficiency is indicated only for cosmetic reasons, if so desired. Treatment options include MB orally at a dose of 100–300 mg/day or ascorbic acid (vitamin C), typically 1,000 mg three times per day; riboflavin (vitamin B2) at a dose of 20–30 mg/day has also been used with some success.

Infants with methemoglobinemia due to metabolic acidosis must be given IV hydration and bicarbonate to reverse the acidosis. The NADPH-dependent methemoglobin reductase enzyme system needs glucose for the clearance of methemoglobin. Therefore, IV hydration with dextrose 5% in water (D5W) is often useful. Vegetables such as spinach, carrots, beets, borage, and chard are high in nitrite or nitrate content and should be avoided by susceptible patients. IV hydration and bicarbonate (for metabolic acidosis) should be given. Cimetidine may be useful in dapsone-induced methemoglobinemia to prevent further formation of its metabolite.

Acquired Methemoglobinemia

Discontinue the drugs which can cause methemoglobinemia. After discontinuation of the causative agent, methemoglobin returns to baseline levels within 36 hours. In lesser degrees of methemoglobinemia (i.e., an asymptomatic patient



(G6PDH: glucose-6-phosphate dehydrogenase; NADH: nicotinamide adenine dinucleotide; NADP: nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate)

FIG. 4: Methylene blue for the management of methemoglobinemia.

with a methemoglobin level <20%), no therapy other than discontinuation of the offending agent(s) may be required. If the patient is symptomatic or if the methemoglobin level is >20%, which is often the case in deliberate or accidental overdoses or toxin ingestion, specific therapy is urgently indicated. Medications: MB and ascorbic acid (vitamin C). *IV injection of 1–2 mg/kg of MB in 5 minutes is an effective emergency therapy* (up to a maximum of 50 mg in adults, adolescents, and older children) as a 1% solution in IV saline over 3–5 minutes (**Fig. 4**). The response is usually rapid; the dose may be repeated in 1 hour if the methemoglobin level is still high (e.g., >20%) by co-oximetry 1 hour after the initial infusion or if the methemoglobin level is rising rapidly due to prolonged absorption of the implicated agent from topical or enteric sites. Caution should be exercised to avoid overdosage because large (>7 mg/kg) cumulative doses of MB can cause dyspnea and chest pain as well as hemolysis in some susceptible subjects. Milder cases and follow-up of severe cases can be treated orally with *MB* (60 mg slow IV 3–4 times per day) or ascorbic acid (300–600 mg/day).

Methylene blue should not be used in patients with G6PD deficiency, since the reduction of methemoglobin by MB is dependent upon NADPH generated by G6PD. As a result, MB is not only ineffective, but also dangerous since MB has an oxidant potential that can produce hemolysis in G6PD-deficient patients, precipitating acute hemolysis, thus further decreasing oxygen delivery. Use Vitamin C here as a single agent: 300–1,000 mg/day orally in divided doses. MB is also not useful in patients with hemoglobin M (Hb M).

Methylene Blue and Serotonin Syndrome

Methylene blue is a potent, reversible inhibitor of monoamine oxidase A (MAO-A), an enzyme responsible for breaking down serotonin in the brain. Usage of MB in patients taking serotonergic medications can result in high, occasionally fatal, levels of serotonin in the brain (i.e., serotonin syndrome). Avoid using MB concurrently with serotonergic psychiatric drugs, unless such usage is absolutely needed for life-threatening or urgent conditions. MB may increase central nervous system serotonin levels as a result of MAO-A inhibition, thus increasing the risk of serotonin syndrome.

Exchange Transfusion

Severely affected patients or G6PD-deficient patients can be treated with blood transfusion, exchange transfusion (which replaces abnormal hemoglobin with normal hemoglobin), and/or hyperbaric oxygen (HBO).

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is another option for patients in whom MB treatment is ineffective or contraindicated. HBO therapy allows tissue oxygenation facilitated by oxygen dissolved in plasma, rather than through hemoglobin-bound oxygen.

SULFHEMOGLOBINEMIA

Sulfhemoglobin is a green-pigmented molecule with a sulfur atom incorporated into the porphyrin ring, which can reduce oxygen affinity that leads to ineffective oxygen transport. Sulfhemoglobin, also in the ferric state, additionally has a sulfur atom incorporated in the hemoglobin. Sulfhemoglobin cannot be converted back to normal Hb A; changes persist for the life of the RBC. Treatment is only prevention by avoidance of exposure of the offending agent.

Causes

Sulfhemoglobinemia is a rare disease which can result from exposure to any substance containing a sulfur atom with the ability to bind to hemoglobin. Sulfhemoglobinemia can be produced by ingestions of phenacetin, dapsone, sumatriptan, and sulfonamides.

Long-term metoclopramide ingestion has also been reported as a cause of sulfhemoglobinemia. Short-term, high-dose metoclopramide treatment with N-acetylcysteine can also cause sulfhemoglobinemia.

It is also associated with industrial chemicals, such as trinitrotoluene, hydroxylamine sulfate, dimethyl sulfoxide, and hydrogen sulfide.

Clinical Features

When comparing with methemoglobinemia, in sulfhemoglobinemia tissue oxygen delivery is somewhat maintained by a rightward shift of the oxygen dissociation curve by decreasing the oxygen affinity of the unaffected hemoglobin. The rightward shift allows for easier oxygen unloading in tissues. Although patients may have a somewhat same percentage of hemoglobin effected as methemoglobinemia patients, sulfhemoglobinemia patients have less severe clinical symptoms because of the difference in their effects on the oxygen dissociation curve.

Diagnosis

Severe sulfhemoglobinemia should be considered in patients presenting with breathlessness oxygen desaturation and cyanosis, especially when methemoglobinemia is excluded. Unlike methemoglobinemia, which can be reversible with

a known antidote, MB, sulfhemoglobinemia can produce irreversible desaturation with no known antidote. Therefore, the blood level of sulfhemoglobin declines gradually over a period of weeks.

Hemoximeters use multiple wavelengths, which can determine the concentrations of oxyhemoglobin, deoxyhemoglobin, CO-Hb, and methemoglobin. Some devices may not distinguish between methemoglobin and sulfhemoglobin because of their similar absorption peaks. Some devices, such as the Chiron Rapidlab 865, indicate the presence of sulfhemoglobin but cannot quantify the concentration of sulfhemoglobin. The laboratory measurement of sulfhemoglobin relies on an absorption peak at 620 nm, which, unlike methemoglobin, can even persist after the addition of cyanide or dithionate.

Treatment

Many patients with sulfhemoglobinemia may also have associated methemoglobinemia. There is no specific treatment available for sulfhemoglobinemia. Treatment is directed at reversing the methemoglobinemia, if present. Severe toxicity may require exchange transfusion or packed red blood cells (PRBC) transfusion.

CARBOXYHEMOGLOBINEMIA—CARBON MONOXIDE POISONING

Carbon monoxide (CO) is a colorless, tasteless, odorless, and nonirritating gas formed by hydrocarbon combustion. The concentration in atmospheric for CO is generally <0.001%, but it may be more in urban areas or enclosed environments. CO binds to hemoglobin with a very high affinity than oxygen, forming CO-Hb and resulting in impaired oxygen transport and utilization. CO can also produce an inflammatory cascade that may lead to central nervous system (CNS) lipid peroxidation and delayed neurologic sequelae (DNS).

Causes

Fire-related smoke inhalation is the major cause of CO poisoning. Other potential sources of CO are poorly functioning heating systems, improperly vented fuel-burning equipment (kerosene heaters, charcoal grills, camping stoves, gasoline-powered generators), and motor vehicles working in poorly ventilated areas (e.g., ice rinks, warehouses, parking garages). Methylene chloride (dichloromethane) is an industrial solvent and a component of paint remover. Inhaled or ingested methylene chloride is converted to CO by the liver and can also cause CO toxicity in the absence of ambient CO.

Carbon monoxide diffuses very rapidly across the pulmonary capillary membrane and binds to the iron moiety of heme with around 240 times more affinity of oxygen. Once CO binds to the heme, an allosteric change occurs that greatly reduces the ability of the other three oxygen-binding sites to release oxygen to peripheral tissues. This leads to a leftward shift of the oxyhemoglobin dissociation curve and impairment in tissue oxygen delivery. CO also reduces the peripheral oxygen utilization. Around 10–15% of CO is extravascular and bound to molecules such as myoglobin, cytochromes, and NADPH reductase, which leads to an impairment of oxidative phosphorylation at the mitochondrial level.

Nonsmokers may have around 3% CO at baseline; smokers may have levels of 10–15%. Severe chronic obstructive pulmonary disease (COPD) patients can also develop a modest but significant elevation in CO-Hb levels compared with a normal individual.

The half-life of CO for a patient breathing room air is about 250–320 minutes, for a patient breathing high-flow oxygen via a nonrebreathing face mask is about 90 minutes, and with 100% HBO is about 30 minutes.

Clinical Features

Mild-to-moderate Carbon Monoxide Toxicity

Patients present with headache (the most common presenting symptom), nausea, dizziness, and malaise. Patients may also present with symptoms ranging from mild confusion to coma. Some may have a "cherry red" appearance of the lips.

Severe Carbon Monoxide Toxicity

Severe CO toxicity can present with neurologic symptoms, such as seizures, syncope, or coma; cardiovascular manifestations, such as myocardial ischemia, ventricular arrhythmias, and lung problems such as breathlessness and pulmonary edema; and metabolic disorder such as profound lactic acidosis.

Delayed Neuropsychiatric Syndrome

In nearly 40% of patients with severe CO toxicity, a syndrome of DNS can arise after apparent recovery within a year. The development of DNS poorly correlates with CO-Hb levels, although a majority of cases are associated with loss of consciousness during acute intoxication. The clinical features of this syndrome are variable degrees of cognitive deficits, personality changes, movement disorders, and focal neurologic deficits. DNS normally occur within 20 days of CO toxicity and may persist for a year or longer.

Diagnosis

Acute CO poisoning is usually suspected on the basis of history and physical examination because the diagnosis of chronic CO intoxication is very much difficult without strong clinical suspicion. Routine pulse oximetry (SpO_2) *cannot* screen for CO intoxication, as it cannot differentiate CO-Hb from oxyhemoglobin. *The diagnosis of CO poisoning is based upon a high* CO-Hb *level measured by co-oximetry of an ABG sample.* In hemodynamically stable patients, venous samples are also accurate and commonly used to avoid arterial prick and it may be very useful when handling a large number of patients in major disasters. Nonsmokers can have up to 3% of baseline CO-Hb; in smokers, this is about 10–15%. Levels more than these values are diagnostic of CO poisoning. A CO-Hb measurement is essential for diagnosis, but levels may not correlate with the degree of poisoning and are not predictive of DNS.

Caution: Treatment with hydroxocobalamin (as might be given for suspected cyanide exposure from smoke inhalation)

can interfere with the measurement of CO-Hb concentration which may lead to inaccurate results. In patients with possible cyanide exposure (e.g., brought to the hospital from a fire area), clinicians should ask about the treatment history that whether hydroxocobalamin was given.

Blood PO_2 levels may be normal because PO_2 reflects O_2 dissolved in the blood, and this process is not affected by CO. In contrast, hemoglobin-bound O_2 (which normally comprises 98% of arterial O_2 content) is severely reduced in the presence of CO-Hb.

ECG and cardiac enzymes are to be done to rule out cardiac ischemia.

Computed tomography (CT) of the head may be asked to rule out other causes of loss of consciousness. CO poisoning may cause hemorrhagic infarction of the globus pallidus and, rarely, the deep white matter.

Treatment

Take care of airway, breathing, and circulation.

High-flow oxygen and hyperbaric oxygen: The half-life of CO for a patient who is breathing room air is about 250–320 minutes, for a patient breathing high-flow oxygen via a nonrebreathing face mask is about 90 minutes, and with 100% HBO is about 30 minutes. The indications for HBO are as follows:

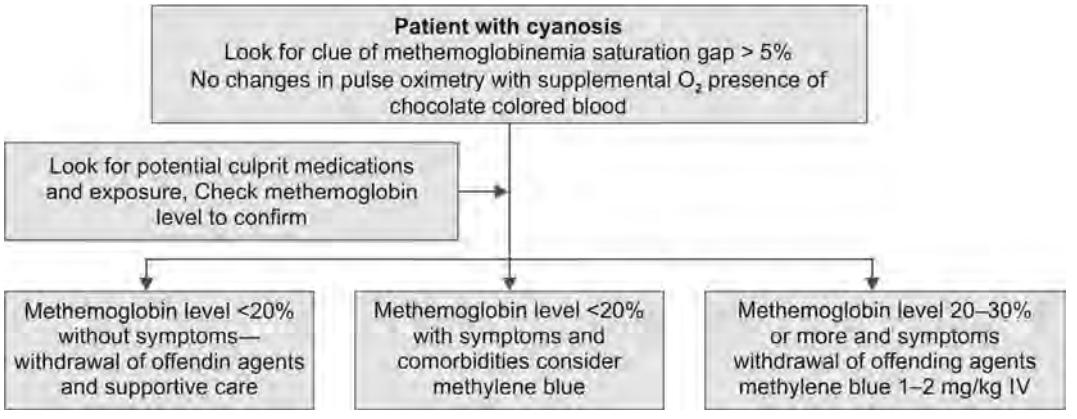
- CO level >25%
- CO level >20% in a pregnant patient
- Loss of consciousness or low Glasgow Coma Scale (GCS)
- Severe metabolic acidosis (pH <7.1)
- Evidence of end-organ damage (e.g., ECG changes, chest pain, or altered mental status)

Hyperbaric oxygen treatment involves exposing patients to 100% O_2 under supra-atmospheric conditions. This leads to a reduction in the half-life of CO-Hb, from about 90 minutes on 100% normobaric oxygen to about 30 minutes during HBO. The amount of oxygen dissolved in the blood also rises from around 0.3–6.0 mL/dL, which substantially increases the release of non-hemoglobin-bound O_2 to the tissues. HBO treatment may be beneficial in preventing the late neurocognitive deficits associated with severe CO toxicity.

Comatose patients, or those with low GCS, should be intubated and mechanically ventilated using 100% oxygen. In smoke inhalation patients (who may suffer from both cyanide and CO poisoning), hydroxocobalamins should be given. The dose of hydroxocobalamin is 70 mg/kg given intravenously (IV).

SUMMARY

Hemoglobin can bind gases other than oxygen, these include carbon monoxide nitrous oxide. Normal hemoglobin can be oxidized to methemoglobin and sulfhemoglobin by exogenous agents or can be found as a result of germline mutations. these modified hemoglobin referred as dyshemoglobinemia. Methemoglobinemia form when iron of the heme group oxidized and converted to ferrous to ferric group. The ferric heme of methemoglobin unable to bind reversely to oxygen. Acquired methemoglobinemia can arise from exposure to many commonly encountered compounds. As methemoglobin levels rise, serious symptoms can develop. Prompt recognition of methemoglobinemia is crucial and may be aided by clinical features that are unique to methemoglobinemia, such as a saturation gap. Management includes the withdrawal of offending medications and methylene blue in certain patients. Treatment with methylene blue should be considered in patients with significant symptoms, elevated methemoglobin levels, or comorbid conditions that compromise oxygen delivery (**Flowchart 1**). Carboxyhemoglobin is related to fire related smoke and The diagnosis of CO poisoning is based upon high carboxyhemoglobin level measured by co-oximetry of an arterial blood gas (ABG) sample. Management consists of high-flow oxygen via a nonrebreathing face mask and hyperbaric oxygen therapy.


Patient with cyanosis
Look for clue of methemoglobinemia saturation gap > 5%
No changes in pulse oximetry with supplemental O2 presence of chocolate colored blood
Look for potential culprit medications and exposure, Check methemoglobin level to confirm
Methemoglobin level <20% without symptoms—withdrawal of offendin agents and supportive care
Methemoglobin level <20% with symptoms and comorbidities consider methylene blue
Methemoglobin level 20–30% or more and symptoms withdrawal of offending agents methylene blue 1–2 mg/kg IV

FLOWCHART 1: Summary treatment of methemoglobinemia.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Toxic Plants

TV Ramakrishnan, Mona Lisa

INTRODUCTION

The incidence of poisoning in India is among the highest in the world, and it is estimated that more than 50,000 people die every year from toxic exposure. The incidence of plant poisoning is around 1.7% of the total poisoning cases. There are a wide variety of toxicities caused by poisonous plants (**Box 1**). This chapter enlightens on the most common plant poisons, their toxic components, symptomatic approach, and management.

THEVETIA PERUVIANA

Synonym: Yellow oleander. It is an ornamental plant belonging to the *Apocynaceae* family (**Fig. 1**). Ingestion of plant parts causes digoxin-like toxicity, affecting cardiac myocytes. Toxic cardiac glycosides of almost eight different types include mainly *thevetin A, thevetin B,* and *neerifolin*. All parts are dangerous, especially the seeds. The toxic dose is ingestion of 8–10 seeds or 5–10 leaves.

Mechanism of Action

Inhibition of the transmembrane $3Na^+/2K^+$ ATPase pump increases intracellular concentrations of Ca^{2+} and Na^+ which cause arrhythmogenic effects on the heart.

BOX 1: Common plant poison in India.

- *Thevetia peruviana*
- *Nerium odorum*
- *Datura metel*
- *Abrus precatorius*
- *Myristica fragrans*
- *Nicotiana tabacum*
- *Strychnos nux-vomica*
- *Gloriosa superba*
- *Ricinus communis*
- *Calotropis*
- *Cannabis sativa*
- *Cleistanthus collinus*

Symptoms

Immediately after consumption, it causes a burning sensation in the mouth, dry throat, nausea, vomiting, and diarrhea. Cardiac manifestations are the major features seen, varying from bradyarrhythmias to tachyarrhythmias. It also causes anxiety, convulsions, and coma.

Specific Investigations

- *ECG*: To identify cardiac conduction defects.
- *Serum electrolytes*: Hypokalemia and hypomagnesemia worsen the toxicity and hyperkalemia is life-threatening.

Treatment

Thevetia peruviana poisoning can be treated by gastric decontamination using activated charcoal, if the patient presents early to the emergency department (ED). Arrhythmia should be managed based on the type identified. Atropine for bradyarrhythmia and lidocaine for tachyarrhythmia are preferred. Administration of digoxin-specific antibody fragments is indicated, if serum potassium >5 mEq/L after an acute overdose or in any cardiac dysrhythmia.

FIG. 1: *Thevetia peruviana* (yellow oleander). ***(For color version, see plate 37)***

Courtesy: Avighna Richhariya.

NERIUM ODORUM

Synonym: Pink oleander. It belongs to the same family as yellow oleander with a similar mechanism of action and contain the cardiac glycosides, *oleandrin* and *neriine* (**Fig. 2**). Both have positive inotropic, negative chronotropic, and cross-reactivity. All parts of the plant are toxic, which cause gastrointestinal effects such as nausea, vomiting to cramping, and bloody diarrhea. Confusion, dizziness, drowsiness, weakness, visual disturbances, and mydriasis are central nervous system (CNS) manifestations. Treatment remains the same as for yellow oleander.

DATURA METEL

Synonym: Indian thornapple, Devil's trumpet. It is a hallucinogenic plant with ornamental and medicinal properties, belonging to the *Solanaceae* family (**Fig. 3**). All parts of the plant are poisonous due to the higher contents of *tropane alkaloids* (especially seeds and fruit). The lethal dose is 0.6–1 g.

FIG. 2: *Nerium odorum* (pink oleander). ***(For color version, see plate 37)***

Courtesy: Avighna Richhariya.

Mechanism of Action

Tropane alkaloids, such as *Atropine, hyoscine,* and hyoscyamine, are the competitive antagonist of central and peripheral acetylcholine receptors. They cause general paralysis of all parasympathetic innervated organs (*anticholinergic syndrome*).

Symptoms

The features are similar to atropine toxicity. Dry skin and mucosa, flushing, mydriasis, tachycardia, hyperpyrexia, decreased bowel activity, and urinary retention are some of the symptoms. CNS manifestations are ataxia, psychosis, confusion, hallucinations, seizures, and coma. Acute kidney injury is a frequent finding (10–50%), due to direct toxicity and secondary myoglobinuria.

Treatment

Gastric decontamination can be done and benzodiazepines are used to sedate an agitated patient. Hyperpyrexia is treated with fluid administration and external cooling methods. In severe cases, physostigmine (cholinesterase inhibitor) is given intravenously (IV) in a dose of 0.5–2.0 mg at a rate of not >1 mg/min. A second dose is given if indicated.

ABRUS PRECATORIUS

Synonyms: Rosary pea, Jequirity bean, Love bean. It is a poisonous, flowering plant belonging to the *Fabaceae* family (**Fig. 4**). The toxic part is the seed; even one crushed seed can be fatal due to the release of *abrin* toxalbumin. The seed when ingested intact passes out undigested. The lethal dose is —one to two seeds.

Mechanism of Action (*Abrus Precatorius* and *Ricinus Communis*)

Ricinus and *Abrus* are differ somewhat in appearance and taxonomy but contain toxins (toxalbumin) that are structurally and functionally similar. Toxalbumins are proteins that bind

FIG. 3: *Datura metel*.

Courtesy: Avighna Richhariya.

FIG. 4: *Abrus precatorius*.

to carbohydrates. Molecular structure of both compounds *Ricin* and *Abrin* are similar, consist of two peptide chains that are cross-linked by two bisulfide bonds. The B chain, or "haptomer," binds to galactose containing receptors on the cell surface. The A chain, or "effectomer," then penetrates the cell and is transported into the cytoplasm to the ribosomes where it interrupts protein synthesis. B chain facilitates entry of A chain into cells and A chain prevents protein synthesis and causes cell death.

Symptoms

Ingestion can cause nausea, severe vomiting, abdominal pain, and bloody diarrhea (classical feature). It can be fatal due to severe dehydration and electrolyte abnormalities. Symptoms can be delayed for 1–3 days after ingestion and the clinical course can last for 10 days. The rare complications are encephalopathy, arrhythmias, and renal failure.[13]

Treatment

No specific antidote is available for *Abrin* poisoning. Treatment is mainly supportive with fluids and correction of electrolyte abnormalities.

MYRISTICA FRAGRANS

Synonyms: Nutmeg, Mace tree. It is an evergreen tree belonging to the *Myristicaceae* family. It is a source of spices (nutmeg and mace). It has psychotropic effects due to the release of *myristicin* and *elemicin.* The lethal dose is ingestion of one to three nutmegs.

Mechanism of Action

Myristicin metabolizes into 3-methoxymethylenedioxyamphetamine which has sympathomimetic action, hallucinogenic effects, and also serotonin agonist which exerts cardiac effects.

Symptoms

It causes varied manifestations, including nausea and vomiting. Cardiac manifestations include tachycardia and hypertension. CNS features are hallucinations, agitation, drowsiness, vertigo, confusion, seizures, and urinary retention (anticholinergic effect). Respiratory depression leads to death.

Treatment

Treatment is symptomatic and supportive. Gastric lavage is done if the patient presents within a couple of hours after ingestion. Sedatives are given to calm the patient and anticonvulsants in case of seizures.

NICOTIANA TABACUM

Synonym: Tobacco. It is a herbaceous plant of the *Solanaceae* family (**Fig. 5**). Every part of the plant, except the seeds, contains the poisonous *nicotine*. Leaves, along with nicotine, also contain *citrate* and *malate.* About 64% of nicotine is seen in leaves and the concentration increases with the age of the plant. The lethal dose is 60–100-mg nicotine or 2-g tobacco. The poisonous *pyridine alkaloids* present apart from *nicotine*

FIG. 5: *Nicotiana tabacum*.

(90–95%) are *nornicotine* and *anatabine*. The methods of entry include oral ingestion, inhalation, and percutaneous absorption.

Mechanism of Action

Nicotine causes stimulation of preganglionic nicotinic acetylcholine receptors of the autonomic nervous system which in turn causes cardiovascular and CNS effects.

Symptoms

The onset of symptoms in acute poisoning is usually rapid. In severe poisoning of the alkaloid, the patient may collapse and die within minutes. The gastrointestinal symptoms include salivation, nausea, vomiting, and diarrhea. Cardiovascular manifestations include hypertension (initially followed by hypotension in later stages), tachycardia, arrhythmias, and labored breathing. Parasympathetic stimulation of CNS leads to mental confusion, giddiness, restlessness, muscle weakness, disturbed vision, seizures, and unconsciousness. Death usually occurs due to complete paralysis and respiratory arrest.

Diagnosis

Diagnosis is based on history and clinical findings. Sample collection for toxic screening is indicated.

Treatment

Stomach wash is indicated for oral ingestion. There is no specific antidote. Convulsions are controlled with benzodiazepines while ensuring that airway patency and respiration are maintained.

STRYCHNOS NUX-VOMICA

Synonyms: Strychnine tree, Poison nut. It is a deciduous tree belonging to the *Loganiaceae* family. It is highly poisonous due to the presence of alkaloids—*strychnine, loganin,* and *brucine* in the seeds, leaves, and tree bark. The possible ways of poisoning are oral ingestion, inhalational, transdermal, and intravenous toxin. The lethal dose is 30–120 mg (1–2 mg/kg).

Mechanism of Action

Strychnine competitively inhibits glycine receptors in the spinal cord (glycine—inhibitory neurotransmitter) which in turn causes uncontrolled stimulation of postsynaptic neurons and involuntary muscle contractions (*awake seizures*).

Symptoms

Symptoms appear fast, within 15–30 minutes of exposure. The initial signs of poisoning include nervousness, restlessness, twitching of the muscles, neck stiffness, and tetanic convulsions of all striated muscles. Convulsions last from 30 seconds to 2 minutes and are more pronounced in the antigravity muscles causing *opisthotonos*. *Risus sardonicus* due to contractions of facial muscles giving a sardonic smile is a classical feature. Tachycardia, hyperthermia, and airway compromise from the stiffness of neck are other features. Rhabdomyolysis, hyperkalemia, lactic acidosis, metabolic acidosis, and kidney failure are later features. Death usually occurs due to respiratory compromise.

Evaluation

Blood assays include arterial or venous blood gas, lactates, serum electrolyte, and urine analysis for detection of rhabdomyolysis.

Treatment

Early intubation is advised. Succinylcholine must be avoided due to the risk of hyperkalemia. Gastric lavage is indicated if presenting early. Benzodiazepines or barbiturates are used to control muscle contractions.

GLORIOSA SUPERBA

Synonyms: Climbing lily, Creeping lily, Glory lily, *Gloriosa* lily, Tiger claw, and Fire lily. It is a flowering plant belonging to the *Colchicaceae* family. Every part of the plant is highly poisonous, especially the tubers. Its toxicity is due to antimitotic effects of the alkaloids, *colchicine* and *gloriosine*, on rapidly proliferating cells. The lethal dose is about 60 mg in adults and the fatal period is 12–72 hours.

Colchicine arrests mitosis in metaphase cell death.

Symptoms

The common clinical presentation in acute poisoning is gastroenteritis; it also causes nausea, burning and tingling oral cavity, bloody diarrhea leading to hypovolemic shock, and renal failure. Other features include delirium, convulsions, acute respiratory distress syndrome, coagulopathy, multiorgan failure, ascending polyneuropathy, and cardiotoxicity with ST-elevation occurring within 12–36 hours. Generalized alopecia is also a recognized feature.

Treatment

Symptomatic treatment is given with stomach wash. Secure airway and maintain ventilation; administer a lot of IV fluids in case of hypovolemia to correct electrolyte imbalance. Maintain urine output; overt renal failure may require hemodialysis. Hemorrhagic complications require transfusion of blood products.

RICINUS COMMUNIS

Synonym: Castor oil plant. It is a flowering plant belonging to the *Euphorbiaceae* family (**Fig. 6**). Toxicity is caused by ingestion of seeds containing highly toxic protein *ricin* (toxalbumin) and less toxic alkaloid *ricinine*. Seeds are toxic only if the outer shell is broken or chewed. The lethal dose is 1–20 mg/kg. Routes of exposure are inhalation, ingestion, and intravenous.

Symptoms

Inhalation causes cough, fever, chest tightness, dyspnea, and distress leading to pulmonary edema. Ingestion causes nausea, vomiting, diarrhea, and abdomen pain. It can cause miosis or mydriasis. CNS manifestations are vertigo, delirium, convulsions, and coma.

Treatment

No specific antidote is available for ricin. Gastrointestinal decontamination using activated charcoal can be done. Treatment is supportive and symptomatic.

CALOTROPIS

Synonym: Milkweed. It is a flowering plant of the *Apocynaceae* family. The milky exudate from stems and leaves is corrosive poisoning. The chemical components from the latex are *calotropin, calotoxin, calactin*, *uscharin,* and *gigantin*. They were used as an arrow poison. Exposure irritates the eye and oral mucosa, cardiotoxicity, and neurotoxicity. Due to anticholinergic responses, it can cause various fatal presentations. The lethal dose is 0.12 mg/kg calotropin. The fatal period varies from 30 minutes to 8 hours.

Symptoms

Ocular exposure causes various effects due to corneal edema. It manifests immediately with irritation, pain, and photophobia.

FIG. 6: *Ricinus communis* (castor oil plant).

After a few hours, it causes painless diminution of vision, toxic iridocyclitis, and secondary glaucoma. On ingestion, it causes burning pain in the throat and abdomen, salivation, vomiting, diarrhea, mydriasis, delirium, tremors, tetanic convulsions, and death.

Treatment

Management remains supportive care with gastric lavage, oxygen administration, and airway protection. Copious irrigation is needed in case of exposure to the eyes and further ophthalmological evaluation.

CANNABIS SATIVA

Synonyms: Indian hemp, Hashish. It belongs to the *Cannabaceae* family. *Marijuana* is tobacco-like preparation from the leaves and flowers of the plant. It is mainly used for recreational purpose and it contains various compounds and cannabinoids; it is important if *tetrahydrocannabinol* (THC). Acute effects depend on the dose and route of exposure (inhalational, ingestion). Approximately 2–3 mg of inhaled and 5–20 mg of ingested THC is enough to cause psychotropic effects. Severe effects are seen with a dose of >7.5 mg/m^2 THC.

Mechanism of Action

Cannabis act by cannabinoid receptors (CB1 and CB2). CB1 in the CNS inhibits the release of gamma-aminobutyric acid (GABA), dopamine, acetylcholine, 5-hydroxytryptamine, and norepinephrine. CB2 receptors act on peripheral nerve terminals.

Symptoms

It presents with conjunctival redness, dry mouth, nystagmus, hyperemesis, and abdominal pain. CNS effects are ataxia, incoordination, impaired judgment, sedation, CNS depression, and coma (more common in children). Psychiatric manifestations include euphoria and relaxation, agitation, anxiety, time disorientation, hallucinations, delusions, and acute psychosis. Tachycardia, orthostatic hypotension or elevated blood pressure, and tachypnea are other signs.

Evaluation

Standard urine drug screen can be used to detect THC carboxylase. ECG and cardiac markers should be done in case of chest pain, to rule out infarction. Always consider co-ingestion.

Treatment

Treatment is supportive and to maintain airway, breathing, and circulation. Benzodiazepines are used in case of agitation or seizures.

CLEISTANTHUS COLLINUS

This is a toxic shrub of the *Phyllanthaceae* family. All parts of the plant are toxic. Ingestion of leaves is more common. The toxic substances are *cleistanthin A, cleistanthin B*, and *collinusin* and *diphyllin*. Cleistanthin inhibits deoxyribonucleic acid (DNA) synthesis and cell division.Cleistanthin B induces chromosomal aberrations.

Symptoms

It presents commonly with gastrointestinal symptoms such as vomiting, abdominal pain, diarrhea, dysphagia, salivation, and abdominal distension. Chest pain, dyspnea, tachycardia or bradycardia, hypotension, and cyanosis are the cardiac symptoms. Neurological features are muscle cramps and weakness, altered sensorium, giddiness, headache, and tremors. Laboratory findings show hypokalemia with metabolic acidosis, elevated hepatic transaminases, hyponatremia, and coagulopathy. Fatal complications are renal failure, respiratory distress, and shock.

Treatment

Treatment is supportive care, gastric decontamination with activated charcoal if the patient presents early. N-acetylcysteine has been suggested as a possible antidote for management.

SUMMARY

Most of the patients presented with mild toxicity after toxic plant ingestion to the ED. Serious toxicity only occurs if taken deliberately in a large amount or taken mistakenly as edible plants. Identification of plants is an important part and management is generally supportive except for those who have cardiac glycosides and present with cholinergic and anticholinergic symptoms. Plant toxins are summarized in **Table 1**.

TABLE 1: Summary of toxic plants.

Toxic plant	*Toxic part*	*Toxic component*	*Lethal dose*
Thevetia peruviana	All parts	Thevetin A, thevetin B, and neriifolin	8–10 seeds or 5–10 leaves
Nerium odorum	All parts	Oleandrin, nerine	
Datura metel	All parts	Tropane alkaloids—atropine, hyoscine, and hyoscyamine	0.6–1 g
Abrus precatorius	Seeds	Abrin toxalbumin	1–2 seeds
Myristica fragrans	Seeds	Myristicin, elemicin	1–3 nutmegs
Nicotiana tabacum	All parts except seeds	Nicotine, nornicotine, and anatabine	60–100-mg nicotine or 2-g tobacco

Continued

Continued

Toxic plant	*Toxic part*	*Toxic component*	*Lethal dose*
Strychnos nux-vomica	All parts	Strychnine, loganin, and brucine	30–120 mg (1–2 mg/kg)
Gloriosa superba	All parts	Colchicine, gloriosine	60 mg in adults
Ricinus communis	All parts (mainly seeds)	Ricin, ricinine	1–20 mg/kg
Calotropis	Exudate, roots	Calotropin, calotoxin, calactin, uscharin, and gigantin	0.12 mg/kg calotropin
Cannabis sativa	Almost all parts	Tetrahydrocannabinol (THC)	>7.5 mg/m^2 THC
Cleistanthus collinus	All parts (leaves mainly)	Cleistanthin A, cleistanthin B, and dyphylline	–

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Pediatric Toxicology

Nisreen Hamza Maghraby, Chafika Lasfer, Mohamad Al Jumaan

INTRODUCTION

Poisoning in pediatrics is a common emergency, mostly unintentional because children are curious by nature about the many household products and medications available to them at home. They will be brought in by anxious parents who may or may not have accurate information regarding suspicion of exposure. Failure to consider the major differences in pediatric toxicology as well as concerning historical and examination features may lead to a delay in detection or treatment of these cases. Fortunately, fatalities are rare, and most young patients ingest substances that are minimally toxic or nontoxic and in smaller quantities than is seen with adolescents and adults. A 2018 annual report of the American Association of Poison Control Centers found that children <5 years of age accounted for 44.2% of exposures, cosmetic analgesics and household cleaning agents being the most common toxins (**Fig. 1**). Other common substances which are exposed to a child are toys, topical preparations, pesticides, antimicrobials plants vitamins, antihistamines, and cough syrups. This chapter is concerned with highlighting the major concerns when managing a pediatric poisoned patient. It provides a clear clinical approach to a suspected poisoned child.

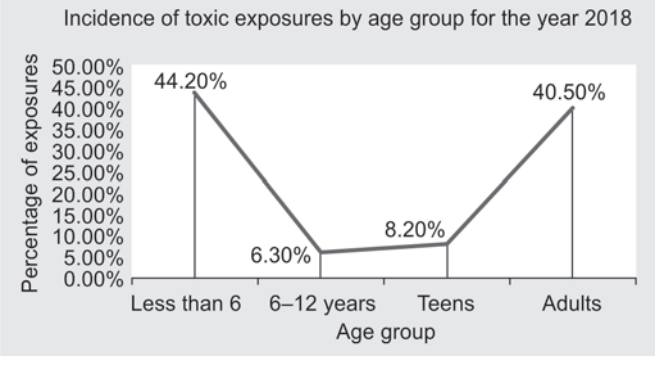


FIG. 1: Incidence of toxic exposures by age group for the year 2018.

PHARMACOKINETIC DIFFERENCES IN PEDIATRIC AGE

The maxim "children are not just small adults" is most valid when we consider the following key pharmacokinetic factors (**Table 1**) that influence the effects of drugs and toxins on a child. It is important to note that these processes are dynamic and continue to develop in children as they age and that they begin to resemble those of the adult population near adolescence.

EMERGENCY EVALUATION

Initial Stabalization and Life Support Measures

The emergency evaluation of the poisoned child begins with the same approach of "airway, breathing, circulation" to identify the patients in need of resuscitation and immediate life-supporting measures. In the context of toxicology, however, the primary survey is also extended to include the following: *Disability, drugs (emergency antidotes), and decontamination.* Other measures include obtaining an *ECG* and management of *fever (hyperthermia)* if present. This approach prioritizes stability of the child over obtaining a complete history and physical examination. For patients who present with signs of instability or shock, the following actions should be rapidly undertaken: Complete set of vital signs should be recorded, intravenous/intraosseous (IV/IO) access obtained with blood drawn for investigations, continuous cardiac monitoring initiated with the placement of pads, bedside glucose measurement, preparation of equipment, and medication according to the patient's weight and age.

Airway: *Ensuring* a patent airway is the first step in stabilization and the threshold for intubating an unstable poisoned child is relatively low, as these patients do not tolerate hypoxia well and will desaturate quickly.

Airway should be protected by intubation in cases of risk of aspiration, e.g., depressed mental state, loss of protective

TABLE 1: Pharmacokinetic factors in the pediatric population.

	Key differences	*Clinical implications*
Absorption	• Smaller gastrointestinal surface area with limited intestinal absorption • Delayed gastric emptying • Thinner skin, higher body surface area • Increased minute ventilation and respiratory rate	• Absorption via nonoral routes can be erratic • Weakly acidic drugs may need higher dosing • Higher toxicity seen with topically applied medicine • Children more susceptible to inhaled toxins such as carbon monoxide
Distribution	• Higher volume of water • Less fat content • Less protein binding • Higher blood–brain barrier permeability	Ceftriaxone is contraindicated in infants younger than 28 days and displaces bilirubin from albumin, leading to kernicterus
Metabolism	• Higher metabolic rate in children • Immature liver enzymes in infants	• Benzyl alcohol is toxic to children at much lower doses than in adults, leading to neonatal gasping syndrome and potential death • Carbamazepine requires higher dosing in children compared to adults
Elimination	• Predominant renal clearance • Decreased glomerular filtration rate • Decreased renal tubular reabsorption	Renally excreted drugs require lower or less frequent dosing regimens to avoid toxicity

airway reflexes oropharyngeal injuries due to caustic ingestion or anticipating deterioration in case of witnessed ingestion of lethal doses of tricyclic antidepressant.

Breathing: The respiratory rate and character of breathing should be noted. Attention should be paid to correlate the rate of breaths with the patient's age and to look for signs of increased work of breathing (nasal flaring, suprasternal or subcostal retractions). Continuous pulse oximetry should be initiated as well. However, this should not delay interventions at the bedside and the physician may rely on clinical judgment to begin ventilatory support.

Supplemental oxygen should be initiated and titrated to a saturation of >94%. One exception is the ingestion of *paraquat*, a corrosive herbicide that can be lethal to children in very small doses. When paraquat poisoning is suspected, supplemental oxygen should be withheld unless saturation is below 90% as free oxygen radicals can cause cellular injury.

If a patient with severe acidemia is intubated, respiratory compensation should be maintained to prevent decompensation. Therefore, a ventilator strategy that allows hyperventilation of the child should be initiated to prevent worsening acidemia.

Circulation: Owing to physiologic differences, cardiac output in children is dependent on changes in heart rate rather than stroke volume. As such, if a pediatric patient is in a state of shock, this may only be subtly evident through a compensatory increase in heart rate. Ingestion of cardiovascular drugs, such as calcium channel blockers, that block this compensatory mechanism is especially dangerous in children. Furthermore, if tachycardia is not addressed in a timely manner, the patient might deteriorate further with evidence of hypotension, which is a late sign. Other signs of shock that should be sought include a delayed capillary refill >2 seconds, skin mottling, and faint pulses. If bradycardia is found, efforts to prevent impending cardiac arrest are necessary by securing IV access early in the resuscitation phase. Assess for signs of shock. Administering fluid boluses at 20 mL/kg up to a total of 60 mL/kg is titrated to clinical effect. Initiation of vasopressors may be necessary.

Disability: When assessing a child's mental status, using the AVPU (Alert-Verbal-Pain-Unresponsive) scale is a faster and more convenient method compared to the Glasgow Coma Scale (GCS). Scores of A, V, P, and U correspond to GCS scores of 15, 13, 8, and 3, respectively. Pupils' size and reactivity should be noted, along with the presence of any nystagmus. A bedside glucose measurement should be obtained quickly upon arrival of the patient as hypoglycemia is common in this age group and may mimic other causes of altered mental status. Any seizure activity should be treated immediately.

Decontamination: As described above, children are more susceptible to toxicity through skin exposure than adults. The patient should be fully exposed with the removal of any contaminated clothes and washing of the skin with water. Care should be taken not to accidentally induce hypothermia and the patient should be covered with blankets. If the eyes are exposed to chemicals, ocular irrigation with normal saline should be started.

Gastrointestinal decontamination with activated charcoal may be considered if patients present immediately after a toxic ingestion of a substance known to adsorb to charcoal. The greatest benefit is seen if it is given within 1 hour of ingestion; however, it may be considered if the patient has taken substances known to delay gastric emptying. Furthermore, if antidotal therapy is subsequently delivered, its absorption may be impaired due to the administration of activated charcoal. In any case, the benefit of activated charcoal administration must outweigh the potential risk of aspiration in an obtunded child whose airway is not secure. In awake and cooperative children, mixing activated charcoal with ice-cream or soda may improve its taste. The dose is 1–2 g/kg.

TABLE 2: Emergency antidotes.

Antidote	*Indication*
Oxygen	Hypoxemia
Naloxone	Opioid-induced respiratory depression
Benzodiazepines	First-line treatment of toxic seizures, agitation
Dextrose	Hypoglycemia
Sodium bicarbonate	Cardiotoxicity due to sodium channel-blocking agents (wide QRS on ECG), tricyclic antidepressant
N-acetylcysteine	Acetaminophen
Flumazenil	Benzodiazepine
Glucagon	β-blockers
Calcium, glucose + insulin lipid emulsion	Calcium channel blocker
Ethanol, fomepizole	Methanol
Methylene blue	Methemoglobinemia
Vitamin K	Coumadin (another similar rodenticide)
Deferoxamine	Iron
Pyridoxine	Isoniazid
Atropine and pralidoxime	Organophosphorus insecticides

Drugs—antidotes: During resuscitation, few emergency antidotes may be indicated in certain scenarios given in **Table 2**.

ECG: Obtain an ECG upon arrival of any patient suspected of poisoning. Changes in QRS width, QTc length, evidence of arrhythmias, heart blocks, or terminal R wave in aVR may point to specific toxicities.

Fever: Presence of fever should raise suspicion of life-threatening poisoning, as is seen with sympathomimetic and anticholinergic toxidromes. Core temperatures should be measured. Presence of fever above 39.5°C should be promptly treated. Initiation of active cooling measures. Intubation with paralysis will help to prevent further heat production. Hypothermia, on the other hand, can be associated with carbon monoxide, sedative-hypnotic, or alcohol toxicity and should be corrected.

HISTORY AND PHYSICAL EXAMINATION

History

As an important step in forming the individualized risk assessment, the history is primarily concerned with answering these following questions: *"What, How, How much, When, and Why"*.

When obtaining history regarding a possible ingestion in a young patient, few challenges may arise. First, most ingestions occur in children too young to be reliable historians. Second, the event of ingestion may have been unwitnessed by caregivers at home. Therefore, a high index of suspicion should be maintained not to miss pediatric poisoning. Whenever in doubt of a clear history, "worst-case scenarios" should be believed. Past medical history should be obtained to detect populations more susceptible to toxicity; e.g., mothball toxicity is more severe in a patient known to have glucose-6-phosphate dehydrogenase deficiency.

Identifying *what* the poison is, *how* it was taken, and *how much* of it was taken: This includes recognizing the substance of poisoning and its route. Although children can also be poisoned by inhalation and dermal contact, ingestion is the most common route. Iatrogenic poisoning is another cause of toxicity, as all medications are weight-based and medication errors may occur. Asking about all available medications at home with their specific formulations is important. Fortunately, most children will ingest medications in small quantities.

However, it is important to obtain the exact dose ingested per weight of any child to determine the level of risk posed to his/her health. *Worst-case scenario*: Assume that the patient has taken the largest dose available to him/her at the time of ingestion. If more than one child is present, assume that all have taken the same maximum dose. For example: If three children were brought by parents who found an empty 30-pill bottle of medicine, assume that all three have ingested all 30 pills. In toddlers, if the ingested pill is unknown, assume it to be one that can kill in small doses, until proven otherwise.

One Pill Can Kill: It is also worth mentioning that certain drugs can induce severe toxicity in the pediatric population if taken in small doses. Known collectively as the *"one pill can kill"* group, they include antimalarials, beta-blockers, calcium channel blockers, camphor, clonidine, tricyclic antidepressants, sulfonylureas, salicylates, and toxic alcohols, to name a few. *A summary of these drugs, the fatal dose, highest dose available, mechanism of toxicity, and signs/symptoms is provided in* **Table 3**.

Identifying the *when* of ingestions: As most of these ingestions occur unwitnessed, it is often difficult to know exactly when ingestions took place. This is important, however, as some medications have delayed onset of symptoms. Prolonged observation time in all pediatric poisoning is warranted as well, owing to their different pharmacokinetics. *Worst-case scenario*: Assume the latest possible time of ingestion. The exception to this is paracetamol, where the earliest ingestion time is assumed. In toddlers, if the time of ingestion is unknown, keep patients for 12-hour observation periods and watch for onset of symptoms.

Identifying the *why* of ingestions: Asking about the circumstances of possible poisoning aims to identify red flags that may raise suspicion of neglect, abuse, or intentional ingestions. Most of the reported poisoning cases between the ages of 1 and 5 years occur unintentionally as children in this age group are more likely to explore their surroundings or mistake medications and substances for candy. Older children and adolescents are less likely to have accidental ingestions, and a history of substance abuse and suicidality should be sought. Other factors that can contribute to poisoning are the arrival of a new baby, moving homes, parental illness, and grandparent's caretaking.

Worst-case scenario: Historical "Red Flags": Suspect neglect or abuse if history is inconsistent with the presentation, if there is

TABLE 3: Summary "one pill can kill."

Drug	*Potentially fatal dose (mg/kg)*	*Highest dose available (mg)*	*Mechanism of toxicity*	*Signs/Symptoms of toxicity*
Calcium channel blocker	15	360	Myocardial suppression	PR prolongation, bradydysrhythmias, hypotension, CHF
Tricyclic antidepressants	15	150	Na channel blockade, alpha 1 blockade	Coma, seizures, tachycardia followed by hypotension and bradydysrhythmias
Antimalarials	20	500	Na channel blockade, direct retinal damage	Prolonged QRS/QT, torsades, hypotension, tinnitus, vision loss, headache, vertigo, seizures
Opiates: Codeine	10	60	Respiratory depression	Miosis, CNS depression, hypopnea
Sulfonylureas	0.1	10	Activates insulin release	Hypoglycemia, irritability, lethargy, seizures, and coma
Class 1 antiarrhythmics	25	1	Na channel blockade	Prolonged PR/QRS, QT (class 1A agents), headache, nausea/vomiting
Camphor	50	550 mg/tsp	Unknown mechanism of neurotoxicity	Nausea, vomiting, agitation, myoclonus, hyperreflexia, intractable seizures
Oil of wintergreen (methyl salicylate)	400	7 g/tsp	Organic ester, crosses BBB and interferes with cellular metabolism	Mixed respiratory alkalosis/metabolic acidosis, vertigo, AMS, coma, pulmonary edema
Liquid nicotine	1–13	35 mg/mL	nAChR agonist at low doses, mAChR agonist at higher doses	Biphasic pattern: Hypertension, tachycardia, vomiting, followed by autonomic ganglionic blockade, hypotension, bradycardia, coma

(AMS: acute mountain sickness; BBB: blood–brain barrier; CHF: congestive heart failure; CNS: central nervous system)

Sources: Bar-Oz B, Levichek Z, Koren G. Medications that can be fatal for a toddler with one tablet or teaspoonful: a 2004 update. Pediatr Drugs. 2004;6(2):123-6; Davis JE. Are one or two dangerous? Methyl salicylate exposure in toddlers. J Emerg Med. 2007;32(1):63-9; Bassett RA, Osterhoudt K, Brabazon T. Nicotine poisoning in an infant. N Engl J Med. 2014;370:2249-50

a history of previous poisoning, if a massive overdose is present in a child younger than 1 year of age, if an illicit exposure is suspected, and if there are multiple siblings presenting at the same time. Suspect intentional ingestions in children above the age of 5 years and substance abuse in adolescents.

Physical Examination

Periodic reassessment of "ABCs" (airway, breathing, and circulation) and vitals during the observation period is essential. A focused examination will aim to detect any signs of toxicity as well as give clues toward certain toxidromes. As such examination is focused on central, autonomic nervous systems and cardiovascular and gastrointestinal systems. Examination of the skin may yield important clues to toxicity with the onset of jaundice, cyanosis, flushing, or discoloration.

INVESTIGATIONS

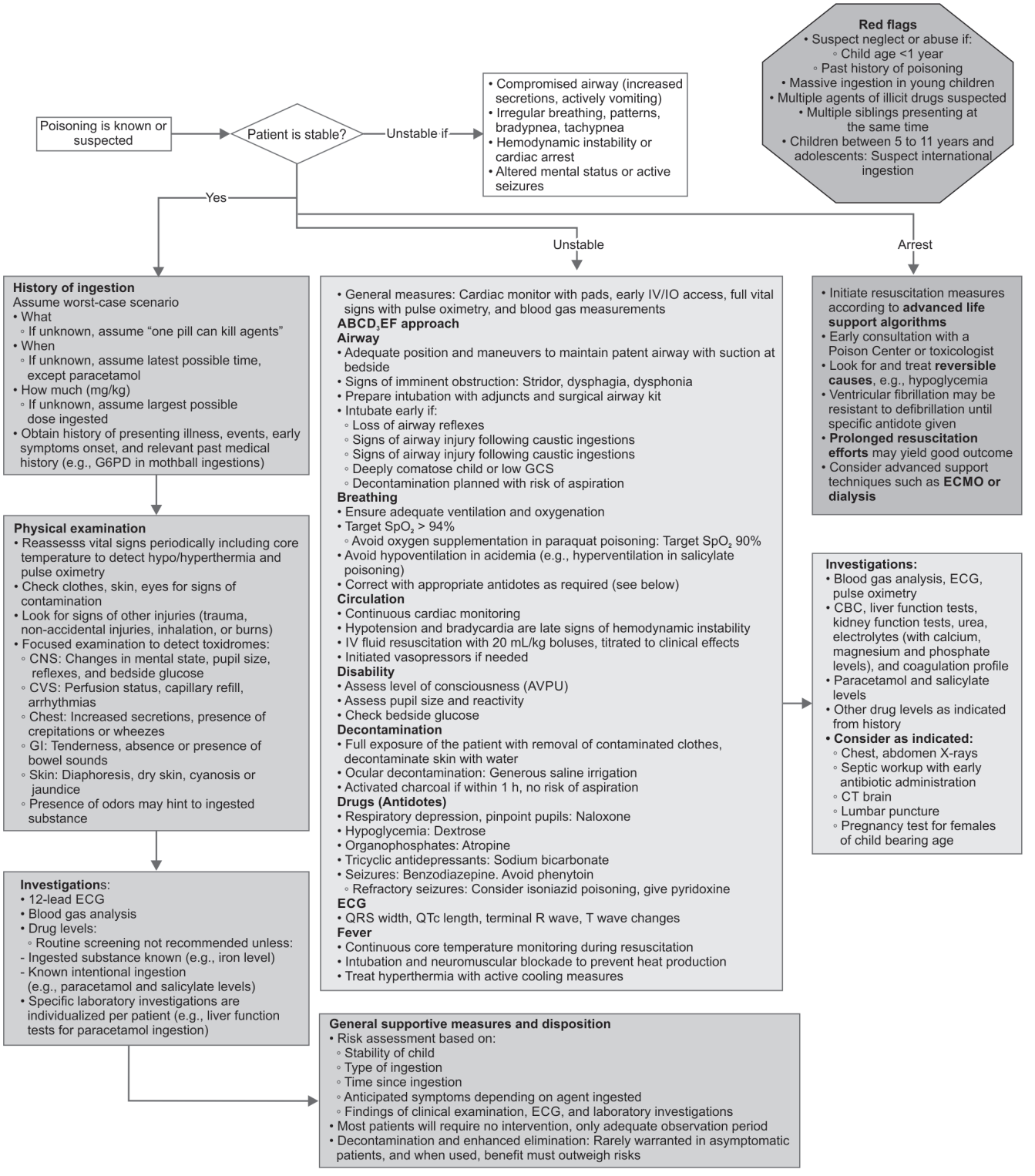
As most unintentional ingestions are asymptomatic and nontoxic, routine investigations and toxicology screens are not always warranted. Obtaining an ECG is a simple, rapid, noninvasive test that can detect signs of poisoning. Laboratory investigations are individualized to the need and clinical course of each patient. In the clinically poisoned child of unknown ingestion, a toxicology screen may be useful. If there is a suspicion of intentional ingestions then an ECG, a blood gas analysis, paracetamol, salicylate, and iron levels should be ordered. In the unstable child, a full workup is usually warranted, and this includes looking for other causes of instability such as infectious, surgical, and metabolic disorders.

MANAGEMENT

Management is usually dictated by the clinical presentation of the patient as well as by the risk assessment formulated by physicians. Most cases of pediatric poisoning are managed through close observation and supportive treatment. The time for observation depends not only on the type, time since, and quantity of ingestion but also on the age of the patient. Lower thresholds for admission and observation are maintained for toddlers with unknown ingestions. Emergency antidotes and decontamination are indicated in the unstable child as discussed above, and generally; most specific antidotal therapies follow the same principles as in adults. However, care should be taken to avoid dosing errors in children. **Flowchart 1** summarizes the emergency approach for managing the pediatric poisoning.

DISPOSITION

If the choice is made to discharge, parents must be educated regarding the dangers of accidental exposures. If neglect or abuse is suspected, then child protective services should be alerted according to local practice guidelines. A psychiatric assessment should be obtained for patients with intentional ingestions. In all cases, early consultation with a toxicologist or poison center will yield the best results.


Red flags
• Suspect neglect or abuse if:
◦ Child age <1 year
◦ Past history of poisoning
• Massive ingestion in young children
• Multiple agents of illicit drugs suspected
• Multiple siblings presenting at the same time
• Children between 5 to 11 years and adolescents: Suspect international ingestion
Poisoning is known or suspected
Patient is stable?
Unstable if
• Compromised airway (increased secretions, actively vomiting)
• Irregular breathing, patterns, bradypnea, tachypnea
• Hemodynamic instability or cardiac arrest
• Altered mental status or active seizures
Yes
Unstable
Arrest
History of ingestion
Assume worst-case scenario
• What
◦ If unknown, assume "one pill can kill agents"
• When
◦ If unknown, assume latest possible time, except paracetamol
• How much (mg/kg)
◦ If unknown, assume largest possible dose ingested
• Obtain history of presenting illness, events, early symptoms onset, and relevant past medical history (e.g., G6PD in mothball ingestions)
Physical examination
• Reassesss vital signs periodically including core temperature to detect hypo/hyperthermia and pulse oximetry
• Check clothes, skin, eyes for signs of contamination
• Look for signs of other injuries (trauma, non-accidental injuries, inhalation, or burns)
• Focused examination to detect toxidromes:
◦ CNS: Changes in mental state, pupil size, reflexes, and bedside glucose
◦ CVS: Perfusion status, capillary refill, arrhythmias
◦ Chest: Increased secretions, presence of crepitations or wheezes
◦ GI: Tenderness, absence or presence of bowel sounds
◦ Skin: Diaphoresis, dry skin, cyanosis or jaundice
◦ Presence of odors may hint to ingested substance
Investigations:
• 12-lead ECG
• Blood gas analysis
• Drug levels:
◦ Routine screening not recommended unless:
- Ingested substance known (e.g., iron level)
- Known intentional ingestion (e.g., paracetamol and salicylate levels)
• Specific laboratory investigations are individualized per patient (e.g., liver function tests for paracetamol ingestion)
• General measures: Cardiac monitor with pads, early IV/IO access, full vital signs with pulse oximetry, and blood gas measurements
ABCD$_s$EF approach
Airway
• Adequate position and maneuvers to maintain patent airway with suction at bedside
• Signs of imminent obstruction: Stridor, dysphagia, dysphonia
• Prepare intubation with adjuncts and surgical airway kit
• Intubate early if:
◦ Loss of airway reflexes
◦ Signs of airway injury following caustic ingestions
◦ Signs of airway injury following caustic ingestions
◦ Deeply comatose child or low GCS
◦ Decontamination planned with risk of aspiration
Breathing
• Ensure adequate ventilation and oxygenation
• Target SpO_2 > 94%
◦ Avoid oxygen supplementation in paraquat poisoning: Target SpO_2 90%
• Avoid hypoventilation in acidemia (e.g., hyperventilation in salicylate poisoning)
• Correct with appropriate antidotes as required (see below)
Circulation
• Continuous cardiac monitoring
• Hypotension and bradycardia are late signs of hemodynamic instability
• IV fluid resuscitation with 20 mL/kg boluses, titrated to clinical effects
• Initiated vasopressors if needed
Disability
• Assess level of consciousness (AVPU)
• Assess pupil size and reactivity
• Check bedside glucose
Decontamination
• Full exposure of the patient with removal of contaminated clothes, decontaminate skin with water
• Ocular decontamination: Generous saline irrigation
• Activated charcoal if within 1 h, no risk of aspiration
Drugs (Antidotes)
• Respiratory depression, pinpoint pupils: Naloxone
• Hypoglycemia: Dextrose
• Organophosphates: Atropine
• Tricyclic antidepressants: Sodium bicarbonate
• Seizures: Benzodiazepine. Avoid phenytoin
◦ Refractory seizures: Consider isoniazid poisoning, give pyridoxine
ECG
• QRS width, QTc length, terminal R wave, T wave changes
Fever
• Continuous core temperature monitoring during resuscitation
• Intubation and neuromuscular blockade to prevent heat production
• Treat hyperthermia with active cooling measures
• Initiate resuscitation measures according to advanced life support algorithms
• Early consultation with a Poison Center or toxicologist
• Look for and treat reversible causes, e.g., hypoglycemia
• Ventricular fibrillation may be resistant to defibrillation until specific antidote given
• Prolonged resuscitation efforts may yield good outcome
• Consider advanced support techniques such as ECMO or dialysis
Investigations:
• Blood gas analysis, ECG, pulse oximetry
• CBC, liver function tests, kidney function tests, urea, electrolytes (with calcium, magnesium and phosphate levels), and coagulation profile
• Paracetamol and salicylate levels
• Other drug levels as indicated from history
• Consider as indicated:
◦ Chest, abdomen X-rays
◦ Septic workup with early antibiotic administration
◦ CT brain
◦ Lumbar puncture
◦ Pregnancy test for females of child bearing age
General supportive measures and disposition
• Risk assessment based on:
◦ Stability of child
◦ Type of ingestion
◦ Time since ingestion
◦ Anticipated symptoms depending on agent ingested
◦ Findings of clinical examination, ECG, and laboratory investigations
• Most patients will require no intervention, only adequate observation period
• Decontamination and enhanced elimination: Rarely warranted in asymptomatic patients, and when used, benefit must outweigh risks

(CBC: complete blood count; CNS: central nervous system; CT: computed tomography; CVS: cardiovascular system; ECG: electrocardiogram; ECMO: extracorporeal membrane oxygenation; GCS: Glasgow Coma Scale; GI: gastrointestinal; G6PD: glucose-6-phosphate dehydrogenase; IO: intravenous; IV: intraosseous)

FLOWCHART 1: Clinical pathway for managing the pediatric poisoning.

SUMMARY

In the medical toxicology field, as compared to adult, children can present with various unique and complex problems to emergency department. Following the accidental toxic ingestions, fatalities in young children are rare however, some specific substances are extremely toxic to children even in small doses. It is necessary that the emergency physician be aware of these substances. Management of pediatric toxins need specialized approach because of its unique considerations

like the physiologic response to poisoning , evaluation and management, the impact on the child and family. Initial resuscitation and supportive care are the cornerstone of treatment in the poisoned child. Antidotes administration and use of enhanced elimination techniques have specific implications in the young pediatric patient.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Obstetrics Toxicology

Sara Nooruddin Kazim, Mahra Nooruddin Kazim, Lara Abumuaileq, Azza Yousif

INTRODUCTION

Poisoning during pregnancy warrants special consideration. 0.6% of all calls to the poison control centers are related to exposure during pregnancy. Toxicity is not only on the mother but also on the fetus. The effect of toxicity on the fetus and mother can be due to the direct impact of the xenobiotic or can be secondary to changes in the maternal circulation. Hypoxia and hypotension, for example, affect fetal circulation and oxygenation and lead to fetal distress and miscarriage. Toxicity can result from either intentional or unintentional exposure. More than 80% of calls to poison control centers are related to unintentional exposure. Intentional exposure represents 50% of severe cases that warrant hospitalization. Over-the-counter analgesics and sedatives are the two most common classes of intentional drug exposure during pregnancy. The risk factors for deliberate overdose include young maternal age (<30 years), early pregnancy (first trimester), smoking and drug misuse, history of miscarriage, and mental illness. Overdose is one of the leading causes of maternal death and a cause of miscarriage early in pregnancy.

DRUG PHARMACOKINETICS DURING PREGNANCY

The physiological changes during pregnancy alter xenobiotic levels in the circulation. These changes affect xenobiotic in maternal and fetal blood concentrations. These changes relate to xenobiotics absorption, distribution, metabolism, and excretion. Xenobiotic absorption during pregnancy results in lower peak concentration due to nausea and vomiting, reduced gastrointestinal (GI) motility, and increase GI transient time. This effect is minimal with oral xenobiotics with repeated dosing. Drug distribution during pregnancy varies with the xenobiotic type. Low protein binding leads to an increase in the proportion of free xenobiotic in the circulation. Dose adjustment is essential in drugs such as phenytoin, valproic acid, and carbamazepine. An increase total body water during pregnancy increases the volume of distribution of water-soluble drugs and lowers the peak plasma concentration. The activity of xenobiotic-metabolizing enzymes is increased during pregnancy. For example, nifedipine, lamotrigine, and antiretroviral drugs will have lower therapeutic levels during pregnancy. Glomerular filtration and renal blood flow rates increase during pregnancy. However, this is counterbalanced with different rates of secretion and reabsorption. For example, lithium's clearance is doubled compared to 20–30% of digoxin clearance. The pharmacokinetic changes in pregnancy determine the blood flow to the fetus and the effect of these xenobiotics on the growing fetus.

PHARMACOLOGY OF DRUG TRANSFER ACROSS THE BLOOD–PLACENTAL BARRIER

Maternal and fetal blood is separated by a complex blood–placental barrier (BPB) regulating the movement of molecules and xenobiotics between the maternal and the fetal circulation. BPB controls the flow of xenobiotics to the fetal circulation and hence determines their implication on the fetus. However, the BPB does not function until the second half of pregnancy. Xenobiotics affect the fetus by affecting blood flow through the placenta or directly on the growing fetus. Beta-blockers reduce placental blood flow and affect fetal growth. Xenobiotics with a direct impact on the fetus cross the BPB by simple diffusion down their concentration gradient. The characteristics of xenobiotics that cross the BPB with are; low molecular weight (<500 Da), low protein binding (free drugs), high lipid solubility, and unionized drugs. Benzodiazepines, paracetamol, and opioids cross the BPB by simple diffusion. Xenobiotics also cross the BPB by active or facilitated diffusion (cephalosporins and glucocorticoids).

FETAL TOXICOLOGY

During the fetal period, organs continue their cellular differentiation and growth to functional systems. Most of the chemicals causing fetal developmental adverse outcomes are xenobiotics, i.e., exogenous chemicals. The reference organism does not utilize exogenous chemicals as nutrient materials. Xenobiotics are not essential for maintaining the normal physiologic or biochemical function and are not part of the conventional array of chemicals synthesized by the reference organism. The outcomes of maternal exposure to xenobiotics are directly linked to the stage of fetal development

and the sensitivity of that organ system to the toxic effect. Such exposure leads to an adverse impact varying from organ malformation, carcinogenesis, or even fetal demise.

ORGANOGENESIS

Organogenesis occurs during the embryonic stage of development between days 18 and 60 of gestation. Most gross malformations are determined before day 36, though genitourinary and craniofacial anomalies occur later. **Figure 1** demonstrates critical periods in fetal development.

TERATOGENESIS

Teratogenesis is defined as the dysgenesis of fetal organs as evidenced either structurally or functionally (e.g., brain functions). Adverse teratogenesis outcomes are restricted growth or death of the fetus, carcinogenesis, and malformations. Studies of reproductive toxicology are conducted on animals by administering a drug or a xenobiotic at the period of organogenesis. The outcome is compared to the outcome in untreated (control) animals. **Table 1** provides a list of drugs found to be teratogenic in humans with similar teratogenic effects in animals.

GENERAL APPROACH TO POISONING IN PREGNANT WOMEN

Early resuscitation and identification of reversible life-threatening conditions are crucial to optimize the management of overdose during pregnancy. Risk assessment is an essential phase of the management of xenobiotic toxicity. It identifies the xenobiotic's risk on the mother and the fetus. Management is mainly supportive with consideration of decontamination and antidote administration when indicated. The use of activated charcoal and whole-bowel irrigation is similar to nonpregnancy cases, and only after protecting the airway. Although there is no conclusive evidence for the safety of antidote uses during pregnancy, it is prudent always to weight the inconclusive teratogenicity of the antidote against the risk on the mother. Specific cures, such as naloxone or flumazenil, can precipitate severe withdrawal and lead to fetal distress. Prompt administration of an antidote is crucial whenever a maternal indication exists. Specific management of certain xenobiotics is described in the following section.

ACETAMINOPHEN

Acetaminophen overdose is common during pregnancy due to its excellent safety profile. One third of intentional overdoses in North America are secondary to nonopioid analgesics [(acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs)]. Much of the available information about acetaminophen poisoning during pregnancy is derived from case reports and case series. Acetaminophen crosses the BPB, and toxic levels were found in fetuses of women who had toxic acetaminophen levels.

The clinical presentation of acetaminophen toxicity in pregnant women is similar to that in the nonpregnant women. Early recognition of acetaminophen toxicity is the key to successful management and a good prognosis. Toxicity from acetaminophen occurs when metabolism through the nontoxic pathways is saturated, and N-acetyl-p-benzoquinoneimine (NAPQI) is produced through alternative routes. NAPQI is a toxic product causing liver necrosis (**Fig. 2**).

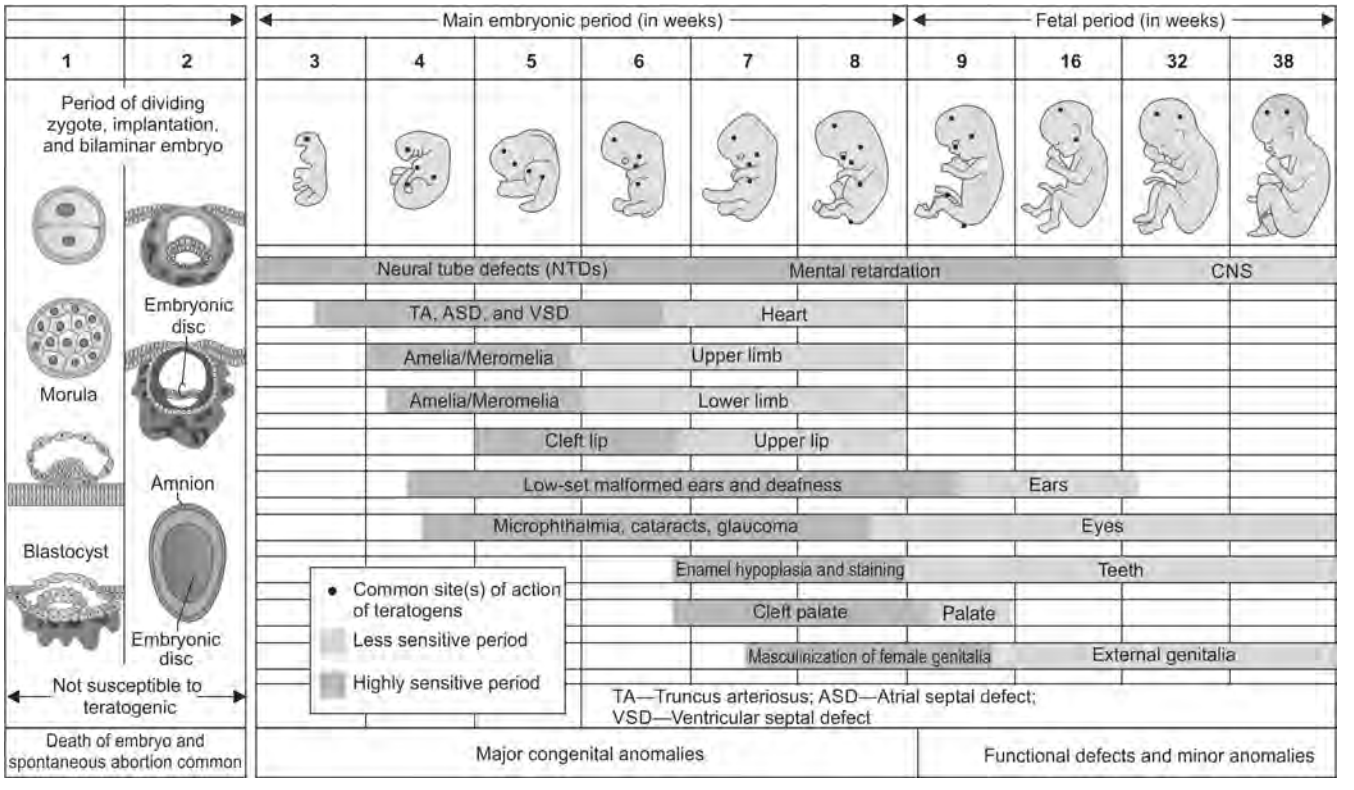


FIG. 1: Critical periods of human prenatal development.

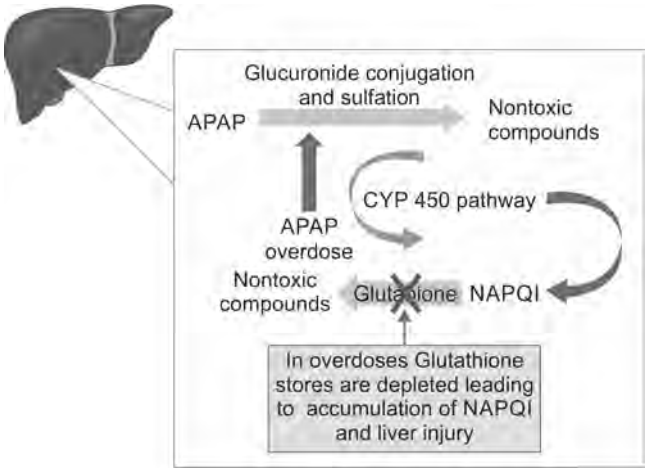
TABLE 1: Teratogenic effects of xenobiotics.

Drug	*Teratogenic effects (known, possible)*
Aminopterin, methotrexate (amethopterin)	CNS facial defects, malformed extremities or fingers, reduction in derivatives of the first branchial arch, developmental delay
Amiodarone	Transient neonatal hypothyroidism, with or without goiter; hyperthyroidism
Androgens	Virilization of the female external genitalia: Clitoromegaly, labioscrotal fusion
Angiotensin-converting-enzyme inhibitors	Prolonged renal failure in neonates, decreased skull ossification, renal tubular dysgenesis, fetal or neonatal death, prematurity, oligohydramnios, IUGR, secondary skull hypoplasia, limb contractures, pulmonary hypoplasia
Antithyroid drugs (propylthiouracil and methimazole)	Antithyroid drugs (propylthiouracil and methimazole)
Carbamazepine	Upslanting palpebral fissures, epicanthal folds, short nose with long philtrum, fingernail hypoplasia, developmental delay, neural- tube defects
Carbon monoxide	Cerebral atrophy, intellectual disability, microcephaly, convulsions, spastic disorders, intrauterine death
Cocaine	IUGR, microcephaly, neurobehavioral abnormalities, vascular disruptive phenomenon (limb amputation, cerebral infarction, visceral or urinary tract abnormalities)
Cyclophosphamide	CNS malformations, secondary cancer, Danazol and other androgenic drugs
Diazepam	Cleft palate
Diethylstilbestrol*	Vaginal carcinoma and other genitourinary defects in female and male offspring
Ethanol	Fetal alcohol syndrome (FAS): Pre- or postnatal growth retardation, intellectual disability, fine motor dysfunction, hyperactivity, microcephaly, maxillary hypoplasia, short palpebral fissures, hypoplastic philtrum, thinned upper lips, joint, digit anomalies
Fluconazole	Fluconazole craniofacial defects, humeral radial synostosis, femoral bowing
Hypoglycemic drugs	Neonatal hypoglycemia
Lithium	Ebstein's anomaly
Misoprostol	Moebius sequence
Nonsteroidal anti-inflammatory drugs	Constriction of the ductus arteriosus,† necrotizing enterocolitis
Paramethadione*	Facial and CNS defects
Paroxetine	Cardiovascular malformations, mostly VSD and ASD
Penicillamine	Cutis laxa, hyperflexibility of joints
Phenytoin	Fetal hydantoin syndrome: Microcephaly, intellectual disability, cleft lip or palate, hypoplastic nails, or phalanges, characteristic facies—low nasal bridge, inner epicanthal folds, ptosis, strabismus, hypertelorism, low-set ears, wide mouth
Psychoactive drugs (e.g., barbiturates and opioids)	Neonatal withdrawal syndrome when the drug is taken in late pregnancy
Quinine	Hypoplasia of eighth nerve, deafness, abortion
Ionizing radiation	Microcephaly, intellectual disability, eye anomalies, growth retardation, visceral malformations
Streptomycin	Hearing loss
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular, and other defects
Tetracycline	Anomalies of teeth and bone
Thalidomide	Limb-shortening defects, internal-organ defects
Trimethadione*	Facial and CNS defects
Valproic acid	Neural-tube defects
Vitamin D	Possible association with supravalvular aortic stenosis, elfin facies, and intellectual disability
Warfarin	Skeletal and CNS defects (fetal warfarin syndrome), Dandy–Walker syndrome

*The drug is not currently in clinical use.

†Sulindac probably does not have this effect.

(ASD: atrial septal defect; CNS: central nervous system; IUGR: intrauterine growth retardation; VSD: ventricular septal defect)



(APAP: acetaminophen; NAPQI: N-acetyl-p-benzoquinoneimine)

FIG. 2: Acetaminophen toxicity pathway.

Acetaminophen crosses the BPB, and fetal serum concentrations of acetaminophen are similar to maternal serum levels a few hours after acute ingestion. Fetal metabolism is unclear; however, the rate is insufficient to produce significant NAPQI levels due to immature cytochrome P450 pathways. Poor maternal and fetal prognosis is mainly due to late recognition and massive overdoses.

Early recognition of toxicity and rapid risk assessment are the keys to successful management of acetaminophen overdose. Early initiation of N-acetylcysteine (NAC) is crucial since NAC crosses the BPB and proves to be safe during pregnancy. Fetal complications are mainly related to maternal illness and delayed treatment of acetaminophen overdose by NAC.

ANTIDEPRESSANTS

Antidepressants are widely used during pregnancy. In the United States (US), the prevalence of antidepressant use among pregnant women is 8%. Studies in Europe report that 3% of pregnant women received antidepressants during their pregnancy. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy. During pregnancy, SSRIs' use is associated with preterm labor and postpartum hemorrhage. SSRIs do not increase the risk of hypertensive disorders of pregnancy or miscarriage. The majority of SSRIs are not associated with fetal congenital malformations or birth defects. However, there is an increased risk of cardiovascular defects, especially with the use of paroxetine.

IRON

Iron toxicity is among the 10 most common overdoses during pregnancy. While most multivitamins contain 15–18 mg of iron, the dose is remarkably higher in prenatal vitamins, reaching 60–65 mg of iron per tablet. While similar effects are seen in mothers with iron toxicity, a study on intentional iron overdose in pregnant women reported increased rates of spontaneous abortion, preterm delivery, and maternal death due to organ failure. There are no reports of direct toxicity on the fetus due to the saturable manner of placental absorption, which prevents iron from accumulating. The risk to the fetus presents when the mother develops multiorgan failure. Several case reports favor the use of deferoxamine in pregnancy for its safe outcome in both mother and fetus. Although animal studies reported skeletal anomalies with deferoxamine, these have not been described in humans. In one study on 24 pregnant women treated with deferoxamine for iron overload during organogenesis, only one case reported spontaneous abortion.

OVER-THE-COUNTER MEDICATIONS

Over-the-counter (OTC) medications are readily available for use. Although they do not cause clinically significant toxicity in overdose, some of these OTC medications can have significant toxicity, not only on the mother but also on the fetus.

Ibuprofen and Nonsteroidal Anti-inflammatory Drugs

One third of reports of pregnant women presenting to the emergency department with an overdose are nonopioid analgesics (acetaminophen and NSAIDs). Acute overdose from NSAIDs causes a minimally significant effect, with no evidence of fetal malformation. Hepatotoxicity and severe metabolic acidosis are reported in rare cases of overdose. In the third trimester, chronic exposure results in premature closure of the ductus arteriosus and oligohydramnios. Management is mainly supportive with one reported case in 2012 of treatment with hemodialysis in an intentional ibuprofen overdose in a pregnant woman.

Antihistamines

Diphenhydramine is commonly available as an OTC cold remedy. Intentional overdose results in significant toxicity. In addition to its effect as an anticholinergic and a sodium channel blocker agent in overdose, they have an oxytocin-like effect. They cause prolonged uterine tetany and fetal bradycardia. Management is mainly supportive, early resuscitation, and decontamination, especially in massive overdoses. Physostigmine is used as a potential antidote with variable results. However, physostigmine lowers the seizure threshold; thus, its use in pregnancy is unfavorable. Benzodiazepines and tocolytics are preferred in the treatment of toxicity from antihistamines.

Decongestants and Expectorants

Pseudoephedrine and dextromethorphan are commonly used decongestants in pregnancy. Pseudoephedrine causes elevated blood pressure and uterine arteries vasoconstriction. Its use in the first trimester is thought to be associated with gastroschisis. Cardiac dysrhythmia is described with pseudoephedrine toxicity. A 36-year-old, 19-week pregnant woman with a repeated supratherapeutic overdose developed ventricular arrhythmia. Management is mainly supportive in overdose cases.

Gastrointestinal Medications

Acute toxicity from gastrointestinal medications is rare. Toxicity is mainly described with chronic use. The two classes pregnant

women use during pregnancy are antidiarrheal agents and antacids, respectively. Bismuth-containing compounds are available OTC as antidiarrheal medication. Its use during pregnancy is controversial due to its effect on stimulating salicylate absorption. Salicylate causes premature closure of the ductus arteriosus. Acute kidney injury is described in cases of acute bismuth toxicity. A case report of a 16-year-old pregnant woman with acute bismuth overdose resulted in acute kidney injury. The patient received chelation therapy and renal replacement therapy. The patient had an uneventful recovery and delivered a healthy child. Aluminum hydroxide and cimetidine are common antacids used during pregnancy. Acute cimetidine has a benign toxicity profile, and management is mainly supportive. Chronic use of cimetidine is safe during pregnancy, and there is no conclusive teratogenic effect. Aluminum hydroxide antacids are poorly absorbed and are safe during pregnancy. Severe toxicity necessitates chelation therapy. There is no evidence of teratogenic effects from their use during pregnancy, and its use is safe when used for overdose cases. Drug–drug interaction is described between antacids and phenytoin. Antacids reduce the rate of phenytoin absorption and reduce plasma levels. Thus, phenytoin levels need to be monitored during pregnancy for better seizure control.

SUBSTANCE MISUSE

Heroin/Opioids

In the US, approximately 0.2% of pregnant women report heroin use, 0.8% report illicit use of prescription analgesics, and 0.1% report using oxycodone during pregnancy. Opioid misuse increases the risk of miscarriage, abruptio placentae, preeclampsia, premature rupture of membrane, and increased maternal cardiac events and septic thrombophlebitis. Fetal complications related to opioid misuse include intrauterine growth retardation (IUGR), preterm labor, and fetal demise. The American Society of Addiction Medicine and the American College of Obstetricians and Gynecologists suggest using methadone or buprenorphine for treating opioid misuse. Pharmacological therapy is superior to supervised withdrawal or heroin use and is associated with reduced incidents of maternal and neonatal withdrawal syndromes.

Cocaine

International studies suggest that the use of cocaine and other stimulants during pregnancy is increasing. Among pregnant women, 0.1% report using cocaine in the previous month. Cocaine use increases uterine vascular resistance in addition to oxidative injury from oxygen radicals and reperfusion injury. Acute cocaine use is associated with maternal cardiovascular complications and abruptio placentae. Other less common presentations include perinatal seizure, stroke, and intracerebral hemorrhage. Fetal exposure to cocaine caused IUGR and reduced birth weight, length, and head circumference. Other less common complications include genitourinary malformations, cardiovascular malformations, and limb-reduction defects. Cocaine use in the perinatal period leads to changes during early infancy and childhood, such as decreased muscle tone, reflexes, alertness, and cognition. Hydralazine is the preferred antihypertensive agent in treating hypertension in pregnant individuals who use cocaine.

Ethanol

The Center for Disease Control and Prevention (CDC) estimated that 7.3% of pregnant women are exposed to ethanol during pregnancy. The exposure rate is highest during the first trimester. Because there is no recommended safe ethanol level during pregnancy, medical societies recommend complete abstinence from alcohol use. Ethanol toxicity is mediated via direct cell necrosis from the oxidative effect of free radicals, alterations on serotonins, and development and function of N-methyl-D- aspartate (NMDA) receptors. During pregnancy, alcohol consumption increases the incidents of spontaneous abortion, preterm labor, stillbirths, and neonatal and maternal withdrawal symptoms. Fetal exposure during pregnancy is associated with fetal alcohol spectrum disorders (FASD). Severe FASD include intrauterine and postnatal growth retardation, intellectual disabilities, behavioral abnormalities, and facial dysmorphogenesis. Examples of facial dysmorphogenesis include micrognathia, epicanthal folds, maxillary hypoplasia, cleft palate, and microcephaly. Management of chronic ethanol abuse is multidisciplinary. It includes maternal and fetal surveillance, in addition to pharmacological and psychological support. Naltrexone is used in managing ethanol abuse disorders with no evidence of clinical toxicity.

Benzodiazepines

Although use of benzodiazepines during pregnancy is not associated with congenital malformations or congenital disabilities, their use in the first trimester is associated with miscarriage. Antenatal use of benzodiazepines is associated with preterm labor. Neonatal toxicity occurs with chronic maternal use of benzodiazepines during the third trimester. Examples of neonatal toxicity include low Apgar score, apnea, hypothermia, hyperreflexia, irritability, and poor feeding. Neonates are also at risk of developing benzodiazepine withdrawal that persists up to 3 months of age. Benzodiazepine withdrawal presents with tremor, diarrhea, poor feeding, or vomiting.

ANTICONVULSANTS

Approximately 0.3–0.8% of pregnant women have epilepsy requiring medical treatment. In every 200 pregnancies, at least one woman is treated with antiepileptic drugs. Valproate, phenytoin, and carbamazepine are all associated with major congenital malformation when used during the first trimester. The risk increases significantly with higher doses. Lamotrigine is commonly used due to its relatively safe effect during pregnancy; likewise, lamotrigine may cause major congenital malformation during the first trimester in doses higher than 325 mg/d. Also, anticonvulsants are associated with a higher risk of stillbirth and preterm delivery.

Women on anticonvulsants are at a high risk for antepartum and postpartum hemorrhage, and preeclampsia. The most significant finding in toxicity includes central nervous system depression, hypotension, and respiratory depression. Lamotrigine dose often needs to be increased in

late pregnancy because of an increase in the activity of liver metabolizing enzymes. Thus, the lamotrigine dose needs to be adjusted after delivery to avoid toxicity. Mothers affected present with altered mental status, ataxia, and nystagmus. Management is mainly supportive with fluid resuscitation, endotracheal intubation, and mechanical ventilation for altered mental status. Naloxone, which is considered safe in pregnancy, can be used in overdose cases with sodium valproate.

ANTICOAGULANTS

Use of most anticoagulants during pregnancy is associated with a teratogenic effect on the growing fetus. Nevertheless, pregnant women are at a high risk for thromboembolic events. Besides, some women need to be on long-term anticoagulation for conditions such as women with prosthetic valves. Fortunately, an anticoagulant overdose is not common during pregnancy. Toxicity results from molecules that cross the BPB, such as warfarin, and less likely with large molecules that do not cross the BPB, such as heparin and low-molecular-weight heparin. Toxicity results not only from an acute overdose but also from poorly controlled anticoagulation. The use of warfarin during the second or third trimester is associated with central nervous system anomalies and mental retardations. Spontaneous abortion, stillbirth, and death occur as well throughout pregnancy. Direct-acting oral anticoagulants (DOACs) use during pregnancy showed variable results. The use of apixaban is associated with a higher risk of spontaneous abortion than warfarin. However, data are inconclusive since most studies on DOACs excluded pregnant women from their research population. Management is supportive mainly with no reported contraindication for using vitamin K, fresh frozen plasma, and protamine to reverse the anticoagulant effect of warfarin and heparin.

CARBONE MONOXIDE

Carbon monoxide (CO) is a common substance involved in unintentional poisoning in North America during pregnancy. 13% of all accidental exposures during pregnancy are due to fumes, gases, and vapors. CO poisoning diagnosis is always a challenge since the symptoms are nonspecific, ranging from simple flu-like symptoms to seizures and come. Headache is almost always present in all cases of CO poisoning. CO poisoning causes tissues, hypoxia, and fetal distress. CO has a higher affinity for hemoglobin than oxygen and reduces tissue oxygenation (**Flowchart 1**). CO poisoning on the fetus is either due to the direct effect of CO on fetal blood or secondary to maternal systemic hypoxia. Fetal hypoxia results in miscarriage, stillbirth, and fetal neurological complications at birth. Management cornerstone is to remove the source of exposure and reduce CO half-life. Hyperbaric oxygen therapy (HBO) is safe and effective for lowering CO half-life. HBO has proven to be safe and effective during pregnancy for patients with CO poisoning.

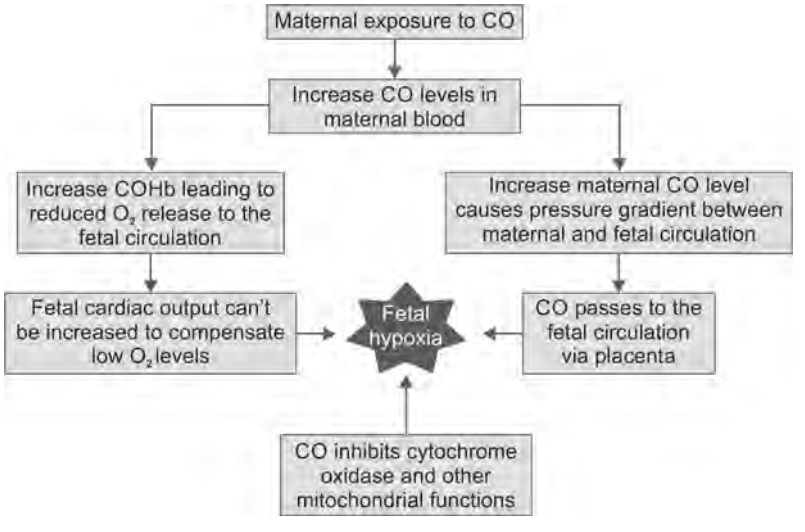
CARDIOVASCULAR DRUGS

Angiotensin-converting Enzyme Inhibitors, Angiotensin II Receptor Blockers

Exposure during the second or third trimester causes significant renal dysgenesis, oligohydramnios, and skull hypoplasia in fetuses. Excessive exposure in mothers can lead to hyperkalemia and severe hypotension. Management is mainly supportive of early resuscitation and management of hypotension. There is no known antidote for the management of toxicity.

Beta-blockers

Common drugs of choice for treating hypertension during pregnancy are also known to increase the risk of intrauterine growth retardation, preterm birth, fetal bradycardia, and hypoglycemia. In excessive doses, they cause hypotension, bradycardia, pulmonary edema, and cardiogenic shock. Cardiogenic shock reduces blood flow through the placenta and leads to fetal demise. Management is mainly supportive of early resuscitation. Glucagon does not cross the placenta and can be used in overdose cases. High-dose insulin euglycemia therapy can also be used in cases of cardiogenic shock.


Maternal exposure to CO
Increase CO levels in maternal blood
Increase COHb leading to reduced O_2 release to the fetal circulation
Increase maternal CO level causes pressure gradient between maternal and fetal circulation
Fetal cardiac output can't be increased to compensate low O_2 levels
Fetal hypoxia
CO passes to the fetal circulation via placenta
CO inhibits cytochrome oxidase and other mitochondrial functions

(CO: carbon monoxide)

FLOWCHART 1: Fetal carbon monoxide toxicity.

Calcium Channel Blockers

Exposure to calcium channel blockers during the third trimester of pregnancy increases the risk of neonatal seizures in infants. In acute toxicity, mothers suffer from significant hypotension, bradycardia, and cardiogenic shock. Management is mainly supportive and the use of calcium salts and high-dose insulin euglycemia therapy for severe cardiogenic shock.

Diuretic Agents

Diuretic agents are mostly safe in regular doses during pregnancy, although some studies reported low birth weight, thrombocytopenia, and neonatal jaundice while using hydrochlorothiazide. Acute toxicity causes hypovolemia and electrolyte imbalance. No known antidote or treatment is mainly supportive with fluid and electrolyte correction.

SUMMARY

The general approach to toxicity in pregnant women is similar to nonpregnant women. However, it is essential to understand the impact toxicity has on the mother and the growing fetus. Xenobiotics can cause either direct toxicity or indirect toxicity. Direct toxicity relates to xenobiotics that cross the BPB and exert their immediate effect on fetal tissue. At the same time, the indirect effect is mainly secondary to the hemodynamic effects of the xenobiotic. Hypotension and cardiogenic shock impair fetal blood flow and cause fetal demise. Resuscitation and risk assessment are the cornerstones for the successful management of patients with toxicity. Other essential factors to consider when dealing with drug toxicity and management are the changes in the drug pharmacokinetics and variable flow of a specific treatment (e.g., antidote) in crossing the BPB. Maternal resuscitation in case of toxicity is the ultimate goal in management and in supporting fetal circulation.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Integrated Trauma System

Prasad Rajhans, Purushotham Godavarthy

INTRODUCTION AND EPIDEMIOLOGY

Trauma is defined as physical damage or harm to the body as a result of exposure to environmental, social, or behavioral determinants. Trauma is one of the leading causes of mortality, morbidity, and disability in younger population. It not only causes loss of precious lives but also imposes direct and indirect economic and social costs to the community. It is estimated that 1 million people die and 20 million are hospitalized every year due to various injuries in India. Amongst all the causes, road traffic accident (RTA) is one of the leading causes of trauma. According to the National Crime Records Bureau (NCRB), about 4,13,457 people died in road accidents in India in 2015. Injuries occur across a broad spectrum of events and the level of care delivered depends on the nature of injury, geographical location of the event, and availability of the resources.

CONCEPT OF AN INTEGRATED TRAUMA SYSTEM

An integrated trauma system is an organized and coordinated approach for care of the injured and includes prehospital emergency care, triaging, transportation, and definitive care of the injured. An ideal trauma system includes a continuum of medical services to provide seamless transition between each phase of care, integrating the existing resources of the public health systems within a definitive area to achieve improved patient outcomes. An integrated trauma system helps in appropriate and judicious use of available resources and delivers the best possible services within budget constraints. The "model trauma system policy" developed by the World Health Organization (WHO) envisages an *integrated approach toward trauma care* (**Flowchart 1**) and includes the following:

- Prehospital care
- Acute care facilities
- Posthospital care (rehabilitation)
- Injury prevention

The advantages of trauma system include the following:

- Evacuation of casualties to designated injury care facilities
- Reduction of injury incidence and severity
- Rigorous system performance improvement standards
- Cost containment and efficacy enhancement

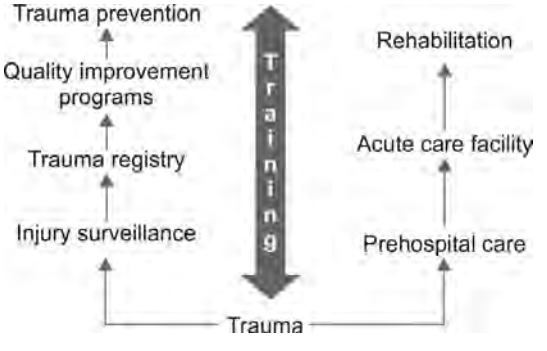
PREHOSPITAL TRAUMA CARE

The Golden Hour

"There is a golden hour between life and death. If you are critically injured you have less than 60 minutes to survive. You might not die right then; it may be three days or two weeks later --but something has happened in your body that is irreparable."

—R Adams Cowley

Prehospital trauma care involves trauma care at the site of incident and en route to definitive treatment facilities. Early identification and safe transportation of injured patients to an appropriate facility within the golden hour help in reduction of mortality and morbidity. Prehospital care is provided by emergency medical services (EMS) responders who are trained to recognize the nature of a disaster, evaluate the situation, and determine the need for resources, including medical resources. In India, the first responders are usually the bystanders, home guards, police, or the fire brigade who do the basic assessment and activate the EMS. Mortality due to injuries follows a trimodal phase of distribution and includes the following (**Fig. 1**):



FLOWCHART 1: Integrated approach for trauma management.

- Immediate—death occurs immediately within seconds or minutes as a result of overwhelming injury, e.g., injury to aorta, heart, brainstem, spinal cord, or acute respiratory distress.
- Early—death occurs within hours of the injury and is frequently the result of treatable conditions, e.g., hemorrhage, central nervous system (CNS) injury. These patients can be saved by appropriate treatment during the "golden hour."
- Late—death occurs in days or weeks after the initial injury and is the result of infection, multisystem failure, or other late complications of trauma.

Approaches to Prehospital Care

The elements of prehospital trauma include the following (**Table 1**):

- Communication and activation
- Response from the system
- Onsite care
- Care en route
- Transportation to a definitive medical facility

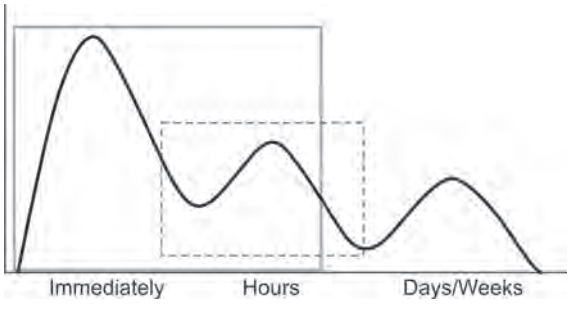


FIG. 1: Trimodal distribution of death.

Stay and play: The trauma team provides treatment and/or stabilization on scene before transporting the patient to the hospital. Few interventions include airway protection and intubation for securing airway, obtaining intravenous lines, starting the fluid resuscitation therapy, splinting of fractures, thoracotomy, administration of medications, etc.

Scoop and run: The patient is transported to the hospital as fast as possible by the trauma team after provision of basic care at the scene of accident. Both the approaches have advantages and disadvantages (**Table 2**).

Communication and Activation

Detection of injury and activation of emergency medical services: Immediately following an accident, bystanders, volunteers, or community health workers who are witnesses to the incident need to recognize the severity of accident and activate the EMS. In India, issues such as legal liability and ethical considerations dissuade bystanders from helping these victims. Initiatives such as Good Samaritan Law help in empowering people to aid injured people without fear of adverse consequences. There is multiplicity of services in India providing EMS including government and private players. The introduction of 108 calling service has simplified the activation of EMS.

Response from the System

Immediately on receiving call regarding the accident, the call center assigns an ambulance along with paramedical staff to reach the site of the accident. Training of call center staff in triaging, central location of ambulance vehicles, tagging with global positioning system (GPS) and public-private partnerships, etc., could help in faster response times of EMS.

TABLE 1: Components of prehospital care.

Prehospital care				
Core components		***Trauma care providers***	***Problems***	***Solutions***
Communication and activation		First responders	Legal issues, hesitation, ethical issues, delay in information	Training in BLS Good samaritan law
↓	Detection of injury	Bystanders, volunteers community health workers, home guards, fire brigade, police		
	Activation of EMS		Multiplictiy of services	Unified ambulance service (108 service)
Response from system				
↓	Dispatch of ambulance and trained manpower		Delay in dispatch, availability of resources	Central loction of ambulance, GPS mapping of ambulance, training of staff at call centers in triaging
Onsite care				
↓	Prehospital triage	Advanced trauma care (Paramedic/Nurses/EMS physician)	Availability of trained manpower	Training in trauma scoring system, ATLS
	BLS, First aid, Resuscitation		Availability of monitoring and medical resources	Upgradation of medical infrastructure
Care en route				
Transportation to definitive facility			Availability of definitive resources	Involvement of healthcare systems at various levels

(ATLS: advanced trauma life support; BLS: basic life support; EMS: emergency medical services; GPS: global positioning system)

Onsite Care

The onsite care is provided by the EMS team consisting of trained paramedics and doctors. Immediately on arrival at the site, scene management including clearing of traffic and hazardous material is carried out followed by initial assessment, field triage, and provision of basic first aid. Basic life support (BLS) including airway, breathing, and circulation is carried out and the patient is transported to a higher medical center.

TABLE 2: Advantages and disadvantages of strategy for transfer of patient.

Approach	*Advantages*	*Disadvantages*
Stay and play	Patient stabilized at scene of accident following principles of A, B, C	• Delay in definitive investigations and treatment • Requirement of trained manpower including EMS physicians
Scoop and run	Patient is transferred to definitive care as soon as possible where a team of multispecialty doctors can care for patient	• Delay during transportation like traffic • Availability of advanced ambulance vehicles for transport

(EMS: emergency medical services)

En Route Care

Patients being transported are constantly monitored and appropriate medical care is provided in the ambulance vehicle till they are taken to a healthcare facility.

Transportation to a Definitive Facility

Based on the mechanism of injury, field triage (**Table 3**), geographical location of accident, and availability of resources, a decision regarding the transportation of patient to a definitive center is taken and the patient is transported. In India, the level of care and facilities at different centers vary and include community health centers, district hospitals, medical colleges, and tertiary care centers. There is a requirement of close coordination between different agencies and EMS staff for faster transportation and to a definitive center as per the requirement and triage.

TABLE 3: Guidelines for field triage of injured patients.

Assess vital parameters and level of consciousness	• Glasgow Coma Scale • Systolic blood pressure (SBP) (mm Hg)	≤13 <90 mm Hg	Transfer to trauma center with multidisciplinary facilities—medical college/ university hospital/tertiary care center
	Respiratory rate	<10 or >29 breaths/min* (<20 in infant aged <1 year) or need for ventilatory support	
	NO		
Assess anatomy of injury	• All penetrating injuries to head, neck, torso, and extremities proximal to elbow or knee • Chest wall instability or deformity (e.g., flail chest) • Two or more proximal long-bone fractures • Crushed, degloved, mangled, or pulseless extremity • Amputation proximal to wrist or ankle • Pelvic fractures • Open or depressed skull fracture • Paralysis		
	NO		
Assess mechanism of Injury	• Falls: ○ Adults: >20 feet (one storey is equal to 10 feet) ○ Children†: >10 feet or two or three times the height of the child • High-risk auto-crash: ○ Intrusion‡, including roof: >12 inches occupant site; >18 inches any site ○ Ejection (partial or complete) from automobile ○ Death in same passenger compartment ○ Vehicle telemetry data consistent with a high risk of injury • Auto versus pedestrian/bicyclist thrown, run over, or with significant (>20 mph) impact§ • Motorcycle crash >20 mph		• Transfer to any trauma center with facilities • Community health center/ university hospital/ medical college/tertiary hospital depending upon time involved
	NO		

Continued

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Assess special patient or system considerations	• Older adults:[††]
	  ○ Risk of injury/death increases after age 55 years
	  ○ SBP < 110 mm Hg might represent shock after age 65 years
	  ○ Low impact mechanisms (e.g., ground-level falls) might result in severe injury
	• Children: Should be triaged preferentially to pediatric capable trauma centers
	• Anticoagulants and bleeding disorders: Patients with head injury are at a high risk for rapid deterioration
	• Burns:
	  ○ Without other trauma mechanism: Triage to burn facility[¶]
	  ○ With trauma mechanism: Triage to trauma center[¶]
	• Pregnancy >20 weeks
	• EMS provider judgment
		• Consult with control room
		• Transport to the trauma center or hospital capable of timely and thorough evaluation and initial management of potentially serious injuries

When in doubt transport to trauma center		

*The upper limit of respiratory rate in infants is >29 breaths/min to maintain a higher level of overtriage for infants.

[†]Age < 15 years.

[‡]Intrusion refers to interior compartment intrusion, as opposed to deformation which refers to exterior damage.

[§]Includes pedestrians or bicyclists thrown or run over by a motor vehicle or those with estimated impact > 20 mph with a motor vehicle.

[††]Age > 55 years.

[¶]Patients with both burns and concomitant trauma for whom the burn injury poses the greatest risk for morbidity and mortality should be transferred to a burn center. If the nonburn trauma patient presents a greater immediate risk, he/she may be stabilized in a trauma center and then transferred to a burn center.

(EMS: emergency medical services)

ACUTE CARE FACILITIES

Code Trauma

A trauma center is a medical facility having a team of multidisciplinary professionals and specialized resources available round the clock to care for victims with critical injuries. The level of trauma center is defined based on the availability of resources and manpower.

Trauma Team Definition

A trauma team is a group of multidisciplinary healthcare workers who work together as a team to assess and manage severely injured patients. The aim of the team is to rapidly resuscitate and stabilize the patient and reduce the time to diagnosis and treatment with the overall objective of improving survival rates. The team consists of specialists from emergency medicine, surgery, anesthesia, intensive care, orthopedics, nursing, and allied health and support staff coordinated by a team leader (**Fig. 2**).

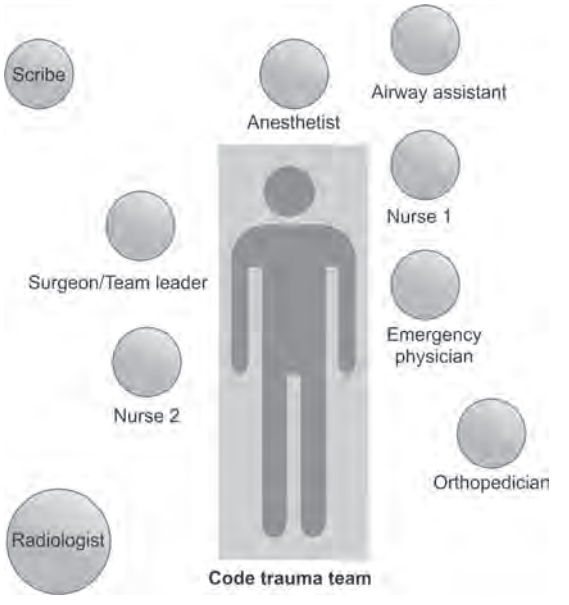

FIG. 2: Code trauma team.

Composition of Team

- Team leader—trauma surgeon/emergency physician
- Emergency physician
- Anesthetist
- Trauma trained nurse
- Radiographer
- Operation room staff
- Scribe/data recorder
- Social worker/manager

Other members as per availability and requirement are:

- Orthopedic surgeon
- Neurosurgeon
- Vascular surgeon
- Laboratory medicine
- Blood bank

Based on the information about the type of trauma, the team meets before the patient reaches the trauma center. Upon arrival, initial assessment and resuscitation are carried as per defined protocol. Trauma centers must clearly define the following (role and responsibilities) (**Box 1**):

- Who all constitute the trauma team?
- When must the team assemble?
- Where must the team assemble?
- Whom to respond?
- Team leader

BOX 1: Roles and responsibilities of trauma team members.

Team leader—trauma surgeon/ER physician

The team leader is usually a trauma surgeon or ER physician who takes all diagnostic and therapeutic decisions regarding the patient. Responsibilities of a team leader include:

- Assesses hospital notification and activates trauma team if trauma criteria are met
- Trauma checklist and prearrival team briefing prior to every trauma presentation
- Discusses potential injuries, procedures, and treatment prior to arrival of patient
- Allocates roles and tasks according to skill and experience
- Presence of all assigned team members and activation of backup plan in case of any absence
- Ensures that requisite drugs, material, and equipment are readily available and functional
- All the team members don personal protection equipment (PPE) and other precautions.
- Ensures good team communication through use of clear and concise statements, along with closed-loop communication
- Ensures correct documentation and handing over of patient to another team leader on completion of duty

Assessment—trauma surgeon/ER physician

- Donning of PPE
- Transfer of patient to ED trolley
- Primary survey:
  - Airway and cervical spine
  - Breathing
  - Circulation
  - Disability
  - Exposure and environment
- Reassess patient; if unstable shift immediately to operating room/trauma center. If stable, carry out the secondary survey.
- Secondary survey—patients' history and physical examination
- Reassure patient on arrival, explain what is happening
- Clearly state findings to team leader, nurse, and scribe
- Order required investigations through nurse
- Delivery of required medication

Airway lead—anesthetist/airway assistant

- Donning PPE
- Check the preintubation checklist; prepare equipment and drugs and difficult airway cart
- Discusses airway plan and backup plan with team leader and nurse
- Cervical spine immobilization during transfer and assessment
- Airway assessment
- Definitive care—intubation/cricothyroidotomy/LMA, etc.
- Places patient on ventilator support
- Sedation and appropriate during ventilation
- Accompanies patient during intra- and inter-hospital transfer

Trauma nurse

- Don PPE
- Transfer of patient to ED trolley
- Attach patient monitors and oxygen if required
- Establish IV access
- Collect samples for investigations
- Administration of medications
- Prepares and checks procedure trolleys
- Assists in various procedures such as intercostal chest drainage
- Liaison with various departments for bed management
- Liaison with blood bank, laboratory

Radiographer

- Prior loading of X-ray plates
- Patient positioning
- X-ray for primary survey (chest X-ray, cervical spine)
- X-ray for secondary survey
- Preparation for transfer to CT scan facility

Scribe

- Documents of trauma team members, their time of arrival, and allocated roles
- Time of patient arrival and details
- Examination findings of primary and secondary assessment
- Recording of vital signs
- Record of drugs/intravenous fluids and blood administration

(CT: computed tomography; ED: emergency department; ER: emergency room; IV: intravenous; LMA: laryngeal mask airway)

- Who all should respond during a particular incident?
- Communication about the trauma

Criteria for Activation of Trauma Code

Though there are no definitive criteria for activation of trauma code, the team leader based on information received during field triage, mechanism of injury, anatomy of injury, physiological parameters of patients, and other factors at his/her discretion can activate the trauma code (**Table 4**).

Advantages of Trauma Code

- Early mobilization and involvement of more experienced medical staff
- Shorter time to primary and secondary surveys and to performing diagnostic investigations
- Reduction in time from injury to critical interventions due to distribution of tasks in assessment
- Effective communication, supervision, leadership attributes influencing clinical outcomes
- The introduction of trauma teams has improved patient outcomes. Data from Petrie and colleagues showed that patients with an injury severity score (ISS) > 12 had a significantly better outcome when a trauma team was activated than when they were treated on service-by-service basis.

REHABILITATION

Patients sustain disabilities of speech, cognition, neurological deficits, locomotor activities, and psychosocial functioning following life-threatening injuries and require rehabilitation care. Nearly 100% of those with severe injuries,

TABLE 4: Criteria for activation of trauma code.

Mechanism of injury	
Motor vehicle accident	• Speed over 80 km/h • Ejection/rollover/trapped • Unrestrained/fatality
Two-wheeler	Any with speed >30 km/h
Fall from height	• Adult >3 m and/or five stairs • Elderly on anticoagulant therapy
Physical assaults	Shooting, stabbing or blunt trauma, head injury with GCS <13
Others	Bomb explosion, hanging, drowning
Type of injury	• Airway injuries/obstruction/respiratory distress • Penetrating injury to the head/neck/chest/abdomen/pelvis/back/limbs • Burns >10% BSA
Physiological	• Respiratory rate <10 or >30 • Blood pressure <90 mm Hg systolic at any stage • Heart rate <40 or >120 • GCS <14
Others	• Pregnant patient with trauma • Infants • Transfer from other hospitals

(BSA: body surface area; GCS: Glasgow Coma Scale)

50% of those with moderate injuries, and 10–20% of those with minor injuries carry disabilities of a physical and/or psychological nature requiring long-term rehabilitation services. Patients with ventilator dependence, tracheostomy, or other similar conditions are sent to skilled nursing facilities while those with brain or spinal cord injuries are sent to inpatient facilities for an intensive rehabilitation program. Patients with minor conditions such as limb trauma, fractures, or other bony injuries are discharged to continue rehabilitation at outpatient rehabilitation services.

INJURY EPIDEMIOLOGY AND PREVENTION

Injuries are caused by a complex interaction between human beings, environment (roads, infrastructure), and agents (vehicle, product). Studying the causes and burden of injuries is crucial to understanding the magnitude of the problem and developing mechanisms for intervention and allocation of resources (physical, financial, and human resources) to control and prevent them. Injury prevention and control is an intersectoral activity requiring inputs from different agencies such as the police, road transport agencies, municipalities, health departments, media, and others. Governments, community organizations, and trauma centers need to implement coordinated injury prevention programs that address the most common injuries in a community, region or state and the population group (e.g., children, elders, teen drivers, specific occupations, etc.) in which they occur and which are important to reduce the number of injuries in the population.

SUMMARY

An integrated trauma system is a need of the local public health system in which an organized, coordinated effort and full range of care is delivered to all injured patients in a defined geographic area. With integration of existing resources to achieve improved patient outcomes, the true success of a trauma system is defined by seamless transition between each phase of care. Trauma system can be initiated region wise by using efficient health care resources. Trauma systems are based on the requirements of the particular group of population such as rural, sub-urban, urban. In the context of community health every trauma system must emphasize the prevention of injuries. Success of a trauma system is largely determined by the degree to which it is supported by public policy. Ultimately, nationwide development of trauma systems would allow for seamless and effective trauma care of injured across the nation with the ability to expand to meet the medical needs of the community.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Initial Assessment and Management of Polytrauma

Sanjay Shah

INTRODUCTION

India, the world's largest democracy and the second most populous country, is in the midst of an economic boon and hence in the phase of domestic product growth and hike in the standard of living. But unfortunately, despite this overall economic growth, we are still lacking in an effective system of delivering trauma care and emergency services to the majority of our citizens. There is an overall increase in the incidence of polytrauma as a consequence of increased urbanization and industrialization. The *World Health Organization* (WHO) has predicted that trauma-related deaths in India would move up from the ninth position up to the third position by the year 2020. The National Crime Records Bureau in India reported that in 2010, at least 10.1% of deaths were due to road traffic accidents and injuries. There were a total of 6,78,326 cases of accidents, which caused 3,59,583 deaths and 5,03,932 people were rendered injured and the affected population belonged to the productive age group—15 to 44 years. This chapter outlines the steps in the assessment and management of polytrauma patients. The main *objectives of the chapter are*:

- To identify the *correct sequence of priorities* for assessment of the polytrauma patient and *triage*
- To know and apply the principles outlined in *primary and secondary surveys*
- To apply guidelines and techniques to *initial management and definitive care*
- To correlate the patient's *medical history and mechanism of injury* with the identification of injuries
- To *re-evaluate,* when the patient is not responding appropriately to resuscitation and management
- To understand the importance of *teamwork and* recognize patients who require *safe transfer* for definitive management

TRIMODAL DISTRIBUTION OF TRAUMA MORTALITY

A person may get injured by various modes such as road traffic accident, fall from height, assault or thermal and blast injury. These *injuries may give rise to three patterns of death*: (1) Immediate, (2) early, and (3) late death (**Fig. 1**).

Immediate deaths: These deaths usually occur within the first hour and include death on spots. Major vascular, brain, and cardiac injuries are the main causes. About 50% of trauma-related deaths are immediate deaths.

Early deaths: Deaths occurring within hours are included in early deaths. The main causes are hemorrhage and breathing issues.

Late deaths: These deaths occur after 3 days and peak at 3–4 weeks. The main causes are sepsis and multiorgan failure. It is very important to have a robust trauma management system at both prehospital and in-hospital stages. The preparation for a trauma patient in two different clinical settings is described below.

Prehospital phase: This phase refers to field management. It includes the following principles of *intervention at the injury site:* Resuscitation and evaluation of the trauma patient begin at the injury site. The goal is to get the right patient to the right hospital at the right time for definitive care without any delay. In the stay and play approach, the patient receives treatment and stabilization on scene before being transported to the hospital (airway maintenance, control of external bleeding and shock, immobilization of patient). Scoop and run is the approach where the patient is transported to the hospital as soon as possible without making efforts to stabilize him/her at the scene. A scoop and run principle is better than stay

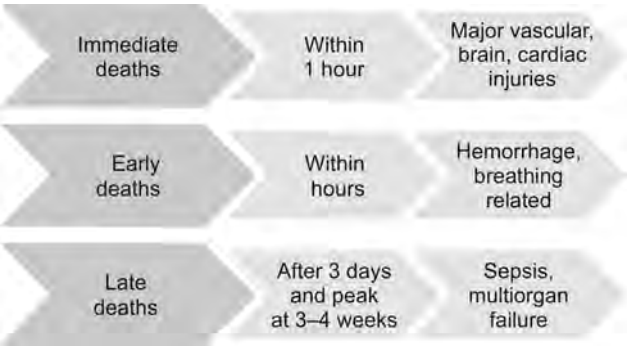


FIG. 1: Trimodal distribution of deaths in polytrauma.

and play in prehospital settings. It is important to notify the receiving hospital before transport of patient from the scene so as to allow time for mobilization of personnel and resources beforehand only.

Hospital phase: It includes the following: A resuscitation area should be made available. Airway equipment should be organized, checked, and placed in an accessible location. Warmed intravenous crystalloid solutions should be made available. Appropriate monitoring devices should be available. Additional medical assistance should be called for. Laboratory and radiology personnel should be notified. Standard precaution gears are mandatory due to concerns of communicable diseases. Management of life-threatening trauma must be prioritized according to physiologic necessity for survival, that is, active efforts to support airway, breathing, and circulation (ABC). The systematic management of a polytrauma patient, i.e., triaging, primary survey, resuscitation, secondary survey and monitoring, definitive treatment, and transfer in the emergency department (ED), is described in the following text.

PRIMARY SURVEY AND INITIAL RESUSCITATION

During initial assessment, an empirical sequence of lifesaving therapeutic and diagnostic procedures is pursued. The goal is to establish adequate oxygen delivery to the vital organs. In most of the tertiary care hospitals, primary survey and resuscitation go hand in hand by a team of trained doctors and nurses. The primary survey consists of five important steps:

1. Airway with restriction of cervical spine movement
2. Breathing and ventilation
3. Circulation and control of hemorrhage
4. Disability
5. Exposure and control of environment

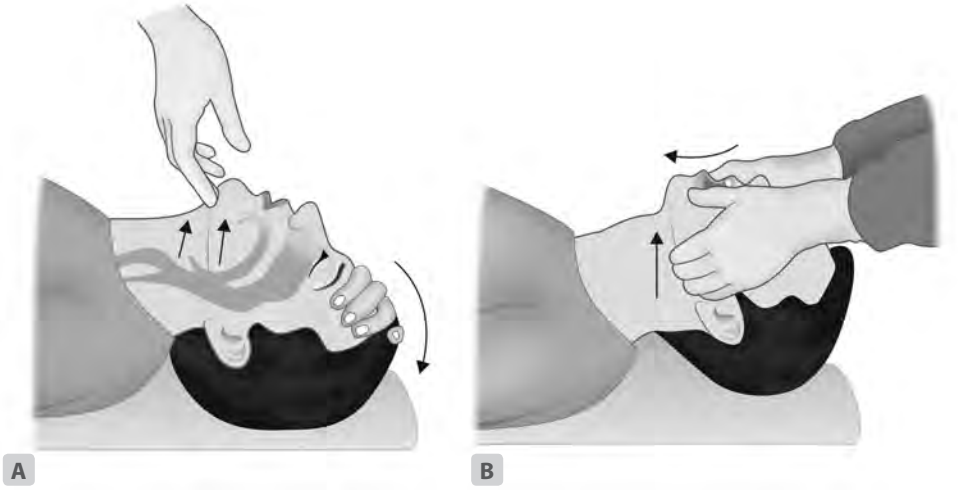
Airway with Restriction of Cervical Spine Movement

In cases of polytrauma, airway control should proceed along with the assumption that there is an injury to the cervical spine in all patients and hence, extension of the neck must be avoided. Evaluation begins by asking the patient "How are you?" A response given in a normal voice indicates that the airway is not in immediate jeopardy, whereas a breathless, hoarse response or no response at all indicates that the airway may be compromised.

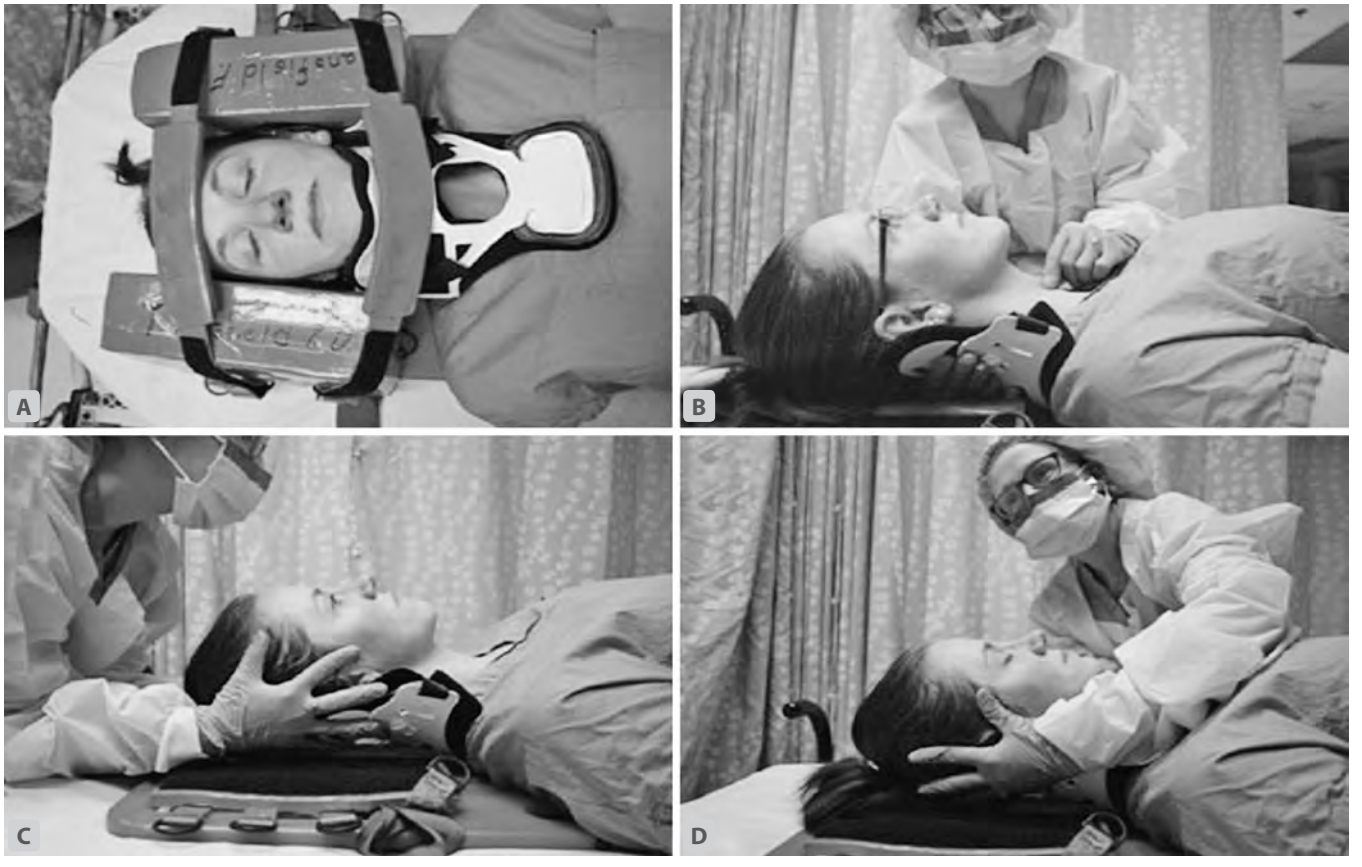
Airway obstruction and hypoventilation are the most likely causes of respiratory failure. The critical decision is whether active airway intervention is needed or not. The first maneuver is to clear the airway of debris and to suction secretions. In the obtunded patient, this procedure is followed by elevation of the angle of the mandible (head-tilt, chin-lift, or jaw-thrust; **Figs. 2A** and **B**) to alleviate pharyngeal obstruction and placement of an oropharyngeal or nasopharyngeal airway to maintain airway patency. Supplemental oxygen is given via a nonrebreathing oxygen mask at 10–12 L/min. Cervical spine protection is integral to airway management but should not be allowed to delay necessary intervention (**Figs. 3A** to **D**). Bag-mask ventilation is an effective temporizing measure, but it consumes the attention of a skilled trauma team member, it may insufflate air into the stomach, and it can be resisted by spontaneously breathing patients. It is also ineffective in the presence of severe maxillofacial trauma.

The decision for urgent airway control is made on clinical grounds. Persistent airway obstruction or signs of inadequate ventilation mandate prompt intervention. Patients with expanding neck hematomas, deteriorating vital signs, or severe head trauma are also best managed with an aggressive airway approach. Patients in respiratory distress with severe maxillofacial trauma may warrant a surgical airway. Cricothyroidotomy is the preferred approach in adults and has replaced tracheostomy in the ED. The rare exceptions are in rapidly deteriorating patients with extensive laryngeal trauma or tracheal disruption.

In all other patients, the current standard approach is rapid-sequence intubation (RSI) of the trachea orally with in-line immobilization. In adults, a large (8-mm internal diameter) cuffed endotracheal tube is inserted to a distance of 23 cm from the incisors. In children, the tube size is gauged to equal the diameter of the little finger. The proper depth (in centimeters) to which the tube should be inserted can be estimated by multiplying the tube's internal diameter (in millimeters) by 3. After successful intubation, re-examination of the patient must be done for bilateral chest rise, five-point



FIGS. 2A AND B: (A) Head tilt-chinlift; (B) Jaw-thrust maneuver.



FIGS. 3A TO D: Cervical spine protection by immobilization.

auscultation, and confirmation with presence of end-tidal carbon dioxide ($ETCO_2$) waveform on the monitor. A chest X-ray should be obtained as soon as possible to rule out the possibility of right mainstem intubation.

Breathing and Ventilation

Rapid assessment of chest examination should be carried out by inspection, palpation, and auscultation (percussion is discouraged in a trauma patient as it is painful and not able to give conclusive findings). Also, look for trachea which shall be central and jugular venous pressure (JVP). Patients who are having severe tachypnea, raised JVP, deviation of trachea on the opposite side, and hypotension should be immediately diagnosed as tension pneumothorax. In such adult patients, immediate needle thoracocentesis via a large-bore over the needle catheter (12–14 G) in the intercostal space, anterior to the mid-axillary line, is done followed by intercostal tube drainage. In pediatric patients, needle thoracocentesis is done in the 2nd intercostal space with the midclavicular line on the affected side. Suspected hemopneumothorax should be vented immediately with large-bore chest tubes inserted in the 5th intercostal space, anterior to the midaxillary line in unstable patients. Clinical evidence of hypoventilation includes poor air exchange at the nose and mouth, diminished breath sounds, and decreased chest wall excursion. The most likely causes are head injury, spinal cord injury, hemopneumothorax, flail chest, and profound shock. Extended FAST (focused assessment with sonography in trauma) is a very useful point-of-care test available with the emergency physician to diagnose pneumothorax, hemothorax, and pericardial tamponade. Intubated patients should be placed on a high fraction of inspired oxygen (FiO_2), and their SaO_2 should be monitored by pulse oximetry. In cases of lung injury patients who are on a ventilator, low tidal volume, low *positive end-expiratory pressure* (PEEP), and higher respiratory rate shall be kept to prevent further barotrauma. Hyperventilation should also be avoided. A low arterial carbon dioxide tension ($PaCO_2$) can cause cerebral vasoconstriction, which can be deleterious in patients with traumatic brain injury (TBI). An arterial blood gas (ABG) analysis should be obtained to assess pH, $PaCO_2$, and base deficit.

Circulation and Control of Hemorrhage

Once alveolar ventilation is ensured, the next priority is to optimize oxygen delivery by maximizing cardiovascular performance. External hemorrhage shall be controlled by means of manual compression, elevation of limb, and if required by tourniquet in field area remote from hospital but should not be >90 minutes' duration. If the patient arrives in shock or has obvious multiple injuries, a short 16 or 18 French venous access should be taken in each antecubital vein. Intraosseous infusion through a cannula placed in the medullary cavity of a long bone is a safe and effective method for emergency vascular access in infants and children younger than 6 years. This procedure is typically performed in the anteromedial aspect of the tibia in an uninjured extremity; the distal femur, the distal tibia, and the sternum are other potential sites. Intraosseous infusion generally allows administration of sufficient fluid to facilitate subsequent access of peripheral venous cannulation.

With establishment of the first IV line, blood should be drawn for hematocrit, white blood cell (WBC) count, electrolyte, blood group type and cross-match, and coagulation profile in most of the polytrauma patients. 1 L of warmed isotonic crystalloid (20 mL/kg in children) is used for initial resuscitation in the ED. Lactated Ringer (LR) solution is preferred to normal saline (NS) unless the patient has an obvious brain injury. Excessive early administration of crystalloids has been identified as a risk factor for adverse outcomes; hence, the amount infused should be monitored closely. If the patient does not respond to crystalloid infusion at levels exceeding 30 mL/kg, blood should be administered. Early empirical blood transfusions are indicated in patients who arrive in severe shock (class III or IV hypovolemic shock) or who have injuries associated with significant bleeding (e.g., a vertical shear pelvic fracture or multiple long bones fractures), especially if the patients are elderly. Type-specific blood should be available within 20 minutes. If type-specific blood is not available, reconstituted O-negative packed red blood cells (PRBCs) may be used.

Disability

After adequate resuscitation, it is required to assess the patient's neurological status. The initial Glasgow coma scale (GCS) may not be correct as the patient may be in shock but it works as baseline GCS on presentation and needs to be documented. Assess the pupillary size on both sides and its reaction to light bilaterally. Monitoring of the patient's neurological status by assessing GCS and pupil examination is very important to identify rapid deterioration in neurology. If the patient's GCS < 8, then airway protection via an endotracheal tube is of utmost importance to prevent hypoxia and aspiration.

Exposure and Control of Environment

Complete exposure of all polytrauma is very essential to identify certain missed injury, especially in the penetrating injury group. Penetrating injury in axilla, back, gluteal cleft, and perineum is easily missed if the patient is not exposed completely and log rolled. After complete exposure and assessment, one needs to take care for prevention of hypothermia. Secondary to severe hemorrhagic shock and resuscitation with IV fluids stored at ambient temperature, hypothermia may occur. Moderate hypothermia (<32°C) causes platelet sequestration and inhibits the release of platelet factors that are important in the intrinsic clotting pathway. Core temperature often falls insidiously because of exposure at the scene and in the ED and because of administration of resuscitation fluids stored at ambient temperature. The first step is to prevent further heat loss by covering with blankets and infusing warm blood and fluid. Active external rewarming with heating blankets and increased room temperature should also be employed.

Evaluation and Continued Resuscitation

Identification of hemodynamic instability, recognizing the presence of shock, and assessing its severity are key factors in early decision-making. During the initial ABCs, palpation for the presence of pulses can be used to get a rough estimate of systolic blood pressure (SBP). In general, a radial pulse is detected when SBP is >80 mm Hg, a femoral pulse when SBP is >70 mm Hg, and a carotid pulse when SBP exceeds 60 mm Hg. The initial blood pressure (BP) measurement should be made with a manual cuff; automatic cuff BP measurement machines may overestimate SBP in hypovolemic trauma patients. An SBP < 90 mm Hg in conjunction with a heart rate > 130 beats/min is generally considered indicative of major shock. Most patients, however, especially young ones, can compensate for hypovolemia and maintain a normal BP even in case of significant ongoing hemorrhage.

The initial hemoglobin level is also notoriously misleading, either because the patient has not yet been adequately resuscitated or because there has not been sufficient time for influx of interstitial fluid into the intravascular space. It is more informative to measure the hemoglobin level again after initial volume loading for purposes of comparison.

Management of Nonresponsive Unstable Patients

Shock that persists despite initial volume loading may be due to severe hypovolemia, cardiogenic causes, or neurogenic causes. Given that neurogenic shock is fairly well tolerated, the key concern at this point is to quickly distinguish hypovolemic shock from cardiogenic shock because cardiogenic shock may necessitate immediate ED intervention. This distinction can usually be made by measuring *central venous pressure* (CVP) in conjunction with physical examination. In hypovolemic shock, CVP is generally <5 mm Hg, whereas in clinically significant cardiogenic shock, CVP usually exceeds 20 mm Hg.

The differential diagnosis of traumatic cardiogenic shock depends on the mechanism of injury and may include tension pneumothorax (**Fig. 4**), pericardial tamponade (**Fig. 5**), myocardial contusion, and air embolism. Typical physical signs may be difficult to appreciate in a noisy ED and timely diagnosis requires a high index of suspicion. Tension pneumothorax, the most common cause of cardiogenic shock in both blunt and penetrating trauma, is treated with emergency chest tube placement.

In traumatic pericardial tamponade, the classic components of the Beck triad (hypotension, muffled heart sounds, and raised JVP) are frequently absent, and pulsus paradoxus is rarely detectable. ED ultrasonography is the first test employed by emergency physicians in patients with high-risk penetrating wounds. Occasionally, a blunt trauma

FIG. 4: Tension pneumothorax.

FIG. 5: Cardiac tamponade.

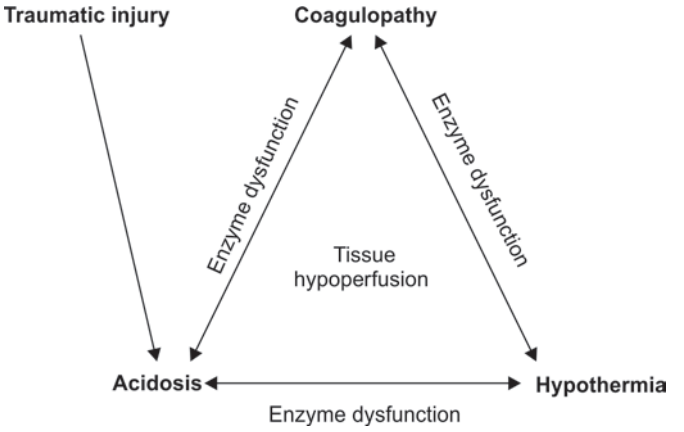


FIG. 6: The lethal triad.

patient can be salvaged through timely diagnosis of a blunt atrial tear. Myocardial contusion should be suspected in any blunt trauma patient with unexplained cardiogenic shock or persistent arrhythmia. ECG changes and elevated troponin levels are usually nonspecific. Fundamental interventions include correction of acidosis, hypoxia, and electrolyte abnormalities; judicious administration of fluid; and pharmacologic suppression of life-threatening arrhythmias. Bronchovenous air embolism into the left atrium from a pulmonary laceration typically occurs after penetrating trauma and is more common than is generally detected. Hemodynamic instability develops after positive-pressure ventilation is initiated as air is forced from the pulmonary bronchioles into the adjacent open pulmonary veins and, ultimately, into the coronary arteries. ED thoracotomy is essential for pulmonary hilar cross-clamping, air aspiration from the left ventricle, and cardiac massage. The patient is then transferred to the operation theater for definitive management of the pulmonary lesion before the hilar clamp is released.

Emergency department thoracotomy is an integral part of the initial management of the patient who deteriorates to imminent cardiac arrest. The physiologic rationale is to minimize the duration of profound shock. ED thoracotomy permits release of pericardial tamponade, internal cardiac massage, cross-clamping of the descending thoracic aorta to enhance coronary and cerebral perfusion and to reduce subdiaphragmatic bleeding, and control of intrathoracic blood loss. Internal cardiac massage should be done bimanually; otherwise, a forceful thumb may rupture the relatively thin right ventricle as it becomes distended.

Damage Control Resuscitation

Damage control resuscitation (DCR) is a strategy that emphasizes to maintain or restore homeostasis in trauma patients. The name "damage control" was coined from naval tactics aimed to keep a damaged ship as combat-capable as possible until definite repair can be done. The concept goes hand in hand with damage control surgery. The major threats in DCR are acidosis, coagulopathy, and hypothermia which makes a forward feedback loop that leads to progressive worsening of a patient's hemodynamic status and eventually death (**Fig. 6**). Lactic acidosis is a result of tissue hypoxia or hypoperfusion when the patient is in shock. Coagulopathy in polytrauma patients is multifactorial. It occurs when the enzymes that cause blood to clot are unable to function or due to deficiency of clotting factors. So, it may be due to overconsumption of clotting factors called consumptive coagulopathy. Additionally, infusion of crystalloids deficient of clotting factors aggravates this by causing dilution. Metabolic acidosis and hypothermia further worsen this coagulopathy. Identifying which patients will require DCR is very difficult but one can predict its requirement with anatomical and physiological criteria. Anatomic parameters for DCR include: injury severity score > 36, penetrating neck, chest or abdominal injuries, unstable pelvic fracture, multiple long bone fracture with head injury, or traumatic amputation above wrist or ankle. Physiologic parameters include: weak or absent radial pulse, core body temperature <35°C, SBP < 100 mm Hg, and heart rate >100.

Damage control resuscitation is also known as hypotensive resuscitation and hemostatic resuscitation. Appropriate fluid administration might help to maintain homeostasis. Inappropriate fluid administration will do just the opposite. In cases of penetrating trauma to the torso, research shows that withholding isotonic IV fluid had a mortality benefit. Hence, it is assumed that the benefit may come from decreased dilatational coagulopathy and hemostatic maintenance. However, in head injury patients, this strategy of allowing a low BP and restricting fluid is contraindicated. The key point is that resuscitation with a minimum amount of isotonic fluid needed to maintain mental status or mean arterial pressure of 65 mm Hg is probably the best strategy for patients without a significant head injury. Transfusion of blood products is potentially lifesaving for polytrauma patients. The ideal initial ratio for the massive transfusion of blood products is generally accepted to be one unit of fresh frozen plasma (FFP) to one unit of platelets to one unit of PRBCs (1:1:1). At many centers, it is lowered at a ratio of platelets and plasma to packed cells 1:1:2. Early transfusion with blood products, especially early plasma transfusion, is more beneficial than high volume isotonic fluid and it reduces mortality in polytrauma patients significantly.

Pharmacologic treatments that may have a role in treating trauma-induced coagulopathy include: prothrombin complex concentrate (PCC), cryoprecipitate, calcium, and tranexamic acid (TXA). PCC is used to reverse pharmaceutical anticoagulation. Cryoprecipitate contains clotting factors VIII

and XIII in addition to fibrinogen and von Willebrand factor. Calcium is essential in the clotting cascade for conversion of factor X to factor Xa and for the conversion of prothrombin to thrombin; both of these steps are critical for blood clot formation. With increasing early blood product use, trauma victims are at a risk of hypocalcemia. Also, calcium helps to increase myocardial contractility resulting in increased BP. TXA stabilizes blood clots by competitively binding to the lysine-binding site on plasminogen and preventing its conversion to plasmin. This stops clot breakdown and hence helps to reduce bleeding. As per the CRASH-2 (clinical randomization of an antifibrinolytic in significant hemorrhage 2) trial, the dosage in adult patients is 1 g loading over 10–15 minutes and 1 g in IV infusion over the next 8 hours when the patient has presented with 3 hours from time of injury.

SECONDARY SURVEY

Further assessment and management are governed by the initial severity of shock and its response to ongoing resuscitation. Life-threatening injuries should be addressed first followed by limb-threatening injury and finally, a search is made for occult trauma. Prioritization is also guided by the mechanism of injury. Penetrating trauma typically results in a localized injury, whereas blunt trauma frequently results in multiple injuries involving several body regions. When hemodynamic instability recurs, the underlying cause must be identified and corrected promptly by going back to primary survey. The length of time spent in the ED, the decision for urgent operation, and the ordering of special radiologic studies are critical decisions that must take into account the mechanism of injury, the severity of shock, and the availability of an operation theater with well-trained staff. The following regions should be examined from top to bottom to prevent missed injuries: Head, face, neck, chest, abdomen, pelvis, each extremity, detailed central nervous system (CNS) examination, spine, and perineum examination including per rectal and per vaginal.

Penetrating Trauma

Systematic Assessment

The secondary survey is more focused on cases of penetrating trauma, but the most common error is failure to identify multiple injuries. The priorities are (1) to identify all of the wounds, (2) to decide whether an urgent operation is indicated, and (3) to determine whether further investigations are needed to assist with intraoperative management. The decision-making process is driven by hemodynamic stability and the location of the wounds. Efforts should focus not only on resuscitating the patient until vital signs are normal but, rather, on obtaining adequate IV access, ensuring that blood products are available, and notifying the operating room (OR). Hemodynamically unstable patients should be rapidly sent to the OR with minimal testing. Any delay in doing unnecessary investigations will be adversely affecting the final outcome. The most valuable tests are plain X-rays to determine missile trajectory. Any impaled foreign body such as knife or rod which has caused a penetrating injury must never be pulled out in the emergency room (ER) else it can cause torrential life-threatening bleeding which may not be possible to control in ER.

Neck

Patients who have an obvious life-threatening penetrating injury (e.g., a gurgling wound, pulsatile bleeding, or a compromised airway) or are in severe shock should undergo operation theater promptly. ED management should be limited to airway control, external compression to control bleeding, IV access, and chest X-ray. A neurologic examination should be performed and documented in the event of a spine or carotid artery injury. Management of hemodynamically stable patients without an obvious injury is selective. Patients with zone I wounds should undergo computed tomographic angiography (CTA) scanning or angiography to rule out occult vascular injuries. Alert patients with zone II injuries but without significant hematoma, crepitation, dysphonia, or dysphagia may be managed expectantly. The exception is a transverse gunshot wound (GSW) where computed tomography (CT) scanning is usually done because of the high risk of an occult injury. Symptomatic patients with zone III injuries should undergo CTA scanning or angiography to assess for arterial injury that may warrant angioembolization.

Chest

In unstable patients with thoracic injuries, a chest tube should be placed into affected hemithorax, followed by a chest X-ray to confirm tube placement, lung expansion, and the presence of foreign bodies. If a cardiac wound is suspected, ED ultrasonography should be performed. Persistent instability without evidence of intrathoracic bleeding or pericardial tamponade should raise the suspicion of intra-abdominal bleeding. Occasionally, a thoracic spinal cord injury contributes to hemodynamic instability. The challenge in this setting is to quickly identify those patients who require an urgent operation.

Patients with documented pericardial tamponade and persistent tachycardia should undergo pericardiocentesis to relieve any ongoing subendocardial ischemia even if the SBP is normal, and a pigtailed catheter is inserted for repeated aspiration during transport to the OR. Patients who exhibit persistent signs of pericardial tamponade (e.g., CVP > 20 mm Hg) despite negative results from ultrasonography should be transported to the OR for creation of a subxiphoid pericardial window. If the patient is in extremis or deteriorates suddenly, ED thoracotomy should be performed promptly. Most patients diagnosed with intrathoracic bleeding outside the pericardium stabilize after tube thoracostomy and fluid resuscitation.

Urgent thoracotomy is indicated for massive hemithorax where an initial chest tube output is higher than 1,500 mL in an adult (20 mL/kg in children) or a persistent output is higher than 200 mL/h for 3–4 hours. Patients with an initial chest tube output higher than 10 mL/kg should be closely observed for hemodynamic instability in the intensive care unit (ICU). Abrupt cessation of chest tube output may be deceptive; if hypotension persists or recurs, a new chest tube should be inserted. Patients with large air leaks, massive subcutaneous emphysema, or a persistent pneumothorax may require high-resolution computed tomography (HRCT) or bronchoscopy to exclude a tracheobronchial injury. Patients with transmediastinal GSW or penetrating wounds close to the great vessels should undergo a CT scan with IV contrast and angiography. Lower chest wounds located below the nipples anteriorly or the tips of the scapula posteriorly may penetrate the diaphragm and cause significant intra-abdominal or retroperitoneal injuries. If the patient is unstable,

tube thoracostomy, chest X-ray, and FAST are indicated. If instability persists, the patient should be transported to the OR. If the patient stabilizes after tube thoracostomy, additional testing must be done to exclude associated injuries.

Anterior Abdomen

Unstable patients should be transported to the OR with minimal resuscitation and testing. Biplanar abdominal X-rays are often helpful in clarifying bullet trajectories; entrance and exit wounds should be marked with radiopaque objects. Management of stable patients depends on the mechanism of injury. Although there is some enthusiasm for selective nonoperative management of GSWs, laparotomy is generally recommended for GSWs that violate the peritoneal cavity. Contrast-enhanced computed tomography (CECT) of the abdomen or laparoscopy is indicated for suspicious tangential GSWs. Laparotomy is indicated in patients with overt peritonitis after a stab wound. In other patients, the stab wound should be explored. If there is no violation of the anterior fascia, the patient can safely be discharged. If the fascia is violated, the patient should be admitted for serial clinical assessments and further investigations.

Retroperitoneal Structures

Unstable patients with injuries to the flank, the back, or the pelvis should undergo immediate laparotomy. Stable patients are difficult to evaluate. With the exception of blood on rectal examination, the findings from physical examination are unreliable. Gross hematuria is indicative of bladder or kidney injury. Triple contrast CT scanning may be helpful in patients with high-risk wounds. Most retroperitoneal colon injuries are identified on the basis of extraluminal gas or fluid rather than of contrast extravasation. Sigmoidoscopy should be performed if a rectal injury is suspected. High-risk wounds should be explored to ensure that retroperitoneal colon injuries are not missed. Delayed diagnosis is associated with significant morbidity. Hence, stable patients with stab wound of flank are to be admitted for serial physical examination and intervention if required.

Extremities

Unstable patients with isolated penetrating injuries to the extremities should be managed with external compression to control bleeding. Blind clamping for vascular injuries should not be done because it may inadvertently cause injury to the adjacent vein or nerve. IV access with moderate volume resuscitation, compression bandage over the bleeding site, and prompt triage to the OR for exploration and definitive treatment is the best approach. Inappropriate use of tourniquets can cause considerable harm. Although extremity injuries are common in civilian trauma, death from extremity exsanguination is uncommon. Management of stable patients with penetrating extremity injuries begins with a search for *"hard" signs of arterial injury* (e.g., an expanding or pulsatile hematoma, absent distal pulses, a palpable thrill, an audible bruit, or signs of distal ischemia). The presence of any of these hard signs prompts further evaluation. If signs of distal ischemia exist, the patient should be taken to the OR, where on-table angiography is performed to identify the injury site. If knowledge of the patient's specific vascular anatomy is needed and no signs of ischemia exist, a formal angiography is reasonable. If *"soft" signs of vascular injury* (i.e., a history of arterial bleeding prior to ED admission, wound proximity to an artery, small nonpulsatile hematoma over the artery, nerve deficit originating in a nerve adjacent to the artery) are present, distal BPs should be measured in the injured extremity and nonaffected extremity. If the ratio of the BP in the injured extremity to that in the contralateral extremity is 0.90 or higher, arterial injury is virtually excluded and no additional testing is needed. These patients can be discharged from the ED but should follow up in the outpatient clinic because a small percentage will eventually come to operation as the original undetected injury progresses rather than heals. These ratios are not, however, reliable for excluding arterial injuries in the axilla or the groin. Furthermore, the presence of a "good" Doppler signal does not exclude an arterial injury.

Blunt Trauma

Systematic Assessment

The goal is to identify all potentially life- and limb-threatening injuries. A comprehensive assessment is crucial to facilitate triage from the ED to the OR, the CT scanning suite, the interventional radiology suite, or the ICU. The details of the patient's medical history, as well as the details specifically related to the injury, are critical. The prehospital emergency medical technicians are encouraged to provide comprehensive details of the event and a thorough patient assessment. A minimal review of the patient's medical history should include AMPLE, i.e., history of known allergy, current medications (especially anticoagulation status in the elderly), past medical illnesses, the time of the last meal, and event/mechanism that caused injury. A detailed systematic physical examination is done, from head to toe and front to back. Patients are completely disrobed and log rolled from side to side so that the back and the flanks can be inspected. A rectal examination is done to look for blood and to evaluate sphincter tone; the perineum and the axillae are inspected; and neurologic function and peripheral pulses are documented. The cervical spine is rigidly immobilized, and long-bone fractures are splinted to minimize pain, blood loss, and softtissue damage. Insertion of a gastric tube decompresses the stomach and reduces the risk of pulmonary aspiration. In patients with a maxillofacial injury, the tube should be placed orally to avoid intracranial insertion from the nasal route. Blood in the gastric aspirate may be the only sign of an otherwise occult injury to the stomach or the duodenum.

Placement of an indwelling catheter empties the bladder and permits output monitoring. Also, one can easily watch for frank hematuria if the color is red. The catheter should not, however, be inserted until abdominal ultrasonography is completed, and it should not be placed on an urgent basis in male patients with suspected urethral injuries (i.e., those with blood at the meatus, a perineal hematoma, a high-riding prostate, or an extensively displaced anterior pelvic fracture; **Figs. 7A** and **B**). If a urethral injury is suspected, a retrograde urethrogram, followed by a cystogram (to exclude bladder injury), is obtained before catheterization. In females, the urethra is shorter and better protected and thus is rarely injured. Routine X-rays performed simultaneously with the ABCs include anteroposterior chest and pelvic films. CT scanning has virtually replaced plain X-rays for

FIGS. 7A AND B: Pelvic fracture. (A) Open book fracture; (B) Pubic ramus fracture.

diagnosing potential spinal injuries. Once life-threatening injuries have been addressed, X-rays of extremities with suspected fractures (including the joint above and the joint below) should also be obtained. Given that trauma victims are uniquely susceptible to hypothermia, a rectal temperature probe is essential in those who have been exposed to a cold environment or who require massive volume replacement. At core temperature reading <35°C, re-warming measures appropriate for the degree of hypothermia should be initiated. Tetanus prophylaxis is routine. Systemic antibiotics should be given as per the hospital's antibiogram. An ECG is obtained after blunt chest trauma, and an ABG analysis is done in selected patients to confirm adequate ventilation and metabolic balance. In patients with evidence of hypovolemia, a blood sample should be sent for blood-group typing and coagulation studies.

Rapid Hemorrhage Control

Blunt trauma patients who arrive in shock and remain hemodynamically unstable pose difficult triage decisions. Initial screening must be directed at identifying life-threatening bleeding that necessitates immediate intervention. Most hospitals do not have an interventional radiology suite immediately available; early notification is crucial in assembling the team. There are only five causes of severe bleeding leading to hypovolemic shock, that is one on the floor (external bleeding) and four more (intrathoracic, intra-abdominal, pelvic and retroperitoneum, and long bone fracture). A chest X-ray is the most reliable screening test for intrathoracic bleeding; it also confirms the location of endotracheal, nasogastric, and thoracostomy tubes as well as that of the central venous catheter. The presence of pleural fluid may be difficult to confirm on a supine chest X-ray: A total of 1 L blood may produce only a hazy appearance in a hemithorax. Hemothoraces should be drained promptly via tube thoracostomy. Continued bleeding must be monitored carefully by measuring chest tube output, obtaining serial chest films to detect retained intrapleural blood, and observing vital signs. The criteria used to decide when thoracotomy is indicated are similar to those used in cases of penetrating trauma, but far fewer blunt trauma patients meet these criteria, and intrathoracic bleeding is rarely a reason for immediate OR triage.

The abdomen is difficult to evaluate and is much more likely than the chest to harbor occult life-threatening bleeding. The peritoneal cavity can accommodate as much as 3 L of blood with only minimal abdominal distention. Head injury or intoxication frequently alters the patient's response to acute injury, and pain from associated fractures may mask peritoneal irritation secondary to bleeding. Ultrasonography is the most rapid method of identifying free blood, but it fails to determine the source of blood and may yield false-negative results in as many as 15% of patients on initial examination. Assessment of bony stability by means of physical examination and plain films of the pelvis is crucial for the early identification of major pelvic fractures. Life-threatening hemorrhage occurs most commonly with fracture patterns involving the posterior columns. Appropriate initial management of unstable patients who have a high-risk pelvic fracture on the initial pelvic X-ray includes blood volume replacement (including early blood and FFP) and application of a pelvic binder; wrapping with a sheet is also effective. The next step is to evaluate the response to initial resuscitation and then perform FAST or diagnostic peritoneal lavage (DPL) to determine whether significant intra-abdominal bleeding is present. DPL is a good screening test for intra-abdominal injuries in unstable patients where FAST is not available. Laparotomy is performed if there is free aspiration of blood, gastrointestinal contents, vegetable fibers, bile or red blood cell counts > 100,000/mm^3, >500 WBC/mm^3 or positive Gram stain for bacteria. Left-sided penetrating injuries should be pursued more aggressively because of the increased risk of delayed visceral herniation. A CT scan may assist in diagnosing occult retroperitoneal injuries but is not reliable for excluding penetrating diaphragmatic injuries.

An unstable patient with clearly positive findings from FAST or DPL should undergo laparotomy because of the high probability of major hepatic, splenic, or mesenteric bleeding. If there is a large pelvic hematoma at the time of laparotomy and the patient is unstable, extraperitoneal pelvic packing should be done. The role of pelvic packing versus angioembolization is controversial, but these modalities should be viewed as complementary.

Fast-track CT Scanning

In patients who became stable after resuscitation, the priorities are to (1) identify and quantitate ongoing sources of bleeding, identify TBI, especially in those patients who require immediate craniotomy; and identify any other injuries that call for urgent intervention [e.g., thoracic aortic injury (TAI) or special precautions (e.g., spine fractures)]. With the wide-

spread availability of CT scanners in proximity to the ED, rapid whole-body imaging is now feasible, permitting accurate triage for these competing priorities. The decision to order CT scanning is made early, while the ABCs are being addressed and FAST and initial plain X-rays are being performed, any obvious injuries identified, and the patient's hemodynamics are stabilized. Whenever the patient is being sent for CT scan of brain, always go for CT cervical spine screening to rule out cervical spine injury as it is more confirmatory than X-rays as well as less time-consuming. For abdominal injuries, always ask for contrast-enhanced triple-phase CT scan of abdomen to get complete information. For chest injuries, usually HRCT plain is sufficient but if the patient has signs of active bleeding or is suspected of mediastinal injury, always do CTA.

Identification of Abdominal Injuries

The decision to perform an urgent laparotomy in a patient with a positive FAST depends on the patient's hemodynamic stability. A CT scan can be helpful in refining the triage category by identifying extravasation of IV contrast (i.e., a blush) and in diagnosing hollow viscus injuries. A blush should prompt consideration of angiography and embolization, if available, or surgical intervention. Early angiography is a helpful adjunct in managing liver, spleen, and kidney. Hollow viscus injury is sometimes notoriously difficult to diagnose. Extravasation of oral contrast is rare; hence, it should not be given. When all signs (e.g., unexplained free fluid, bowel wall thickening, mesenteric streaking, and free air) are considered, the sensitivity of CT scan in making the diagnosis approaches 90%. In questionable cases of a hollow viscus injury in stabilized patients, DPL is useful to determine elevations in WBC count, amylase level, and alkaline phosphatase level. Pancreatic injury is also poorly defined on the initial CT scan. A rising lipase warrants repeat CT scanning (and consideration for endoscopic retrograde cholangiopancreatography or magnetic retrograde cholangiopancreatography). However, in such a patient, serial physical examination by an experienced surgeon is very important for decision-making for further plan of management.

Identification of Traumatic Brain Injury

After ABC, a detailed neurological examination should be done by assessing GCS and pupillary examination to light. Also, GCS evaluation shall be repeated after resuscitation and frequently to be done as required and to be documented. Short-acting sedatives or paralytics should be given sparingly. A GCS score < 8 and a lateralizing neurologic examination indicate a significant risk that emergency craniotomy will be needed and, therefore, justify obtaining a CT scan of the head if hemodynamic stability permits.

Identification of Limb Ischemia

The absence of distal pulses in a fractured or dislocated extremity should be addressed urgently. Fractures and dislocations should be reduced, and the extremity should be closely examined for signs of ischemia. Distal SBP measurements comparing injured limbs with noninjured limbs [i.e., the ankle–ankle index (AAI) or the ankle–brachial index (ABI)] should be obtained. If the ABI or AAI is <0.90 after reduction, CTA should be performed to exclude the presence of an arterial injury if the patient is stable. In an unstable patient, a bedside Doppler examination is very important to rule out vascular injury. A detailed neurovascular examination is required before and after immobilization of fractured extremity.

SUMMARY

There is an overall increase in the incidence of polytrauma as a consequence of increased urbanization and industrialization. Important steps in managing the polytrauma are *correct sequence of priorities* for the assessment of the polytrauma patient and *triage: Primary and secondary surveys, initial management and definitive care, medical history and mechanism of injury* with the identification of injuries. *Re-evaluate,* when patient is not responding appropriately to resuscitation and management. Understand the importance of *teamwork and* recognize patients who require *safe transfer* for definitive management.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Trauma Resuscitation

Ankur Verma

INTRODUCTION

Trauma is one of the most dynamic entities undergoing continuous research over the past many decades. Trauma resuscitation has evolved over the years from a singular approach for all to one customized to patients' physiologies. Yet, resuscitation protocols in trauma will never remain stagnant. Ongoing research will modify the guidelines for future trauma management. That is how dynamic trauma is. Trauma resuscitation is a complex process involving multiple team members (or sometimes just one or two) with various roles, simultaneous evaluations, examinations, management, and disposition in a coordinated manner. Until the development of the now famous advanced trauma life support (ATLS) courses, trauma was managed in a very heterogenous manner by physicians who lacked any trauma training. In 1980, the ATLS course was adopted by the American College of Surgeons and was taught throughout the USA and later adopted by the UK in 1988. The course eventually spread throughout the world and became a standard requirement to be completed by members of trauma teams across the globe. ATLS facilitated a common language among trauma care providers. It emphasized the importance of a team approach and introduced the airway-breathing-circulation-disability-exposure (A-B-C-D-E) sequence to trauma care.

The ATLS sequence of A-B-C-D-E provided a direction and structure to trauma caregivers in the management of major traumas. But the strict adherence to the approach has been questioned in recent times. For example, in recent times the concept of the physiologically difficult airway has been recognized and accepted by many. Management of the physiological disturbances in the human body before securing an airway is being emphasized upon. In trauma, the ATLS would still recommend to secure an airway before managing the shock and preintubation resuscitation. ATLS as a basic course to provide guidance and direction in trauma management is what we recommend.

In this chapter, we attempt to provide the latest evidence-based approach to trauma etiology, pathophysiology, and resuscitation.

SCIENCE BEHIND TRAUMA RESUSCITATION

Blood loss and traumatic brain injury (TBI) are the two leading causes of mortality following trauma. The above two are responsible for more than three fourths of injury-related deaths. Hemorrhagic shock and trauma-induced coagulopathy (TIC) are responsible for >50% of trauma-related deaths alone. Most preventable in-hospital deaths in trauma are attributed to uncontrolled hemorrhage and resultant coagulopathies.

Trauma-induced coagulopathy is a hypercoagulable state which occurs in the most severely injured patients. Acute traumatic coagulopathy (ATC) is an endogenous coagulopathy which may be present in approximately a fourth of patients wheeled into the emergency department (ED). Patients presenting with ATC are four times more likely to die, require massive transfusion, and develop multiple organ failure. ATC is induced by the combination of trauma and shock and is driven by the degree of tissue hypoperfusion. The underlying mechanism appears to include a systemic activation of the anticoagulant protein C pathway and generation of activated protein C. This leads to a reduction in thrombin generation through the inhibition of factors V and VIII, reduced fibrinogen utilization, and hyperfibrinolysis. ATC also seems to cause platelet dysfunction, with reduced aggregation in response to all standard activators, although platelet count is typically maintained after trauma. In other words, TIC/ATC is a multifactorial failure of the coagulation cascade to adequately achieve and sustain hemostasis in massively hemorrhaging trauma patients.

The process of TIC is further augmented by resuscitation-induced coagulopathy which may dominate later in the clinical course. Resuscitation coagulopathy triggers a progressive reduction in procoagulant factors further complicating ATC. Crystalloid and colloid infusions so enthusiastically infused will rapidly dilute circulating coagulation factors, especially when circulating blood volume is already low. This will further worsen the coagulopathy and prognosis for the bleeding trauma patient. Major trauma patients will mostly

present with an established endogenous coagulopathy, which is exacerbated by resuscitation in the face of ongoing bleeding. Damage control resuscitation (DCR) focuses on maintaining the hemostatic potential of blood, by minimizing any resuscitation-induced coagulopathy and correcting any existing coagulopathy. A "resequenced" approach to trauma along with DCR would help the trauma team to manage patients much better and achieve more favorable outcomes for the patient.

RESEQUENCED APPROACH

Case: A 50-year-old male construction worker has a fall from the second floor of a construction site. His Glasgow Coma Scale (GCS) score in the field is 12. In the ED, you evaluate the patient as per the ATLS protocol. His vitals are as follows: Respiratory rate (RR) 28 breaths/min, O_2 saturation 90% on 100% oxygen, heart rate (HR) 115 beats/min (bpm), blood pressure (BP) 103/80 mm Hg, and temperature 98.8°F. His airway is assessed to be patent, and air entry is decreased in the right chest. A focused assessment with sonography in trauma (FAST) examination is positive for free fluid in the right and left upper quadrants. His pelvis is mechanically stable. The peripheral neurologic examination is normal. He has no past medical history, takes no medications, and has no drug allergies.

As per the protocol, your team and you approach the patient in the following sequence:

1. Intubate the patient expecting poor clinical course
2. Chest tube placement
3. Blood product administration and 1–2 L of crystalloid infusion as initial bolus

As soon as you intubate the patient, the BP drops to 60 mm Hg systolic. Suspecting a tension pneumothorax, you do a needle decompression and infuse another liter of crystalloids for the shock. The systolic pressure does not rise till blood products are administered and tranexamic acid (TXA) is given. He is shifted to the radiology department for a computed tomography (CT) scan where his pressure drops again and more blood and fluids are given. He is diagnosed with a frontal hematoma with right-sided pneumothorax with liver and splenic lacerations.

In the "resequenced" approach (**Flowchart 1**), the trauma team needs to address key management priorities. The above mentioned patient requires intubation urgently *but not* immediately, as he is self-ventilating with an oxygen saturation of 90% and is protecting his airway. With a positive FAST and shock index (SI) >1.0, the team leader should choose to achieve hemodynamic optimization before rapid-sequence intubation (RSI), specifically a presumed right-sided tension pneumothorax and intra-abdominal injury. Studies have shown that unstable preintubation hemodynamic if not corrected can lead to devastating outcomes for the patient. These range from severe cardiovascular collapse to cardiac arrests. Optimization and resuscitation prior to endotracheal intubation are now becoming a norm. Resuscitation followed by intubation is also now commonly known as resuscitation-sequence intubation. An important clue to the presence of shock and occult shock is the SI which is defined as the HR divided by the systolic blood pressure (SBP). It is sensitive for predicting critical bleeding, the need for blood products, and the incidence of postintubation hypotension. The team leader should use the resequenced approach by outlining management priorities in the following sequence:

1. Blood product administration and massive transfusion protocol (MTP) activation
2. Right chest decompression with finger thoracostomy
3. RSI using a reduced dose of ketamine

The team should perform regular airway and neurologic evaluations to monitor for clinical deterioration that may warrant more rapid airway intervention. Following finger thoracostomy, the patient's oxygen saturation improves to 95%. Two units of uncrossed packed red blood cells (PRBCs) are administered, HR decreases to 80 bpm, and BP remains 105/50 mm Hg. An uncomplicated and uneventful RSI is performed using a reduced dose of ketamine (0.5 mg/kg). There is no postintubation hypotension. The patient is given postintubation analgesia and sedation and remains hemodynamically appropriate during transport to, from, and during CT imaging. The patient is then shifted to the operating room. In contrast to rigidly following the ATLS algorithm, optimization of the patient's hemodynamic status before intubation results in a more consistent hemodynamic following intubation.

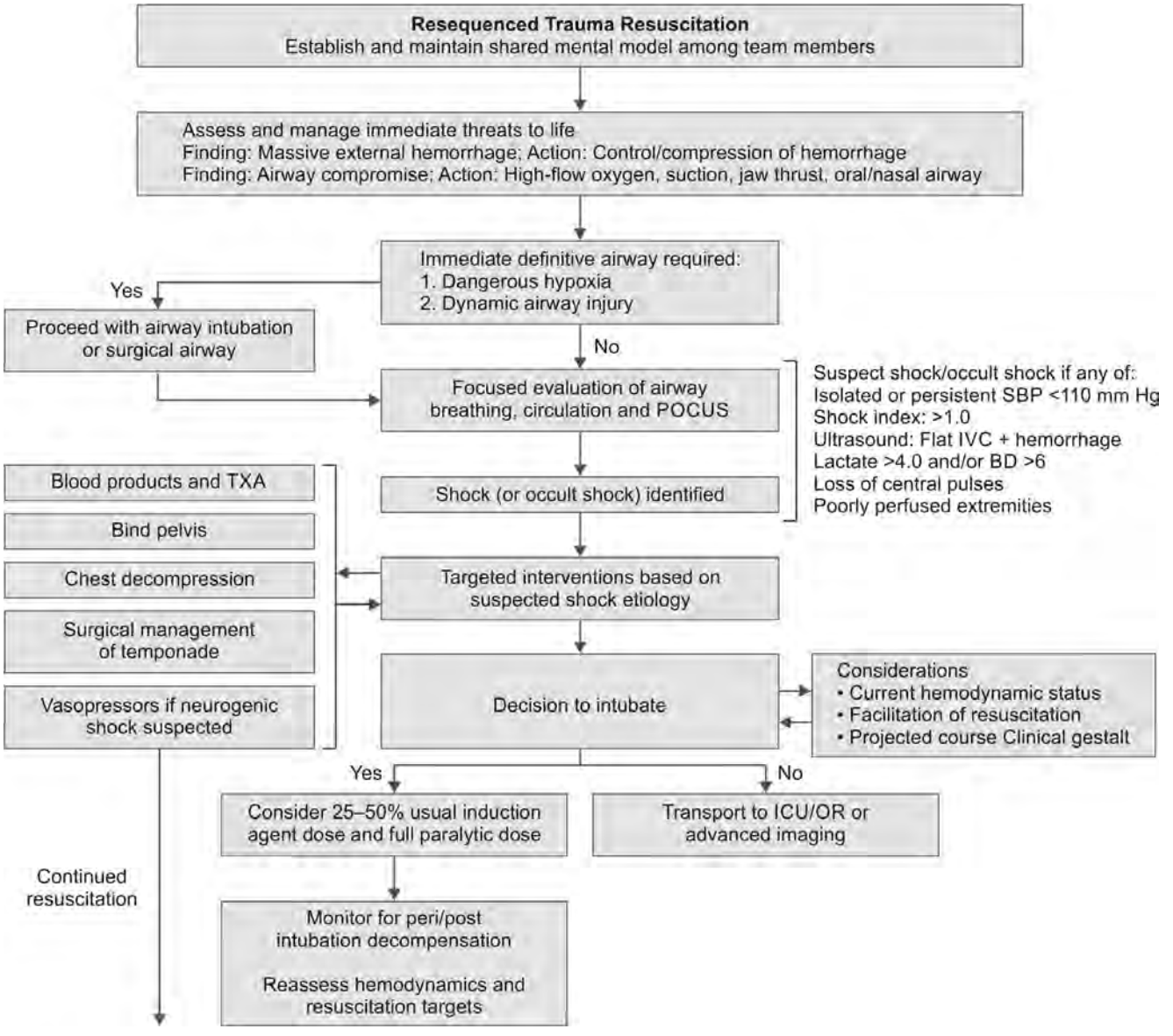
AIRWAY IN TRAUMA

Evaluation of airway remains a mainstay in the management of a trauma patient. As shown in **Flowchart 1**, the decision to intervene with a definitive airway immediately on arrival needs to be assessed by the team leader. Considerable advances in prehospital care, injury prevention, and development of trauma systems have essentially yet not been able to reduce early mortality from trauma.

A "difficult airway" is defined as difficulty in laryngoscopy, bag-mask ventilation (BMV), supraglottic devices, and/or cricothyrotomy. The "physiologically difficult airway" is defined as the nonanatomical factors that can adversely influence the outcome of airway management. Uncorrected hypoxemia, hypocapnia, hypotension, and acidosis can have devastating effects in the peri-intubation period. As a rule, all trauma patients should have their anatomical and physiological difficulties assessed, considered, planned for, and correctly executed as part of airway management plans. The airway can be managed with supportive adjuncts while an airway plan is devised and physiologic risks are assessed and addressed for postintubation hypotension and cardiovascular collapse. Intubations cause increase in intrathoracic pressure and reduced right atrial pressure.

This reversal of intrathoracic physiology has a significant impact on the shock states that are present in trauma patients. In hemorrhagic shock, an already low venous return might decline further with positive-pressure ventilation. In patients of tension pneumothorax or cardiac tamponade, the obstructive shock with reduced venous return may worsen due to positive-pressure ventilation. Focused approach to relieve obstructive causes and optimize hemodynamic in hemorrhagic shock will establish safer peri and postintubation conditions. Conditions in which immediate airway management would be required are as follows:

- *Critical hypoxemia*, even after high flow oxygen and other supportive measures


Resequenced Trauma Resuscitation
Establish and maintain shared mental model among team members
Assess and manage immediate threats to life
Finding: Massive external hemorrhage; Action: Control/compression of hemorrhage
Finding: Airway compromise; Action: High-flow oxygen, suction, jaw thrust, oral/nasal airway
Immediate definitive airway required:
1. Dangerous hypoxia
2. Dynamic airway injury
Yes
Proceed with airway intubation or surgical airway
No
Focused evaluation of airway breathing, circulation and POCUS
Suspect shock/occult shock if any of:
Isolated or persistent SBP <110 mm Hg
Shock index: >1.0
Ultrasound: Flat IVC + hemorrhage
Lactate >4.0 and/or BD >6
Loss of central pulses
Poorly perfused extremities
Shock (or occult shock) identified
Blood products and TXA
Bind pelvis
Chest decompression
Surgical management of temponade
Vasopressors if neurogenic shock suspected
Targeted interventions based on suspected shock etiology
Decision to intubate
Considerations
• Current hemodynamic status
• Facilitation of resuscitation
• Projected course Clinical gestalt
Yes
No
Consider 25–50% usual induction agent dose and full paralytic dose
Transport to ICU/OR or advanced imaging
Continued resuscitation
Monitor for peri/post intubation decompensation
Reassess hemodynamics and resuscitation targets

(BD: base deficit; ICU: intensive care unit; IVC: inferior vena cava; OR: operating room; POCUS: point-of-care ultrasound; SBP: systolic blood pressure; TXA: tranexamic acid)

FLOWCHART 1: An algorithm that focuses on intubation after resuscitation of a trauma patient has begun unless life-threatening hypoxia or dynamic airway injuries are present. It emphasizes on immediate threats to life first and subsequently on the identification and focused management of shock and occult causes of shock.

- *Dynamic airway*—blunt, penetrating, or burn injuries to the head, neck, face, oropharynx that may compromise oxygenation, ventilation, or airway management

These conditions (requiring immediate definitive airways on arrival to the ED) are a small percentage of patients with trauma. Even when the airway is a priority, concurrent management of the shock states should be established. Most patients benefit from aggressive resuscitation before intubations. Interventions include that:

- Achieve hemostasis
- Relieve obstructions
- Optimize perfusions

Once these interventions are completed (time taken will largely depend on the size and training of the trauma team), one should proceed with definitive airway management.

RECOGNITION OF SHOCK, OCCULT SHOCK, AND BLEEDING PATIENT

Shock is a clinical state defined by circulatory failure resulting in insufficient cellular oxygen use, and manifests with clinical and hemodynamic derangements. Homeostasis with peripheral vasoconstriction preserves BP as circulating volume is progressively lost. This potentially leads to inadequate cardiac output for organ perfusion even though BP remains within the normal range. Thus, in trauma patients, it is important to note that adequate cardiac output cannot be inferred from BP in isolation. Only when the blood loss has reached a critical stage, or is rapid, is there a relationship between the two. Patients with overt hypovolemic shock characterized by hypotension, tachycardia, and overt blood loss are easily and readily

identified. But trauma patients may be shocked despite normal BP and pulse, termed cryptic or occult shock; this is when we lose patients and is associated with increased mortality.

Multiple strategies have been proposed using biomarkers [lactate, base deficit (BD)], vital signs (BP, HR), or SI, each of which has specific benefits and limitations for the early identification of occult shock. Early shock identification is critical in order to prevent clinical deterioration and refractory shock states. Early identification of shock in patients with trauma can be a challenging task, especially in the presence of occult shock. Variable pathophysiologic and compensatory mechanisms produce a range of hemodynamic presentations that complicate assessment. During the initial resuscitation period, the indices for shock identification can be organized into two broad categories: (1) Clinical indicators; and (2) Laboratory indicators.

Clinical Indicators: Obtained Exclusively at the Bedside

Vital Signs

Vital signs should be obtained immediately on patient arrival and repeated frequently. Trends in vital signs are often more informative than a single, static measurement. Prehospital vital signs should be informed to the ED before arrival. This will help prepare the trauma team to manage the patient in a more streamlined fashion. Despite their limitations, vital signs are still a central element of the trauma primary survey.

Shock Index

The SI is a simple ratio of HR and can be easily calculated in the field and in the ED. HR divided by the SBP is defined as shock index. A value of 0.7 represents normal SI, whereas SI of >1.0 is highly indicative of hemodynamic instability and mortality. The SI is useful because of its simplicity, strong inter-rater reliability, and accuracy as a predictor of blood loss in trauma patients. SI should be calculated for all patients of trauma. If SI ≥ 1.0, discuss concerns regarding shock with your team. Look for any signs of occult bleeding or obstructive cause. Give TXA and blood products if SI ≥ 1.0 and hemorrhage are suspected. Studies have shown that prehospital SI ≥ 0.9 increases the chances of massive transfusion in trauma patients. Note should be made that SI can be unreliable in:

- Geriatric age groups who might have altered physiologic parameters
- Presence of underlying medical conditions such as untreated hypertension
- Medication-related disturbances (beta-blockers)

Ultrasonography

The FAST is a routine for all trauma patients. The presence of free fluid in the abdomen guides the clinician toward intra-abdominal injuries as a source of hemorrhagic shock. The extended FAST (eFAST) includes an evaluation of thoracic structures for pneumothorax and hemothorax. Evidences show that eFAST is superior to supine chest radiograph [chest X-ray (CXR)] for detecting pneumothorax. Wilkerson et al. demonstrated that compared to supine CXR, emergency physician (EP)-performed eFAST has superior sensitivity (86–98% vs. 28–75%) and equal specificity (98–100% vs. 100%). All trauma patients should undergo FAST and eFAST examinations for all trauma patients.

Laboratory Indicators: Additional Laboratory Testing Required

Base Deficit

The BD is defined as the number of base units required to return the pH of whole blood to 7.4, assuming a normal pCO_2. BD has a close correlation with transfusion requirements, injury severity, and mortality in trauma patients. The higher the BD, the more likely is the patient to receive massive transfusions and more likely to die. It is particularly valuable during the initial phases of resuscitation, because an increased BD can help identify patients who will decompensate. In severely injured patients with prehospital hypotension who are normotensive in the ED, a BD of >6 was predictive of both recurrent hypotension and death (five-fold mortality increase) compared with those with a BD < 6. A BD > 6 detected patients with transient hypotension who were likely to crump (a term used to describe acute and unexpected physiologic deterioration) again. BD > 6 is a useful tool for prognostication and to guide trauma clinicians in the resuscitation of patients.

Lactate

Initial serum lactate levels may be used as an indicator for prognosis and mortality of the trauma patient. Studies have shown conflicting conclusions. Gale and colleagues concluded that the initial lactate level is a superior prognostic marker for in-hospital mortality. Freitas et al. concluded that there was no correlation between admission lactate and mortality in trauma patients. Caputo and colleagues found that lactate and BD had similar test characteristics for predicting shock, defined as the need for operative intervention or massive transfusion. Given all the evidence, it is imperative for the EP to realize that derangement in lactates and BD > 6 should initiate the search for occult shock if not otherwise obvious.

International Normalized Ratio and Viscoelastic Assays

On arrival in the ED, 25–30% of severely injured patients are coagulopathic and fail to form adequate clots in response to hemorrhage. This early trauma coagulopathy [acute coagulopathy of trauma and shock (ACoTS)] is associated with a 4-fold increase in mortality and high rates of organ failure, highlighting the importance of early identification. Initial abnormal coagulation markers such as prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) have been linked to higher mortality rates in trauma patients. A deranged INR has also been shown to be a good predictor of mortality in trauma patients with a high diagnostic accuracy.

Two point-of-care viscoelastic assays have emerged as promising alternatives for early coagulopathy detection in trauma: Thromboelastography (TEG) and rotational thromboelastometry (ROTEM). These assays have not been extensively studied yet but are still recommended in the European

trauma guidelines. For decades, ED physicians have been applying the ATLS shock classification to predict the amount of blood loss—a system comprising four shock classes using vital signs and mental status. The global application of this classification occurred without formal study, evidence, or validation. Recently, the accuracy of these classifications has been called into question.

Trauma files from 1989 to 2007 of the United Kingdom Trauma Registry when audited demonstrated that patients progressing to stage 4 shock (>2 L of blood loss) increased HR from 82 to 95 bpm, while showing no significant changes in GCS, RR, or SBP. The ATLS shock categories are also inaccurate in geriatric patients with trauma and do not account for other causes of shock (obstructive, neurogenic) or mixed shock causes. There is no single indicator that can reliably predict shock or mortality in trauma patients. It is suggested that a combination of the indicators is used by the clinician to come up with a management plan for the trauma patient in shock.

DAMAGE CONTROL RESUSCITATION

The most dynamic and dramatic changes have occurred in the management of the actively bleeding patient. The spectrum has shifted from giving crystalloid boluses to blood product resuscitation. DCR strategies are the measures that directly address TIC. The key elements of DCR are:

- Hemostatic resuscitation
- Permissive hypotension
- Damage control surgery

Hemostatic Resuscitation

The most effective resuscitation fluid in trauma patients is their own blood. Minimizing blood loss and preserving the circulating blood volume are of utmost importance. Techniques include minimal handling, direct pressure on wounds, early closed reduction and immobilization of fractures, hemostatic drugs and blood products, and surgical or radiological interventions for hemorrhage control. Hemostatic resuscitation has two main aims: (1) Arrest hemorrhage; and (2) Prevention and correction of TIC.

Arresting Hemorrhage

Arresting bleeding and restoring blood volume are recognized as the most important step in the management of the severe trauma patient. External hemorrhage can be compressed by applying direct pressure to the site or using tourniquets. There are certain anatomic regions (groin, axilla, neck) that prove difficult for standard tourniquet use. Junctional tourniquets (for injuries in the inguinal and axillary regions) and hemostatic dressings have been developed to control proximal bleeding. A systematic review in healthy volunteers demonstrated the ability to occlude blood flow using four different junctional tourniquets with acceptable effectiveness. Although studies in trauma patient are lacking. Hemostatic dressings which can be applied directly over the wound have been evolving since 2003. These dressings have been used extensively in combat and war zones, but civilian data are still lacking. Nonetheless, using these dressings for hemorrhaging patients would not harm.

Prevention and Correction of Trauma-induced Coagulopathy

Tranexamic acid: The CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2) trial along with other civilian and military studies has shown that TXA administration in trauma patients reduces mortality. It is the only antifibrinolytic of choice for trauma patients across the world. TXA should be given at the earliest and has also shown to reduce head injury-related deaths. Empirically, TXA has been recommended to be given to all patients with severe trauma and in shock. In combat studies, empiric use of TXA has shown the greatest benefit in patients who subsequently required a massive transfusion. TIC is driven by shock, so we recommend to administer TXA to all trauma patients in shock or who are likely to develop shock.

Prevention of Resuscitation Coagulopathy

Resuscitation coagulopathy or acute coagulopathy of resuscitation (ACOR) is mitigated by transfusing balanced blood products (and not crystalloids which lead to dilution and TIC) using a regimen that approaches whole blood. This implies transfusing equal ratios of packed red cells, platelets, and plasma. It has been shown that a 1:1:1 transfusion ratio of platelets, plasma, and packed red cells achieved hemostasis in more patients and had lower deaths due to exsanguination than a 1:1:2 transfusion regimen. Data from multiple studies show that blood component transfusion in massive trauma reduced mortality and improved outcomes.

To minimize the development of a dilutional coagulopathy or ACOR, DCR principles advocate for the minimal (or none) use of crystalloids and the use of plasma, red blood cells (RBCs), and platelets in a 1:1:1 ratio for patients at high risk of death secondary to hemorrhage from traumatic injuries.

Massive Transfusion Protocols

The MTPs are central to DCR and designed to specifically target TIC. Protocolized transfusion avoids dilutional coagulopathy through the empiric provision of RBCs with simultaneous, high-dose clotting products (plasma, cryoprecipitate or fibrinogen concentrate, and platelets). To enable rapid delivery of a 1:1:1 strategy, MTPs are activated based on physiology and suspected active hemorrhage rather than on the diagnosis of coagulopathy. The development of a MTP for patients with severe life-threatening bleeding is important to standardize the approach to such patients and to provide structure, organization, and calmness to what is usually a tumultuous situation. Cotton et al. have studied the clinical effect of the implementation of a standardized MTP compared to historical controls and have documented improved survival and decreased organ failure. Volume resuscitation with RBCs and clotting products from the time of arrival of the severely injured patient avoid the unnecessary use of crystalloids, with blood banks providing a continuous supply of "transfusion packs" until hemorrhage control is achieved through damage control surgery or interventional radiology.

Fibrinogen Therapy

The US Military retrospective review has determined that fibrinogen transfusion had better outcomes and reduces death due to hemorrhage. If fibrinogen replacement is incorporated into MTPs, it is usually relatively late in the transfusion sequence and at a relatively low dose. Some studies have shown that fibrinogen concentrates can be administered rapidly to bleeding trauma patients in both in-hospital and prehospital environments with improvements in functional fibrinogen and plasma fibrinogen levels, while other studies are ongoing.

Calcium

Calcium is a cofactor in the procoagulant clotting proteases. Its levels rapidly fall during massive bleeding. Low ionized calcium has been associated with increased mortality and greater transfusion requirements. Levels should be checked regularly during resuscitation and replaced to maintain levels within the normal range.

Rewarming

In DCR, hypothermia should be managed in conjunction with the efforts to correct the trauma-induced coagulopathy. It is essential to rewarm the torso using passive warming measures, such as insulating foil, blankets, and removal of wet clothes. Hypothermia in trauma can lead to worsening of acidosis and in turn worsen TIC and increase mortality. TIC is multifactorial, with varying degrees of dysfibrinogenemia, hyperfibrinolysis, endothelial dysfunction, and impaired platelet activity. Although most coagulation therapy is empiric, it is of utmost importance to monitor coagulation status to ensure that a hemostatic state is maintained. Point-of-care coagulation monitoring may allow for a more focused approach to the management of TIC during DCR. Early endogenous processes that trigger the adverse response in the coagulation system depend on the severity of trauma and the level of hemorrhagic shock. DCR and the use of MTPs are associated with improved outcomes in TIC.

Permissive Hypotension

Normalization of BP should not be the goal during trauma resuscitation at any point of time. The use of permissive hypotension as a strategy to minimize active bleeding was established in the nineties for ruptured abdominal aneurysms. Permissive hypotension or hypotensive resuscitation, in other words, strategizes the use of limited or no fluids and blood products to maintain a lower than normal BP unless the bleeding has been controlled surgically or radiologically. The aim is to avoid "*popping the clot*" while still maintaining oxygen perfusion to all tissues. Permissive hypotension is by far the most difficult concept to understand and implement as part of the DCR strategies. Giving fluid infusions will cause dilutional coagulopathy, anemia, endothelial damage, and tissue edema, all of which are associated with poor outcomes. High-volume fluid resuscitation causes an increase in trauma-related bleeding, multiorgan failure, and death.

A mean arterial pressure (MAP) of 65 mm Hg should be targeted during hypotensive resuscitation in the trauma patient. One has to be sure that there are no TBIs and the patient is perfusing well at this MAP. If MAP increases beyond 65 mm Hg, one can give fentanyl in 25–50 μg aliquots to bring it down. If it drops below 65 mm Hg, then blood products can be given to bring it to target.

The place of vasopressors in early trauma resuscitation is still controversial. We can maintain BPs above coronary artery perfusion pressure with blood products and early surgical intervention, where required. Permissive hypotension in TBI is still controversial. Hemorrhaging patients with TBI usually have a poorer outcome than those who do not suffer from TBI. Experimental studies have shown that in the setting of hemorrhage and TBI combined, aggressive fluid resuscitation and higher BP targets led to increased cerebral edema, increased intracranial pressures, and mortality. The National Institute for Clinical Excellence (NICE) major trauma guideline suggests that the clinician should focus resuscitation on the predominant injury complex, so a restrictive fluid administration is advocated where bleeding is the dominant pathology being treated. They suggest to use a less restrictive strategy if TBI is the dominant component in the trauma patient to maintain cerebral perfusion.

Permissive hypotension is now an integral part of the DCR strategy in trauma centers throughout the world. One needs to understand that it is a temporizing measure until full hemorrhage control has been achieved by surgery. It is important to realize that hemorrhage control is the goal and not normalization of the BP.

Damage Control Surgery

This is the final cog in the wheel of DCR. Post resuscitation of the trauma patient using all the above techniques, the patient needs to be wheeled for surgery for definite hemorrhage control. Till now, the aim of trauma management in the ED was to ensure that the patient stays alive using the best possible methods and techniques and also does not succumb during or post surgery. Abdominal injuries' damage control entails rapid celiotomy, control of hemorrhage, minimizing contamination, and temporary abdominal closure. Surgical bleeding may be controlled by a combination of packing, clamping, and ligation. Splenectomy and nephrectomy may also be required. Thoracic injuries are more challenging as it is very difficult to achieve hemostasis in these patients. Rapid and definitive control of hemorrhage is required. Pulmonary tractotomy can accomplish rapid control of bleeding in penetrating lung injuries. Vascular injuries can be temporarily controlled by simpler techniques such as ligation, lateral repairs, and temporary shunts. Once coagulopathies are corrected and physiology is normalized, more complex procedures such as vascular reconstructions and patch angioplasties can be undertaken. The critical component of head injury management is the prevention of secondary brain injury.

It is important for trauma providers to be updated regarding DCR strategies as they are clearly lifesaving in many polytrauma patients. The concept has been upgraded and modified over many years, and it is clear that there will be a constant change in guidelines. As trauma is so dynamic, the guidelines will have to be dynamic too.

SUMMARY

The identification and resuscitation of the shocked patients with trauma is a complex and dynamic condition. The traditional rigid approach advocated by ATLS can at times lead

to ineffective prioritization of critical injuries in favor of less urgent interventions. This chapter proposed the application of evidence-based techniques for shock identification combined with trauma resuscitation guided by physiologic priorities. A newer approach in trauma resuscitation represents a unique and important cultural shift in trauma care. It emphasizes upon physiologic optimization before intubation. This "resequenced" approach first addresses immediate threats to life followed by targeted treatment strategies for the diagnosis and management of shock causes. It is both practical and feasible across the varied spectrum of settings in which trauma care is provided across the globe. Some salient points to remember in trauma resuscitation are provided in **Box 1**. Improved resuscitation strategies will inevitably optimize outcomes for patients with trauma. As mentioned before, trauma resuscitation is dynamic and undergoing continuous research. It is recommended for all emergency medicine physicians to stay updated with what is vogue in trauma.

BOX 1: Important points to remember while managing the critically injured.

- Unless critical hypoxia or dynamic airway, defer definitive airway (provide temporizing measures)
- Look for occult shock
- Manage immediate threats to life
- Use clinical and laboratory values—shock index, lactates, base deficit, FAST
- Use tranexamic acid early
- Use the 1:1:1 transfusion protocol of FFP, platelets, and packed red cells
- Permissive hypotension in bleeding patient, avoid crystalloid transfusions
- Reduce dose of induction agent to half in the shocked patient. Normal dose of paralytic

(FAST: focused abdominal sonography in trauma; FFP: fresh frozen plasma)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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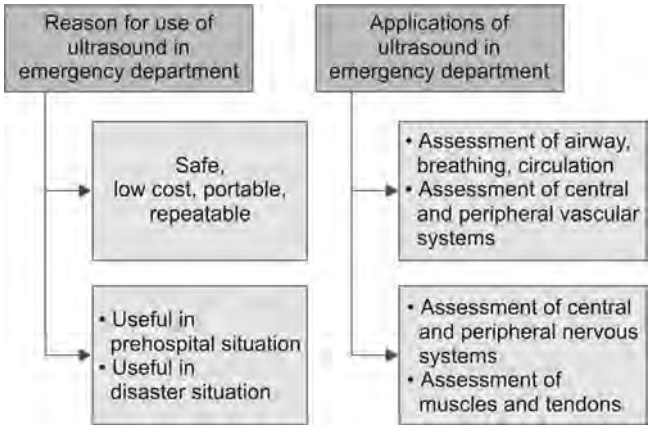
CHAPTER

Focused Assessment with Sonography in Trauma

Devendra Richhariya

INTRODUCTION

Traumatic injury remains the leading cause of death in all age groups and result in a substantial proportion of patients with injuries from blunt abdominal and/or chest trauma treated in emergency departments. Three decades ago, the advent of focused assessment with sonography in trauma (FAST) enabled the clinicians to rapidly screen for injury at the bedside of patients, especially in hemodynamically unstable patients who are not suitable for transfer to the computed tomography (CT) suite. The identification of free fluid within the peritoneal cavity, pericardium, and pleural spaces can be accomplished immediately at patient arrival to the hospital. Usefulness of FAST starts with prehospital transport and multiple casualty settings as a triage tool and further extends toward detection of solid-organ injury, pneumothorax, fractures, and serial examinations. As a radiologist relies more on CT than ultrasound (US) in cases of trauma, use of FAST has migrated to first responders or the emergency physician. In the emergency department, FAST is also typically used as the patient's initial imaging examination at arrival. There are quite a few reasons behind usefulness of ultrasonography (USG) in the emergency department, e.g., safety, low cost, portable, repeatable (**Flowchart 1**). Since the original description of the use of USG in a trauma patient is well known, several new applications of the use of USG in trauma patients have also been described.


Reason for use of ultrasound in emergency department
Applications of ultrasound in emergency department
Safe, low cost, portable, repeatable
• Useful in prehospital situation
• Useful in disaster situation
• Assessment of airway, breathing, circulation
• Assessment of central and peripheral vascular systems
• Assessment of central and peripheral nervous systems
• Assessment of muscles and tendons

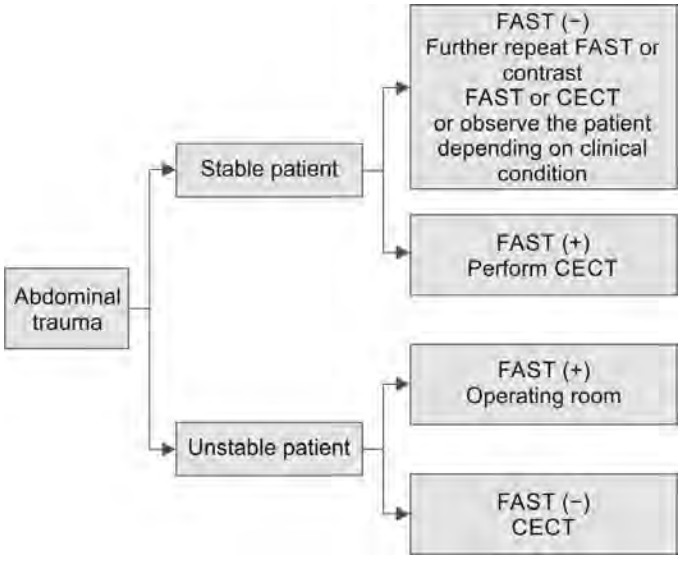
FLOWCHART 1: Usefulness of ultrasound in the emergency department.

EVOLUTION OF FAST

For the examination of trauma patients, USG was first utilized in the 1970s in Europe but until 1990s it was not utilized widely, during which time the FAST acronym was pronounced as "focused abdominal sonography for trauma." Over time, USG was used for more comprehensive examination; hence, the FAST acronym was changed to "focused assessment with sonography for trauma." Since then, FAST has become the common initial screening modality in the majority of trauma centers worldwide, and it is also included in the advanced trauma life support (ATLS) program for evaluation of the trauma patient. A unique aspect of FAST is that, with variable training and experience, it can be routinely utilized by radiologists, emergency physicians, and surgeons.

ACCURACY OF FAST AND CLINICAL DECISION-MAKING

Studies were published regarding sensitivity and specificity for detecting hemoperitoneum which were 80% (Asher and colleagues in 1978) and 70–98% (various studies in the 1990s), respectively. Initially, the outcome was measured and compared with the patient's outcome and not with CT scan, so sensitivity was reported high in studies which were done in the early 1990s. One of the first studies that compared FAST to CT scan showed a lower sensitivity of 65% for FAST in detecting solid-organ injuries. The low sensitivity is due to detection of an isolated solid injury by CT scan without hemoperitoneum. Carter et al. reported a sensitivity of 22% in a retrospective study of 1,671 blunt abdominal trauma patients (25 of 114) in hemodynamically stable patients and 28% (nine of 32) in unstable patients, and they concluded that an intra-abdominal injury may be missed if a negative FAST study was not followed up with further CT scan. It is now well recognized that intra-abdominal injuries may remain underdiagnosed with FAST, so in cases of negative FAST further diagnostic testing with a CT scan of abdomen should be taken on the



(CECT: contrast-enhanced computed tomography; FAST: focused assessment with sonography in trauma)

FLOWCHART 2: Diagnostic algorithm for the use of FAST for triaging of a trauma patient.

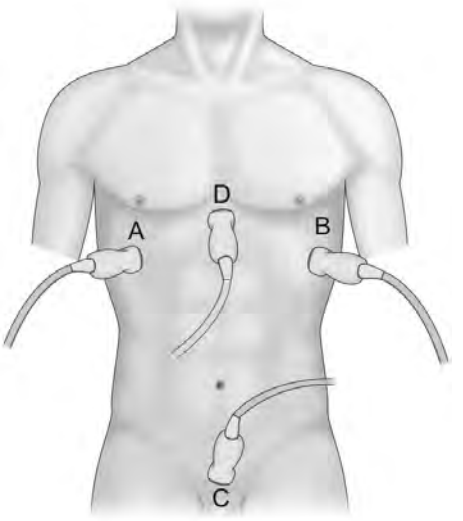


FIG. 1: The four views for the original FAST scan: A = right upper quadrant, B = left upper quadrant, C = suprapubic view, D = subxiphoid view of the heart.

basis of clinical suspicion, mechanism of injury, and change in clinical examination or hemodynamic status (**Flowchart 2**). For patients with a negative FAST study, observation, serial FAST, CT scan, or contrast material—enhanced USG may be chosen. Use of FAST in the evaluation of unstable, hypotensive trauma patients is also recommended. The most effective use of FAST has been rapid triage of hemodynamically unstable trauma patients to definitive intervention, leading to reduced time to appropriate intervention, shortened hospital stays, and lower costs. The need for diagnostic peritoneal lavage (DPL) is also shown to reduce with the FAST examination with one prospective study of 194 patients reporting a reduction from 9 (17 of 194) to 1% (two of 194).

FIG. 2: Fluid in Morison pouch.

FAST TECHNIQUE AND INTERPRETATION

In the evaluation of the trauma patient, probe selection is dependent on what is the main focus of the examination. A multipurpose probe (3–5-MHz sector probe) is best utilized and appropriate for examining solid organs as well as for determining the presence of free fluid in the abdomen or pelvis (**Fig. 1**). A sector scanner can be used to examine the heart for a pericardial effusion or hemorrhage and is also useful to scan between the ribs for pneumothorax. A curved-array transducer is used for better visualization of the abdomen but for imaging of the heart or lung, a curved-array transducer is not ideal, especially when scanning in the intercostal spaces. For detection of pneumothorax, the linear-array transducer probe is placed parallel to the ribs in the intercostal space. The original FAST scan included views of (1) The right upper quadrant, which included the perihepatic area and hepatorenal recess or Morison pouch (**Fig. 2**); (2) The left upper quadrant, encompassing the perisplenic view; (3) The suprapubic view (pouch of Douglas) (**Fig. 3**); and later (4) A subxiphoid pericardial view. The first site which should be scanned for

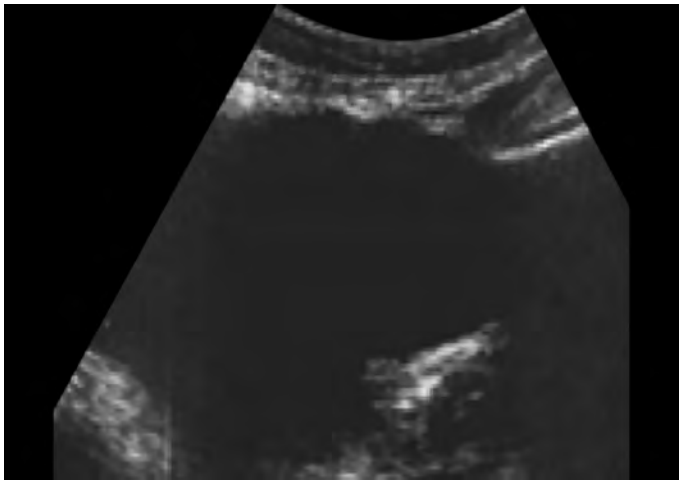


FIG. 3: Fluid in the pouch of Douglas.

detection of free fluid with FAST is the right upper quadrant by using a lower frequency (3.5–5 MHz) sector or curved-array transducer. For examining the hepatorenal fossa or deep pelvis, a sector transducer with far-field optimization is ideal for best visualization. For optimized and deep penetration, a curved-array transducer may also be used. The liver serves as a convenient acoustic window to examine the hepatorenal space and liver parenchyma. As compared with adjacent solid organs, the hemoperitoneum usually appears anechoic or hypoechoic. Prolonged hemorrhage may organize and visualize as more echogenic.

The left upper quadrant view is scanned next and the spleen is targeted for examination in the splenorenal fossa and perisplenic area. Visualization of the left pleural space is performed by cephalad scanning. The probe is moved caudally to visualize the inferior pole of the left kidney and paracolic gutter. Due to difficult physical access, the perisplenic area may be difficult to scan; this may be overcome by rolling the patient to the right side, as small amounts of free fluid may collect superiorly to the spleen.

The suprapubic view allows assessment of the peritoneal cavity which is the most dependent space of the abdomen. The transducer should be placed above the pubic symphysis in a sagittal plane and moved side to side and then rotated transversely and repeatedly. The chances of detection of free fluid in the pelvis are more in reverse Trendelenburg positioning. Small amounts of free fluid of up to 50 mL in the pouch of Douglas are considered physiologic in female patients of reproductive age, and amounts >50 mL should be regarded as pathologic in the setting of trauma. Free fluid should not be found at the rectovesicular space in men, assuming that there is no injury or other pathologic conditions.

Limitations

Regardless of the protocol used, there are limitations to the FAST examination because blunt (mesenteric, bowel, diaphragmatic, and retroperitoneal) as well as isolated penetrating injury to the peritoneum can be difficult to detect during the abdominal examination. False-positive scans may occur due to the presence of ascites, peritoneal dialysate, ventriculoperitoneal shunt outflow, ovarian hyperstimulation, and ovarian cyst rupture. False positive FAST examination may also be evident after large volume fluid resuscitation; transudation of fluid from intravascular area to intraperitoneal area. Although in trauma patients, free fluid detected with FAST is assumed to be hemoperitoneum, it can also be trauma-related urine, bile, and bowel contents. Common obstacles to USG visualization are bowel gas, subcutaneous emphysema, and obesity. Patients who present late after trauma or hemoperitoneum (contain clots) may be missed on FAST due to mixed echogenicity. Perinephric fat may be misinterpreted as free fluid or subcapsular hematoma due to widening of the hepatorenal and splenorenal interface, also known as the "double-line" sign. In these cases, compare the views of each kidney. The certain amount of volume of free fluid necessary to be detected by FAST is the limitation. Visualization of free fluid in the splenorenal and hepatorenal interface can be improved by the Trendelenburg position.

NEWER PROTOCOLS AND EXTENDED FAST

Evaluation of the thorax is also added later on in the traditional FAST examination to detect pneumothorax , thus resulting in extended focused assessment with sonography in trauma (eFAST). The protocol for evaluation of shock, respiratory distress, and cardiac arrest is also added, e.g., protocol for evaluation of dyspnea: BLUE (bedside lung USG in emergency) and RADIUS (rapid assessment of dyspnea with USG). The BLUE protocol includes only lung USG for detection of pneumothoraces as well as pulmonary edema, consolidation, and effusion. The RADIUS protocol is similar to BLUE but also includes evaluation of cardiac and inferior vena cava (IVC).

The RUSH (rapid USG for shock and hypotension) protocol was simplified and described as an examination of the (1) pump, (2) tank, and (3) pipes for better understanding. The "pump" evaluation includes parasternal long and short axes of the heart plus subxiphoid and apical views. The "tank" evaluation involves interrogation of the IVC, FAST examination of the abdomen including pleural views, and US of the lung. The "pipes" portion of RUSH involves visualization of the suprasternal, parasternal, epigastric, and supraumbilical aorta, with additional scans of the femoral and popliteal veins for deep venous thrombosis. The RUSH examination is not specifically for trauma patients; thus the "pipes" portion of the protocol is usually not necessary in the setting of acute trauma.

The number of different protocols for evaluation of the critically injured is a source of confusion. The most practical and time efficient of these protocols are the eFAST examination, which includes evaluation for pneumothorax, and portions of the RUSH examination, which include a brief subcostal view of the heart and evaluation of the IVC (**Fig. 4**). The selective use of eFAST and RUSH specifically for the setting of trauma is discussed below:

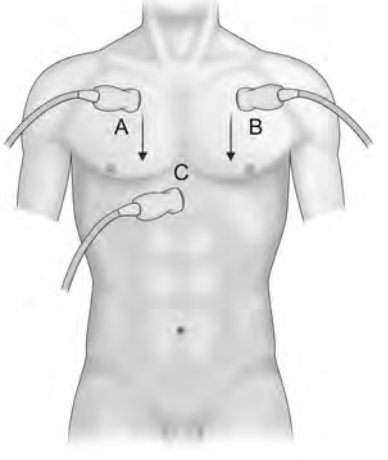


FIG. 4: Additional views that may be helpful in the trauma patient: A = right parasagittal view of the lung for pneumothorax, B = left parasagittal view of the lung for pneumothorax, C = a longitudinal view of the inferior vena cava.

HEART

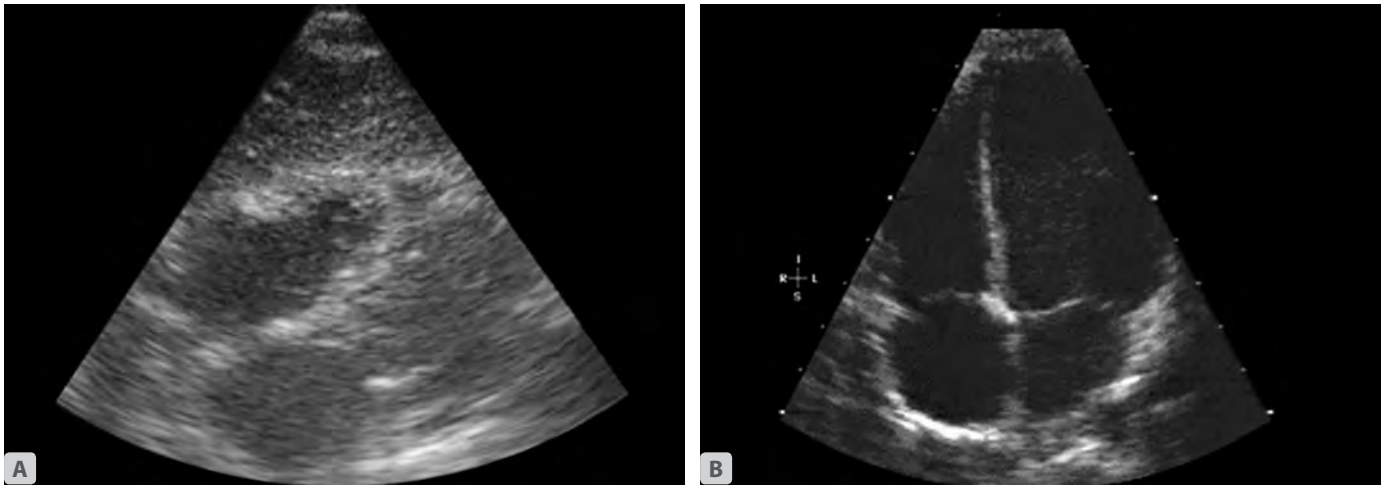
Subxiphoid images of the heart are visualized by keeping the transducer on the upper abdomen and pointing superiorly toward the left shoulder. The volume status of heart can be visualized and assessed (**Figs. 5A** and **B**). Fluid surrounding the heart is seen as an anechoic space surrounding the myocardium and/or ventricle (**Fig. 6**). The liver aids as an acoustic window. If there is difficulty in obtaining the subxiphoid view, parasternal, apical four chamber, and subcostal approach may be attempted. If a substantial amount of hemopericardium is detected, with diastolic collapse of the right atrium, cardiac tamponade is most likely present. Differentiation between fluid in the posterior pericardial space and fluid in the posteromedial pleural cavity may be difficult to distinguish from each other. For differentiation of the two, visualize the descending thoracic aorta, as pericardial fluid is present anterior to the aorta whereas pleural fluid is present posterior to the aorta. Pericardial cyst, fat pad, and preexisting effusion may give false-positive results for hemopericardium. The subxiphoid pericardial area may be inadequately scanned due to a suboptimal acoustic window but can overcome these limitations by increasing the depth for this view or by performing a left parasternal longitudinal scan for pericardial fluid.

HEMOTHORAX OR PLEURAL EFFUSION

The right pleural space is visualized for free fluid as well as for the area between the dome of the liver and diaphragm. This area appears as an echogenic curvilinear line, and echoes similar to liver parenchyma can be seen superiorly. This mirror image is suggestive of the absence of pleural fluid. During normal lung inspiration, this mirror image may seem distorted intermittently, referred to as the "curtain sign." Based on the composition of pleural fluid (e.g., hemorrhage, exudate, transudate, empyema), images may be anechoic or have mixed echogenicity and atelectatic lung can also be visualized with pleural effusion (**Fig. 7**). Detection of pleural fluid can be improved by upright or reverse Trendelenburg positioning.

PNEUMOTHORAX

There are fewer studies evaluating the accuracy of eFAST (relatively a new protocol) in detecting pneumothorax. The diagnosis of small-to-moderate-sized pneumothoraces



FIGS. 5A AND B: (A) Hypovolemic cardiac chamber; (B) Normovolemic cardiac chambers.

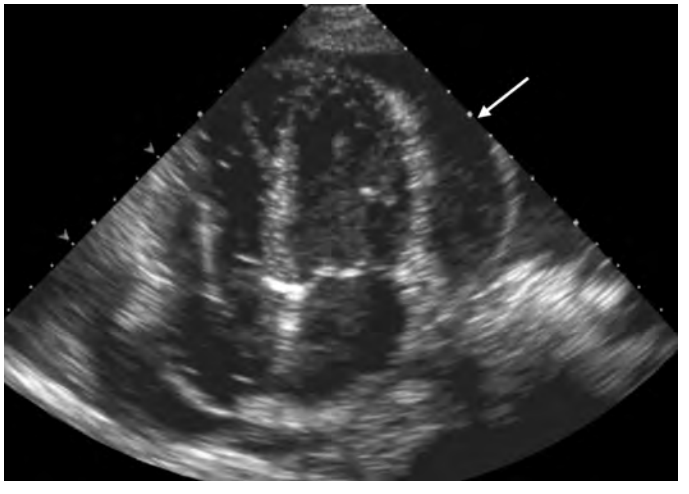


FIG. 6: Pericardial effusion: Four-chamber view of the heart demonstrates moderate-sized pericardial effusion.

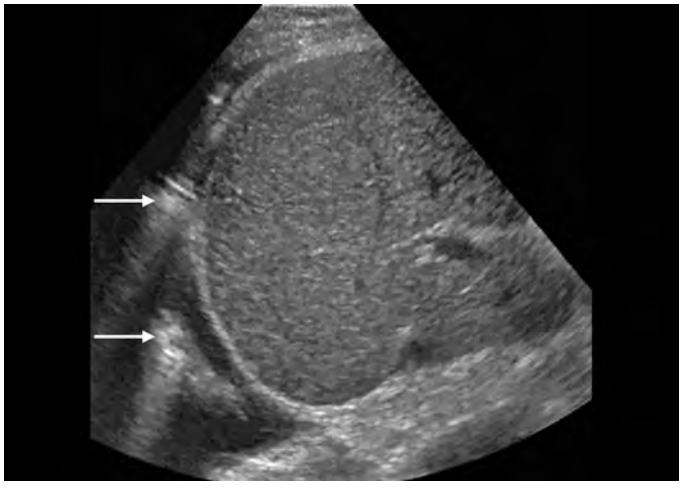


FIG. 7: Pleural effusion and atelectasis. Scan through the liver shows free fluid in the thorax that surrounds the more echogenic lung.

with physical examination and supine chest radiography is challenging, and these occult injuries may be missed in blunt trauma patients. The sensitivity of eFAST is found better than that of supine chest radiography in studies using CT as the reference standard. Kirkpatrick and colleagues performed a prospective blinded study with eFAST in trauma patients and reported a sensitivity of 48.8% for chest USG versus 20.9% for chest radiography. Lanniello and coworkers investigated unstable trauma patients with eFAST and reported a sensitivity of 77% for detection of pneumothorax.

A high-frequency (5-MHz) linear transducer probe is preferred for detection of pneumothorax, but lower frequency sector transducers and even a curved transducer may also be used. The transducer is placed in the second or third intercostal space in the midclavicular line in sagittal orientation and then moved inferiorly (**Fig. 4**). To obtain a larger view of the lung, the probe can also be placed in an oblique fashion between the ribs. Compare the findings of both side of lung, by placing the probe on different positions of anterior chest and also opposite side of the chest. Normal lung can be demonstrated by visualizing the *"sliding lung" sign*, a most helpful USG finding (**Figs. 8A** and **B**). In normal lung, the visceral and parietal pleural interface is always visualized on USG as an echogenic line and the visceral pleura is moved over the parietal pleura (fixed part) giving rise to the *"sliding lung" sign*. If the sliding lung is seen, it excludes pneumothorax at that site. Absence of the normal sliding lung is highly suggestive of pneumothorax but may also be seen in other pathologic conditions where there is no lung movement such as apnea, atelectasis, chronic obstructive pulmonary disease (COPD), bulla formation, pleural thickening, and postpleurodesis. Subcutaneous emphysema can obstruct the visualization of the underlying pleural cavity and is frequently associated with pneumothorax. The severity of illness may also be a factor for absence of lung sliding for detecting pneumothorax in critically ill patients with respiratory failure.

Other findings observed in lung USG are so-called A-lines seen with normal lung, but these are both normal and abnormal A-lines. Normally, A-lines are reverberation artifacts from the visceral and parietal pleura and always equally spaced, horizontal echogenic lines running parallel to the transducer, and are a predominant feature with normal lung. However, abnormal A-lines may be associated with a pneumothorax. "B-lines" are vertical lines extending from the transducer toward the edge of the screen. Both A- and B-lines can be seen in both normal and abnormal lung but with distinction. In normal lung, sliding is always present, the A-lines are perfectly spaced, and the B-lines are very small.

B-lines maybe visualized as many variants including "comet tails," which are thin vertical lines extending only a short distance from the transducer. *With pneumothorax* (1) There is absent sliding lung; (2) A-lines are present, more numerous than normal, and not evenly spaced; and (3) B-lines are no longer present (**Fig. 9**). While small B-lines that do not extend all the way through the image are seen in normal

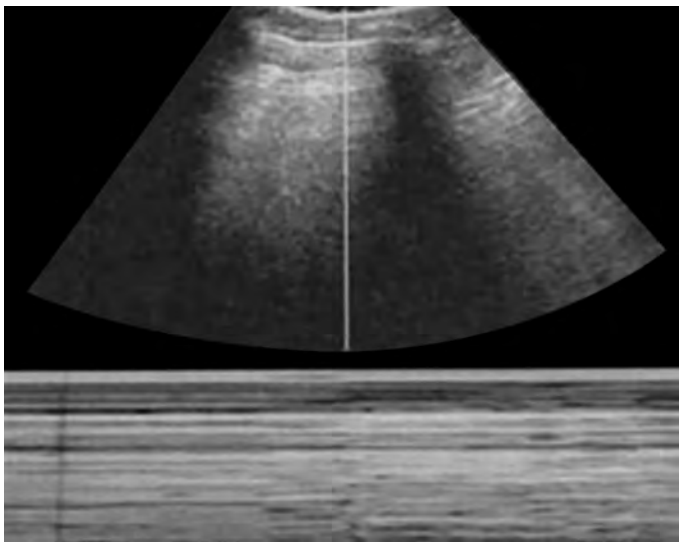
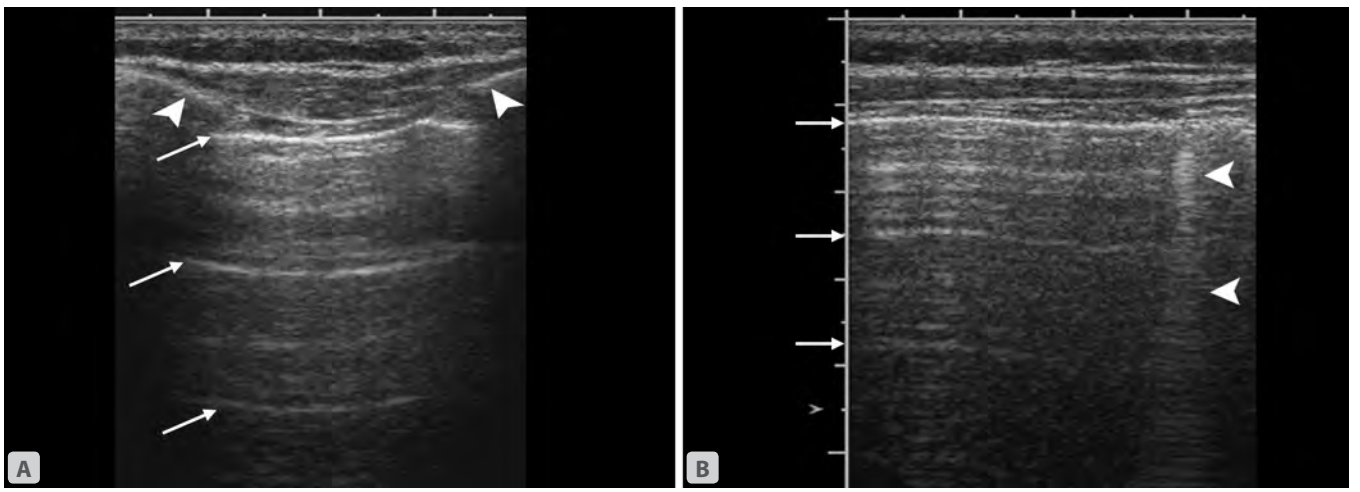


FIG. 9: Right pneumothorax and stratosphere sign with presence of multiple echogenic A-lines but lack of anterior echogenic "sliding lung" interface of parietal/visceral pleura.



FIGS. 8A AND B: Normal lung. (A) Parasagittal view of the lung between the ribs shows shadowing at the anterior ribs (arrowheads). The most anterior echogenic line (arrow just below arrowhead) is the junction of the parietal and visceral pleura, where motion of sliding lung is observed. There are also A-lines (lower two arrows), which are equally spaced reverberation artifacts and decrease in echogenicity with depth. (B) Scan between ribs shows the most echogenic line (anterior arrow) or the junction of parietal and visceral pleura which represents the "sliding lung" sign in real time. Multiple reverberation artifacts are noted (posterior arrows). A- and B-lines or "comet tail" artifact is also seen (arrowheads).

patients, longer and more numerous B-lines are seen in patients with pneumonia or pulmonary edema.

B-lines are never associated with a pneumothorax; if present, this indicates that the lung is not moving but may be diseased. So, detection of B-lines with absent sliding lung is not diagnostic of a pneumothorax. Multiple B-lines that originate from the pleural surface and extend through the image are termed "lung rockets" which are associated with either consolidation or pulmonary edema.

Upper rib, pleural line, and lower rib on USG appear like a "bat sign," which is a normal finding. Visualization of junction between the normal and abnormal lung is termed "lung point." The lung point can be used as a reference point to estimate the size of the pneumothorax. In the M-mode of USG, a "seashore sign" is equivalent to lung sliding and absence of the "barcode sign" is considered as a pneumothorax. "Barcode sign" is also known as "stratosphere sign."

A pneumothorax can easily be detected which are directly under the probe, but smaller, apical, localized pneumothoraces may be missed. Comparison scans of the right and left chest walls may be helpful unless bilateral pneumothoraces are present. The transducer may also be used to identify rib fractures by following the length of the rib longitudinally. Normal ribs are visualized as an echogenic thin interface below the soft tissues of the chest wall with posterior acoustic shadowing. If rib fractures are present, this continuous smooth interface is disrupted. Similarly, the sternum fracture may also be visualized if suspected.

INFERIOR VENA CAVA

At many trauma centers, FAST has been extended even further to include scanning of the IVC during respiration as a noninvasive means of volume status assessment. Utility of USG in estimating right atrial pressure in healthy volunteers is first reported by Simonson and colleagues in the late 1980s. The hemorrhage is the most common cause of hypotension and hypovolemic shock in a trauma patient, but cardiogenic, neurogenic, or distributive shock may also occur due to injuries to the heart or central nervous system. USG of the IVC is helpful in differentiating the various forms of shock.

There is basic science and general correlation between the IVC diameter and the central venous pressure (CVP); thus, IVC is measured by USG and volume depletion is considered if a smaller diameter of the IVC is measured (**Figs. 10A** and **B**).

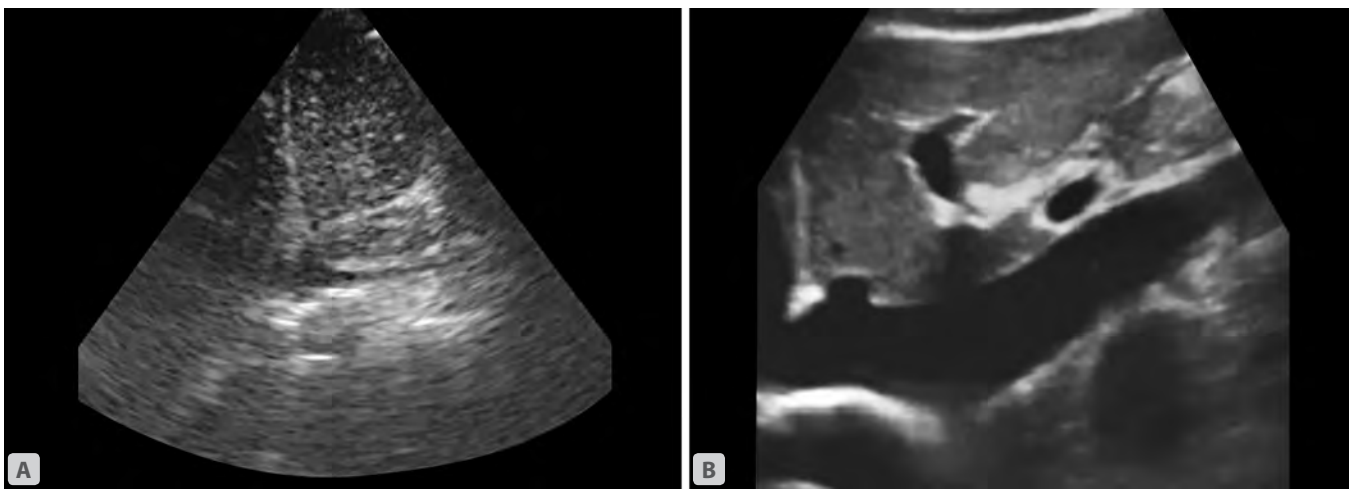
- If IVC diameter is <1.5 cm, (total collapse) estimated CVP would be 0–5 cmH_2O.
- If IVC diameter is 1.5–2.5 cm, CVP would be 6–10 cmH_2O (if >50% collapse with respiratory change) and CVP would be 11–15 cmH_2O (if <50% collapse with respiratory change).
- If IVC diameter is >2.5 cm, CVP would be 16–20 cmH_2O (if <50% collapse with respiratory change).

Ultrasonography of the IVC is visualized and measured with the patient in the supine position using the same low-frequency curvilinear transducer as for the abdominal views. A subxiphoid approach is adopted with the transducer in the sagittal position. The IVC diameter is measured 2 cm below the cavoatrial junction; at this cavoatrial junction, IVC enters the right atrium (**Fig. 11**). For comparison, both inspiratory and expiratory diameters are measured (**Fig. 12**). For more precise measurement of the IVC, M-mode is preferred. Interpretation of IVC is based on the diameter and degree of inspiratory collapse of the IVC in nonintubated patients or in intubated patients not receiving positive-pressure ventilation. The normal expiratory diameter of the IVC with a normovolemic patient is 1.5–2.5 cm and during inspiration, IVC collapses to <50% of its expiratory diameter. *The caval index is calculated as a percentage with the formula:*

Caval index: [(IVC expiratory diameter – IVC inspiratory diameter)/IVC expiratory diameter] × 100

An index approaching 100% indicates almost complete collapse and likely volume depletion whereas an index near 0% indicates minimal collapse, suggesting volume overload. Ferrada and coworkers studied 101 hypotensive acute trauma patients who underwent IVC USG and reported poor prognosis for those patients with a collapsed IVC. For trauma patients, the simplest approach is to visualize and measure the IVC to see if it has substantial collapse with a small diameter (<1.5 cm), indicating volume depletion.

For IVC US, there are diagnostic limitations for its use in the estimation of shock in intubated patients with positive-pressure ventilation, as the IVC diameter will be increased. Severe COPD, pulmonary hypertension, right-sided heart failure, cardiac tamponade, and tricuspid regurgitation may



FIGS. 10A AND B: (A) Small collapsed IVC and hypovolemia; (B) Normovolemic and expanded inferior vena cava.

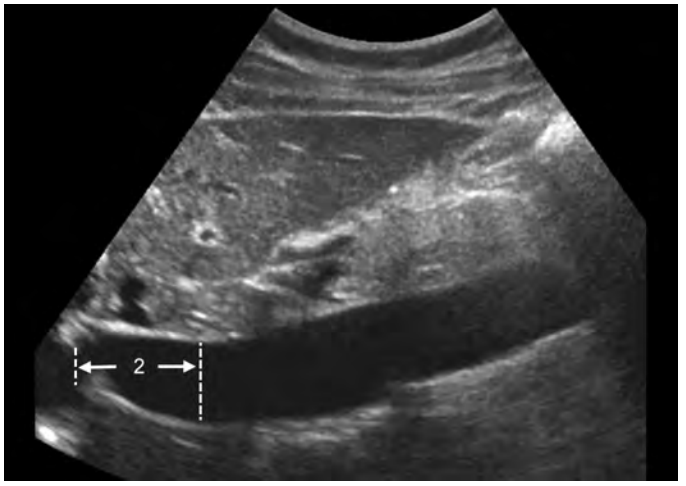


FIG. 11: Normal inferior vena cava. The inferior vena cava diameter is measured 2 cm below the cavoatrial junction (arrows) on this parasagittal view.

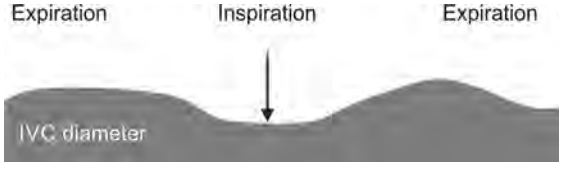


FIG. 12: Normal variation of inferior vena cava diameter with spontaneous breathing in an otherwise healthy patient. This spontaneous change may not be present in certain disease states or positive-pressure ventilation.

also increase IVC diameter and render an inaccurate estimate of shock. Additionally, the IVC can be difficult to detect in hypotensive trauma patients with hypovolemic shock owing to its reduced diameter.

SERIAL FAST

Serial FAST in stable blunt trauma patients may be useful as a sonogram represents real-time examination. A comprehensive USG examination can be performed after trauma stabilization as it gives more time to the operator. Nunes et al. reported that serial FAST examinations decreased the false-negative rate by 50% and increased sensitivity for free fluid detection from 69 to 85%. Other studies have confirmed these results. For detection of intra-abdominal injuries, a baseline CT scan, which has high sensitivity, could be supplemented by FAST performed at bedside if the patient becomes unstable. Serial FAST can be used in stable trauma patients, in patients with a sudden change in hemodynamic status or physical examination, and in pregnant trauma patients to avoid radiation exposure.

SOLID-ORGAN EVALUATION

The FAST examination was originally introduced to detect intraperitoneal free fluid. USG is also helpful in identifying injuries of solid-organ parenchyma, especially during serial FAST. A diffuse heterogeneous pattern is most commonly detected in splenic lacerations whereas a discrete hyperechoic pattern is seen most often in hepatic lacerations. Subcapsular splenic hematomas are detected as either hyperechoic or hypoechoic rims surrounding the parenchyma, and splenic lacerations tend to become hypoechoic over a few days. A USG scan for urological trauma; high grade renal injuries can be visualized as mixed echogenicity with disorganized pattern and bladder hematomas frequently appear echogenic.

BOWEL AND MESENTERIC INJURY

Immediately after a trauma, the volume of hemorrhage and/or extravasated bowel contents is usually minimal; thus, immediately after the injury, detection of bowel and mesenteric injuries with FAST is too difficult. Fluid-filled bowel loops may be confused with free intraperitoneal fluid, but bowel loops can be distinguished from free fluid with the presence of peristalsis. Additionally, pneumoperitoneum from bowel perforation can mimic air within small and large bowel loops at USG or appear as echogenic lines, bands, or spots with posterior reverberation artifacts. Free air in peritoneal cavity changes with patient position and is termed the "shifting phenomenon." The "peritoneal stripe sign" may be visualized with USG when both free fluid and air are present in the peritoneal cavity.

PREGNANT PATIENTS

Blunt and penetrating trauma is the leading cause of nonobstetric maternal mortality, affecting up to 7% of pregnancies. It is an important cause of fetal loss, and most obstetric complications from trauma occur in the third trimester. The most common mechanism of trauma is assault. USG is advantageous in pregnant trauma patients as there is no contrast material or radiation exposure to the mother or the fetus. USG is helpful in rapid assessment of the free fluid as well as in assessment of fetal activity, fetal heart monitoring, amniotic fluid volume, approximate gestational age, and placenta. Placenta examination is very important, as abruption may have a variety of appearances, such as thickened or avascular regions in the placenta without accompanying free fluid in the pelvis. Continuous cardiotocographic monitoring should be started as early as possible to screen for placental abruption in patients with negative or equivocal FAST findings. While every effort should be made to reduce radiation to the fetus, low-dose CT with contrast material (with no known teratogenic effect to the fetus) may be recommended.

FAST AND PEDIATRIC PATIENTS

Several studies of FAST done in pediatric trauma patients have shown similar sensitivities and specificities to those in adults. However, a similar number of studies have shown lower sensitivity as well. For detection of hemoperitoneum, pediatric FAST had an overall sensitivity of 66% and specificity of 95% as per one of the meta-analyses. The use of FAST has decreased the possibilities of radiation exposure from CT in pediatric trauma patients.

TRAINING AND EXPERIENCE

Limitations of USG detection of findings in traumatic chest and abdominal injury are associated with technical errors and

level of operator training. The level of training required for an "experienced" USG operator is not clearly defined and differs between organizations, sonographers, emergency physicians, and surgeons. At least 200 supervised examinations must be performed to be considered experienced according to the definition developed from the first FAST consensus conference in 1999. It was observed that the majority of errors occur in the first 10 examinations; further accuracy improves after 25–50 examinations. Jang et al. reported that inadequate gain and/or depth setting and inadequate anatomic interrogation may also give a false-negative FAST result by emergency physicians in-training.

FUTURE APPLICATIONS

As USG equipment becomes more compact and light weight, the use of FAST in the prehospital setting is becoming more popular and is ideal for rapid triage of injured patients in multiple casualty incidents or battlefield situations. After a natural disaster, an earthquake in Armenia in 1988, the use of FAST was first described by Sarkisian and coworkers. The use of USG in natural disasters has also been reported, such as earthquakes in Turkey (1999), China (2008), and Haiti (2010); floods in Guatemala (2005); and a cyclone in Australia (2007). The use of USG for detecting long bone and pelvis fractures, in mass casualty incidents, is being investigated. The role of contrast-enhanced USG for trauma is not clear yet, but it appears to be a promising method to improve detection of parenchymal organ intra-abdominal injuries. Advantages of contrast-enhanced USG include lack of ionizing radiation exposure, portability, safety, and repeatability, thus making it ideal for conservative injury management, especially in children and pregnant or fertile female patients. Potential applications of contrast-enhanced US include serial scanning of known organ injuries, follow-up imaging in patients with inconclusive CT findings, and use in patients with hypersensitivity to iodinated contrast agents.

SUMMARY

For the past three decades, FAST was extensively utilized and studied in blunt and penetrating trauma. Earlier to diagnose intra-abdominal injury, invasive procedures such as DPL and exploratory laparotomy were commonly utilized. Nowadays, FAST examination is used not only for detecting the free fluid in abdominal trauma but also for visualization and evaluation of heart, chest, and IVC, along with the use of many variations in technique, protocols, and interpretation. Trauma management strategies have also changed over the years such as laparotomy, laparoscopy, endoscopy, computed tomographic angiography, angiographic intervention, serial imaging, and clinical observation.

FAST and eFAST are widely available in most of the trauma centers and performed quickly in real time; FAST can be helpful in identifying free fluid suggestive of hemoperitoneum, hemothorax, and hemopericardium while eFAST can help identify pneumothorax, hemothorax, and atelectasis. FAST has acceptable sensitivity (69–98%) for detection of free fluid and lower sensitivity (63%) for detection of solid-organ injury; FAST may lead to underestimation of injuries and severity, especially in the presence of stable trauma patients without detectable free fluid. For detection of free fluid and/or solid-organ injury, FAST has high specificity (94–100%) and serial FAST examinations increase the overall sensitivity (72–93%). The sensitivity of eFAST for pneumothorax and hemothorax is higher than that of chest radiography (11–21% vs. 43–77%). Evaluation of the IVC during FAST can help distinguish between types of shock in hypotensive trauma patients.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Facial Trauma

Syed Ahmed Adil

INTRODUCTION

Trauma to the facial region causes injuries to skeletal components, dentition as well as soft tissues from the frontal bone superiorly to the mandible inferiorly. Several studies suggest that facial fracture dissipates a lot of force during trauma, in effect protecting the brain. The mandible was the most frequent site involved. Among maxillary fractures, zygomatic bone and arch fractures were most common. The most common causes are motor vehicle crashes, falls, violent assaults, and crashes during bicycling. Cervical spine injury should be considered in a maxillofacial trauma patient until proved otherwise. Up to 44% of patients with severe maxillofacial trauma require endotracheal intubation due to mechanical disruption or massive hemorrhage into the airway.

APPROACH AND MANAGEMENT

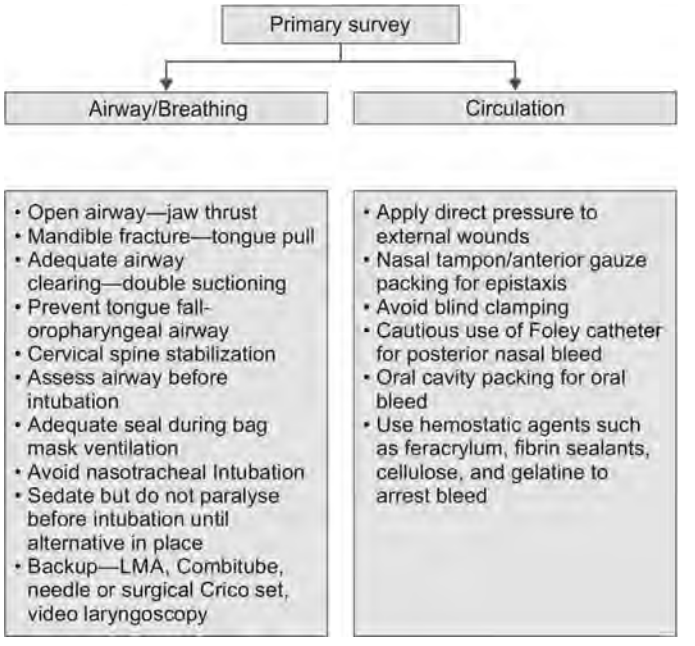
Every trauma patient should be evaluated as per the advanced trauma life support (ATLS) protocol. Primary survey and its management take the utmost priority (**Flowchart 1**). Do not get distracted with other injuries as long as you have airway, breathing, and circulation under control. Next come life-threatening injuries followed by facial injuries. The history indicates the site and direction of force and the possible presence of other injuries, especially to the neck, and other relevant features such as loss of consciousness and head injury. Important issues should be asked/elicited such as vision, facial numbness, bite, pain with eye movements, pain with moving the jaw, and breathing difficulty. Secondary survey includes the following: Inspect the face for asymmetry, inspect open wounds for foreign bodies, and palpate the entire face, supraorbital and infraorbital rims, zygomatic and frontal sutures, zygomatic arch, and oral mucosa.

Sinuses

Frontal bone and sinus injuries usually are a result of a direct blow to the frontal bone with a blunt object. This fracture is frequently associated with intracranial injury, secondary to disruption of the posterior table of the sinus. Dural tears are frequent, and patients may have associated injuries to the orbital roof. Look for disruption or crepitus near the orbital rim. Palpate for subcutaneous emphysema. Look for lacerations or bulging of the forehead. Those with depressed skull fractures and posterior wall involvement should be admitted. A neurosurgical/oromaxillofacial surgery opinion must be obtained. Foreign bodies and bony injuries must be looked for. A patient with frontal sinus injuries may require head, neck, neurological, ENT (ear, nose, throat), and eye examination. Intravenous (IV) antibiotics and tetanus prophylaxis must be considered. Nondisplaced fractures may be treated as outpatients after neurosurgical consultation.

Nose

Nasal fractures account for >50% of all facial fractures in adults (**Table 1**). The bones and cartilage of the nose provide both aesthetic and structural support for the midface and airway;


Primary survey
Airway/Breathing
Circulation
• Open airway—jaw thrust
• Mandible fracture—tongue pull
• Adequate airway clearing—double suctioning
• Prevent tongue fall-oropharyngeal airway
• Cervical spine stabilization
• Assess airway before intubation
• Adequate seal during bag mask ventilation
• Avoid nasotracheal Intubation
• Sedate but do not paralyse before intubation until alternative in place
• Backup—LMA, Combitube, needle or surgical Crico set, video laryngoscopy
• Apply direct pressure to external wounds
• Nasal tampon/anterior gauze packing for epistaxis
• Avoid blind clamping
• Cautious use of Foley catheter for posterior nasal bleed
• Oral cavity packing for oral bleed
• Use hemostatic agents such as feracrylum, fibrin sealants, cellulose, and gelatine to arrest bleed

(LMA: laryngeal mask airway)

FLOWCHART 1: Evaluation of facial injuries.

TABLE 1: Nasal trauma classification.	
Type 1	Injury restricted to soft tissue
Type 2	• 2a: Simple, unilateral, nondisplaced fracture • 2b: Simple, bilateral nondisplaced fracture
Type 3	Simple displaced fracture
Type 4	Closed comminuted fracture
Type 5	Open comminuted fracture

Note: Type II to IV fractures are associated with cerebrospinal fluid (CSF) rhinorrhea, airway obstruction, septal hematoma, crush injury, numbness, severe displacement, or midface involvement.

FIG. 1: Bimanual digital palpation of the nose.

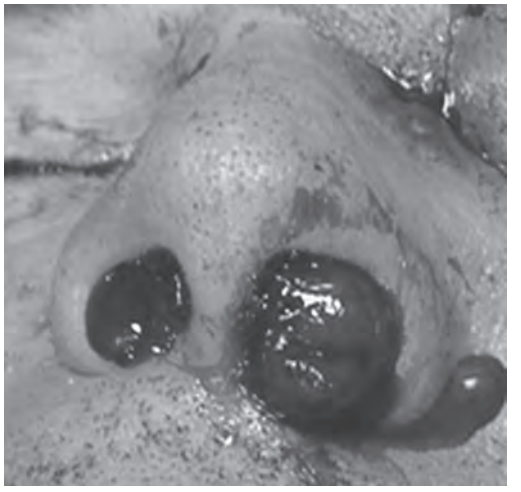


FIG. 2: Septal hematoma. ***(For color version, see plate 38)***

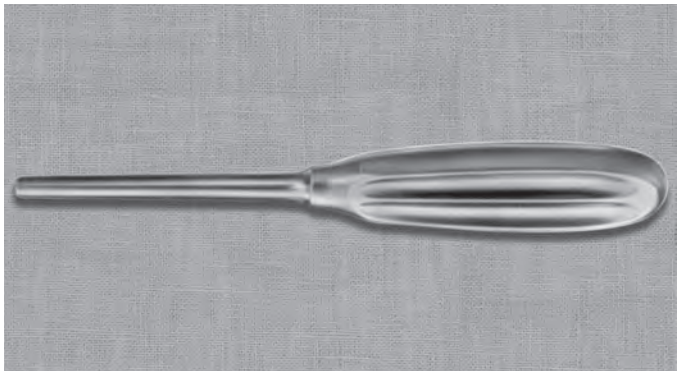


FIG. 3: Goldman's septal elevator.

therefore, proper evaluation and management are necessary to prevent nasal deformity and nasal airway compromise.

Look for asymmetry, tenderness, crepitus, and mobility of the nasal complex. If present, suspect trauma to the nose or medial orbit. Perform bimanual nasal palpation test and check for tenderness over the medial canthus (**Fig. 1**). Inspect the nasal septum for septal hematoma, cerebrospinal fluid (CSF) rhinorrhea, or epistaxis as they may be present. Flattened nasal bridge, widening of the nasal bridge (telecanthus), or a saddle-shaped deformity of the nose suggests nasal bridge fracture with orbital involvement. A septal hematoma appears as a blue/red, boggy, and tender area of swelling along the nasal septum (**Fig. 2**). Control epistaxis by either pinching the nose or anterior/posterior packing. Topical vasoconstrictors can be used. Make the patient sit straight so that he/she does not swallow the blood. Incision and evacuation of the septal hematoma are required to prevent destruction of the cartilage resulting in saddle-nose deformity. To drain septal hematomas, first anesthetize the area. Using a #11 blade, incise the inferior portion of the hematoma and allow it to drain. Then pack the nose with Vaseline gauze to prevent reaccumulation of blood. In the absence of epistaxis or deformity, ice and analgesics may be given. Refer to ENT in 2–5 days for reduction. Rhinorrhea, if present, must be inspected for CSF leak by testing for β-transferrin, glucose, or halo sign. If suspected, a neurosurgical consultation is warranted. The head must be kept elevated and supine positioning avoided to allow healing. Closed reduction is usually reserved for simple, noncomminuted nasal fractures, although exceptions can be made. The key principle is to apply a force opposite to the vector of trauma to achieve fracture reduction. Attention should be paid to the bony nasal pyramid. The Goldman elevator (**Fig. 3**) is applied with upward/outward force with bimanual manipulation of the external nasal bones. Care should be used with this technique over the cribriform plate if injury is suspected.

Ear

Inspect the external auditory canal for any lacerations, CSF leaks, and hemotympanum (**Fig. 4**). Look for battle sign over the mastoid region/auricular hematoma. Check for mandibular condylar fracture by inserting a finger into the external auditory canal and asking the patient to gently open and close the mouth (**Fig. 5**). A number of published studies have shown that the risk of meningitis is significantly reduced when prophylactic antibiotics are used in post-traumatic CSF leakage. Place the patient at bed rest with the head elevated. The basic concept is to decrease intracranial pressure, which in turn should decrease the rate of leakage. Most traumatic leaks will close spontaneously within 7–10 days. If they do not, a neurosurgeon or ENT surgeon should be consulted to consider surgical closure.

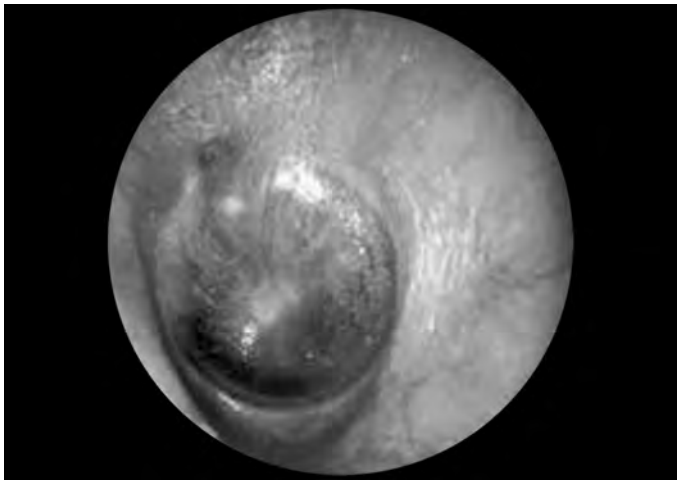


FIG. 4: Hemotympanum. ***(For color version, see plate 38)***

FIG. 5: Finger-in-ear test.
Courtesy: Dr SA Adil.

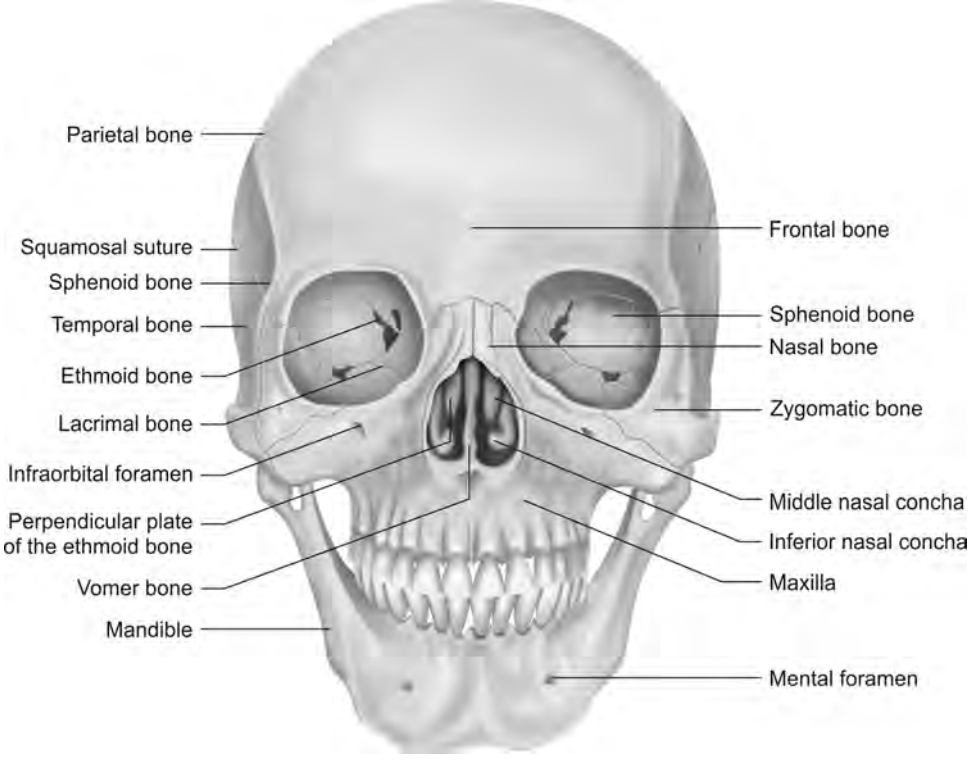


FIG. 6: Facial bones.

MAJOR FACIAL BONES

Major facial bones are shown in **Figure 6**. Zygomatic arch can fracture in two to three places along the arch. These patients present with depressed cheek with tenderness on palpation. The zygomaticomaxillary fracture (tripod fracture) is a rare but complicated fracture (**Fig. 7**). Patients usually present with pain on opening their mouth. Fractures of the maxilla are high-energy injuries. An impact 100 times the force of gravity is required to break the midface. These patients often have significant multisystem trauma. The fractures of the maxilla are classified as Le Fort fractures (**Flowchart 2**). Inspect the face from all sides to detect asymmetry in facial structures from zygomatic, orbital, and Le Fort injuries. Palpate the zygoma along its arch and its articulations with the maxilla and frontal and temporal bones. Open the patient's mouth and grasp the maxilla arch. Place the other hand on the forehead. Push back and forth and up and down and check for movement (**Figs. 8A** and **B**). Emergency care for all these fractures involves airway maintenance, with intubation or cricothyrotomy, if necessary. Airway compromise is probably more common with Le Fort II and III fractures. CSF rhinorrhea is uncommon in Le Fort I fracture but is often seen in Le Fort II and III fractures. If CSF rhinorrhea is present or intracranial air is seen on X-ray or an open skull fracture is present, the patient should be admitted and placed in a head-elevated position (40–60°) if possible. Prophylactic antibiotics are often given to these patients. Patients with maxillary fractures also have significant epistaxis requiring nasal packing. Operative intervention may be needed if bleeding does not resolve

with packing alone. Look for associated injuries, especially intracranial, spinal, thoracic, and abdominal. The incidence of blindness is high for Le Fort II and III fractures, so it is important to get ophthalmology consultation. Patients with complex maxillary fractures require admission for open reduction and internal fixation.

Mandible

Mandibular fractures are the third most common type of facial fracture. Because of their ring shape, fractures are often multiple in up to 50% of the cases. The most common area fractured is the condyle (36%), body (21%), and parasymphysial region (17%). A dental line step-off or ecchymosis of the floor of the mouth is a common finding. There is inability to open the mouth. Periauricular pain while biting is common with condylar fracture. Bilateral body fractures of the mandible may cause airway compromise. Inspect for malocclusion of teeth and bleeding. Ensure that there is no aspiration. Loose and mobile teeth must be counted. Use the tongue blade test to identify fracture of the mandible (**Fig. 9**). Nondisplaced fractures should be treated with adequate analgesia. Orosurgical consultation must be sought. Displaced fractures, open fractures, and fractures associated with dental trauma need urgent orosurgical consultation. These patients require admission and need either closed reduction or open reduction with internal fixation. All patients with mandibular fractures must be administered antibiotics and tetanus prophylaxis.

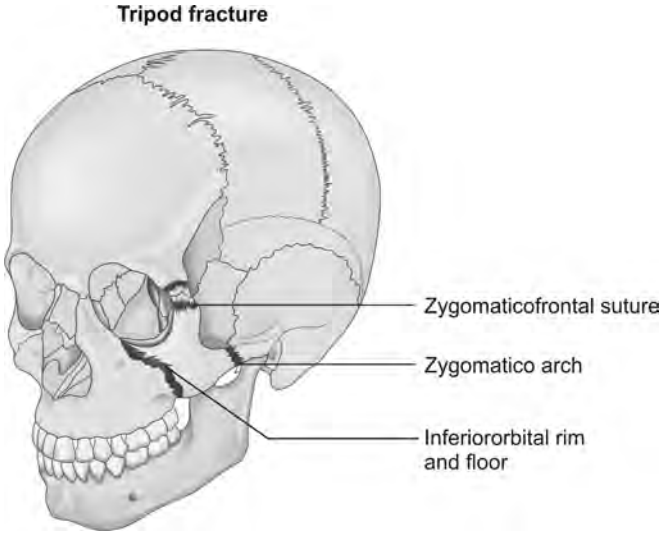
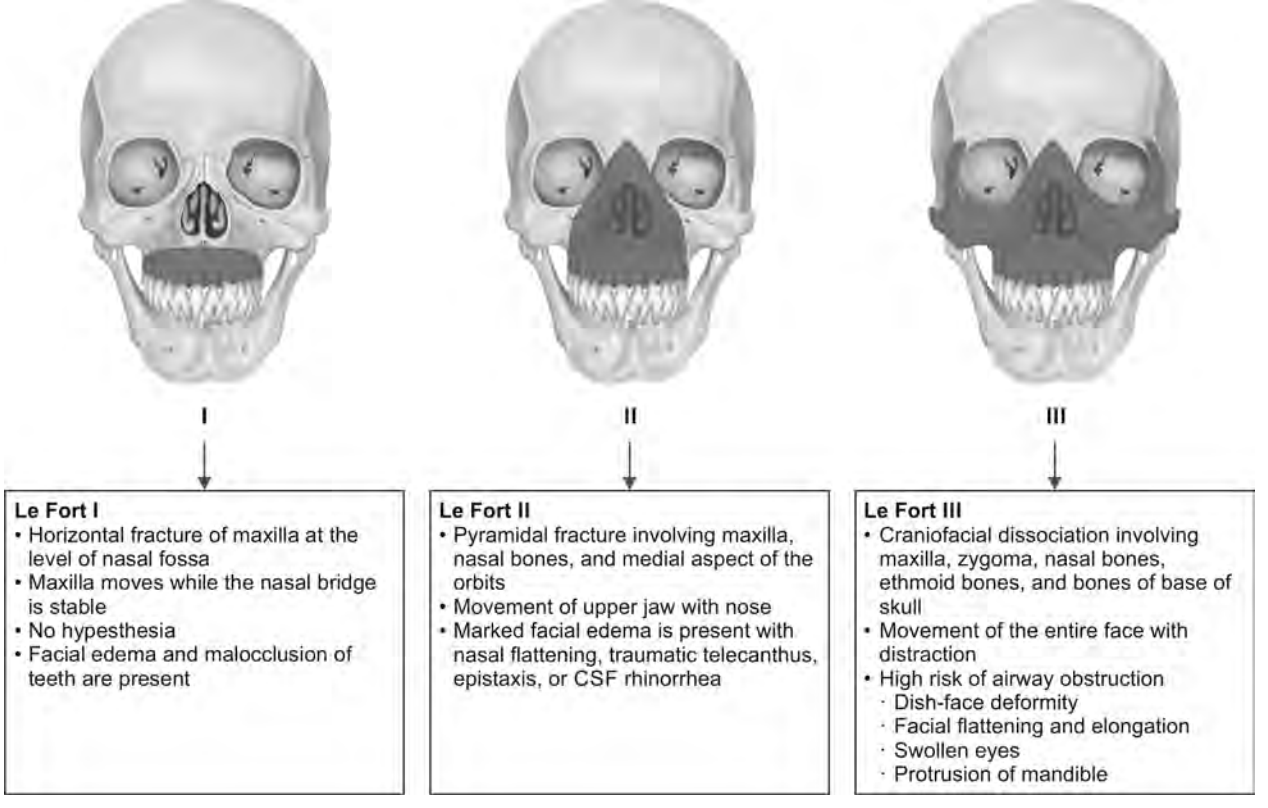


FIG. 7: Tripod fracture.

TEMPOROMANDIBULAR JOINT DISLOCATION

Temporomandibular joint (TMJ) dislocation generally results from a direct blow to the chin while the mouth is open or more commonly during vigorous yawning. The mandible can be dislocated in the anterior, posterior, lateral, and superior planes. Anterior dislocation is the most common and occurs when the condyle is forced in front of the articular eminence. Once the jaw is dislocated, muscular spasm of the temporalis and lateral pterygoid muscles tends to prevent reduction. Dislocations are most frequently bilateral, but they also can


I
II
III
Le Fort I
• Horizontal fracture of maxilla at the level of nasal fossa
• Maxilla moves while the nasal bridge is stable
• No hypesthesia
• Facial edema and malocclusion of teeth are present
Le Fort II
• Pyramidal fracture involving maxilla, nasal bones, and medial aspect of the orbits
• Movement of upper jaw with nose
• Marked facial edema is present with nasal flattening, traumatic telecanthus, epistaxis, or CSF rhinorrhea
Le Fort III
• Craniofacial dissociation involving maxilla, zygoma, nasal bones, ethmoid bones, and bones of base of skull
• Movement of the entire face with distraction
• High risk of airway obstruction
· Dish-face deformity
· Facial flattening and elongation
· Swollen eyes
· Protrusion of mandible

FLOWCHART 2: Types of Le Fort fracture.

FIGS. 8A AND B: Maxilla examination.
Courtesy: Dr SA Adil.

FIG. 9: Tongue blade test. Bite down on the tongue blade and twist the blade to try to break it. Patients with broken jaw will reflexively open their mouth.
Courtesy: Dr SA Adil.

be unilateral. Unilateral dislocations result in deviation of the mandible to the unaffected side. Bilateral dislocations cause the mandible to be displaced anteriorly (**Fig. 10A**). Posterior dislocations are rare. Lateral dislocations are associated with a jaw fracture. Superior dislocations are associated with cerebral contusions, facial nerve palsy, and deafness. These patients present with the inability to close an open mouth and/or pain, discomfort, and facial swelling. Look for deviation of the mandible or anterior dislocation of the jaw with tenderness and swelling at the angle of the jaw. Paresthesia or anesthesia of the face signifies nerve injury.

Traditional Method of Reduction

Temporomandibular joint dislocation should be reduced with a short-acting muscle relaxant and adequate analgesia. A regional block using 2-mL 2% lidocaine may be given in the preauricular depression anterior to tragus. The patient should be seated. Facing the patient, the examiner places his or her thumbs in the patient mouth, over the mandibular molars as far back as possible. The fingers should curve beneath the angle and the body of the mandible. The examiner applies downward and backward pressure with his or her thumbs until the condyle slides back into the articular eminence. A successful reduction must enable the patient to open his or her mouth immediately (**Fig. 10B**).

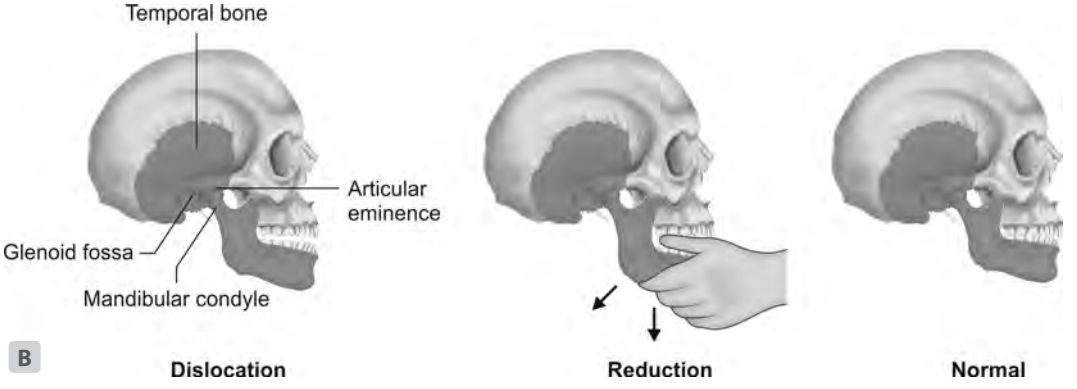
Newer External Method

To reduce the *left side*, the thumb is placed just above the anteriorly displaced coronoid process (black arrow) and the fingers are placed behind the mastoid process (gray arrow) (**Fig. 11A**). Simultaneously, on the *right side*, the fingers hold and rotate anteriorly the mandible angle (black arrow) and the thumb is placed over the malar eminence as a fulcrum (gray arrow) (**Fig. 11B**).

EYES/ORBIT

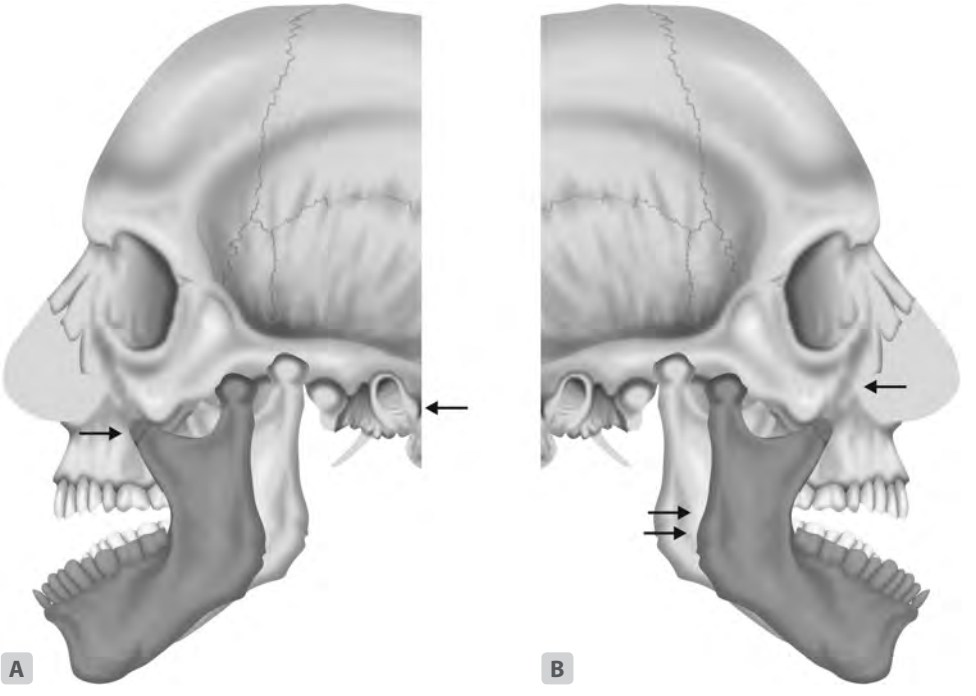
The orbital rim (frontal, maxillary, and zygomatic bones) protects the globe from direct trauma. The weakest parts of the orbit are the medial wall and orbital floor; these fracture first, and the orbital soft tissues can pass through the hole created, causing the globe level to drop (hypoglobus) and sink back (enophthalmos). This is called a pure orbital blow-out fracture. Subconjunctival hemorrhage and chemosis occur with orbital fractures.

Visual acuity, light perception, and pupils must be examined. Look for raccoon eyes (bilateral orbital ecchymosis). Examine the lids for lacerations. Injuries to the medial third of the eyelids can damage the lacrimal apparatus. Test extraocular muscles. Restriction of upward gaze can be seen with zygomatic or infraorbital wall fractures. Examine the cornea for abrasions and lacerations. Examine the anterior chamber for hyphemia. Fundoscopy must be performed for posterior chamber and retinal examination. Palpate the entire orbital rim for tenderness or deformity (**Fig. 12**). Look for hypesthesia of the infraorbital nerve and for periorbital tenderness, swelling, subcutaneous air, ecchymosis, enophthalmos, and impaired ocular motility. Look for infraorbital anesthesia. Check facial stability. Palpate the medial orbit area to rule out naso-ethmoidal-orbital (NEO) fracture. (Place a cotton bud inside the nose to the medial canthus and place your finger outside the medial canthus. If the bone moves, it is known as NEO fractures.)



FIGS. 10A AND B: (A) Temporomandibular joint dislocation. (B) Traditional method: Reduction of temporomandibular joint dislocation.

Courtesy: (A) Dr SA Adil.



FIGS. 11A AND B: Newer method of reduction of temporomandibular joint dislocation. (A) Left side; (B) Right side.

FIG. 12: Periorbital edema. ***(For color version, see plate 38)***

FIG. 13: Laceration of the eyelid. ***(For color version, see plate 38)***

LACERATIONS

Entrapment injury, pinna laceration or avulsion, and intraoral lacerations must be ruled out. Although suturing is preferred for repair, tissue adhesives are similar in patient satisfaction, infection rates, and scarring risk in low skin-tension areas. Surgical consultation for laceration may be warranted in the following:

- Full-thickness laceration of the eyelid (**Fig. 13**), vermillion cutaneous border of the lip or helical rim of the ear, and free margin of alar rim
- Lacerations involving nerves, arteries, bones, or joints
- Penetrating wounds of unknown depth
- Severely contaminated wounds requiring drainage
- Wounds leading to a strong concern about cosmetic outcome

Reconstruction of laceration or avulsion tongue injuries is not usually required. Primary wound healing often occurs rapidly because of the rich vascular supply. Lacerations larger than 2 cm may require intervention (**Fig. 14**). Deep lacerations should be sutured in layers.

FIG. 14: Laceration of the tongue. ***(For color version, see plate 38)***

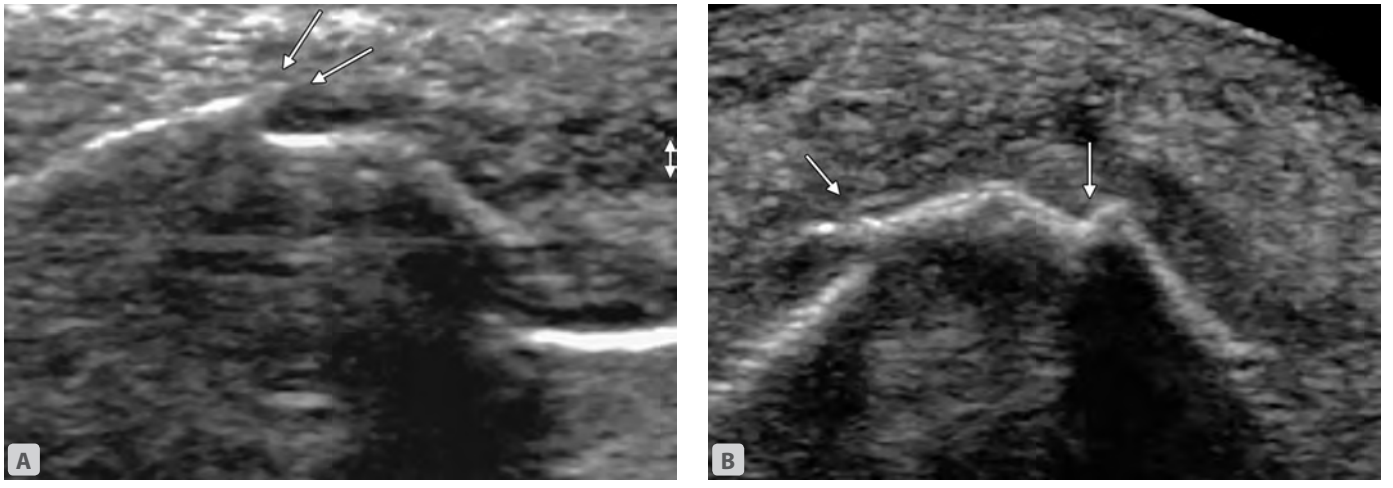
IMAGING STUDIES

Head CT with bone window is a good tool in patients with significant findings of frontal fractures, sinuses, and midface fractures. Plain radiographs remain helpful when CT is not available or to exclude injury in the low-risk patient. The Waters' view X-ray safely replaces the multiple views in a traditional facial series for midfacial fractures. The lateral view for the nose could be helpful. Low-suspicion mandible fractures can be found with the panorex view, but in case of significant findings a mandible CT or a facial CT is warranted. Facial CT with coronal and axial sections is the imaging study of choice for patients with an abnormal Waters' view or as the initial study with significant clinical findings. The other diagnostic tool which is very reliable to detect fracture is ultrasonography (USG). It has been widely used in detecting superficial facial fractures, for example, nasal bone fracture (**Figs. 15A** and **B**), orbital fracture and zygoma fractures in children. It is also used in finding a pupillary reaction through the periorbital edema. Ocular ultrasound plays an important role in differentiating orbital ultrasound from the normal orbit (**Fig. 16A**). It can also detect ocular injuries such as retrobulbar hemorrhage, which is also known as guitar-pick sign (**Fig. 16B**), retinal detachment (**Fig. 16C**), and lens dislocation (**Fig. 16D**).

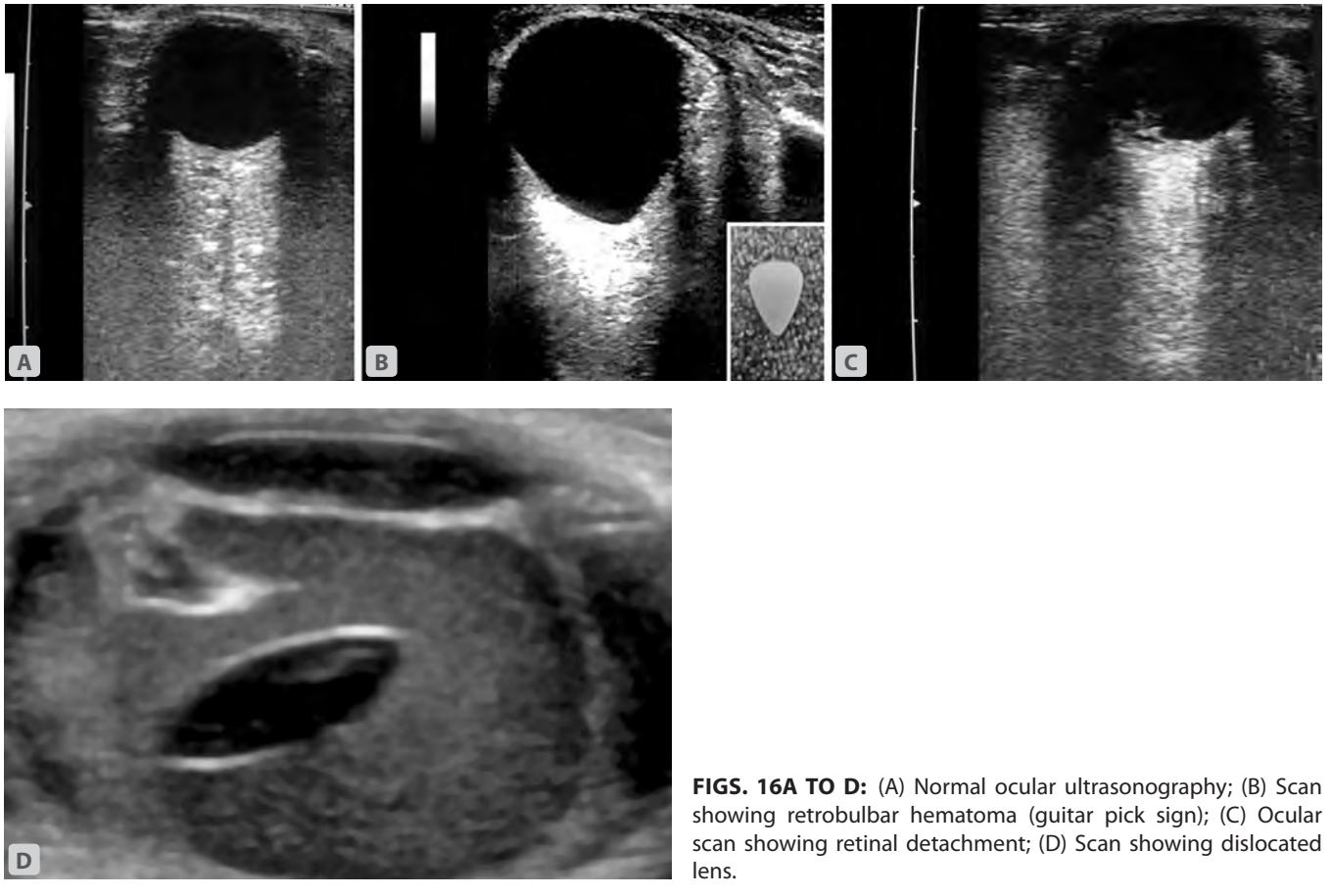
Classic tests for CSF rhinorrhea are not accurate in distinguishing CSF from serous nasal discharge in the presence of nasal bleeding. The double-ring or halo sign occurs when clear CSF diffuses around blood when dropped on a paper towel. The glucose test is likewise not reliable. Nasal discharge does not contain glucose, whereas CSF does. Blood from the injury may create a false-positive test. A beta 2 transferrin assay marker is very specific to CSF. However, the test is expensive and results may take several days to a few weeks. In the absence of a CT scan, X-ray along with USG can detect most of the injuries.

SUMMARY

Facial trauma is a common complaint in the emergency department. Interventions can range from simply diagnosing a fracture and providing referral to very complex management of severe fractures requiring stabilization of the airway,

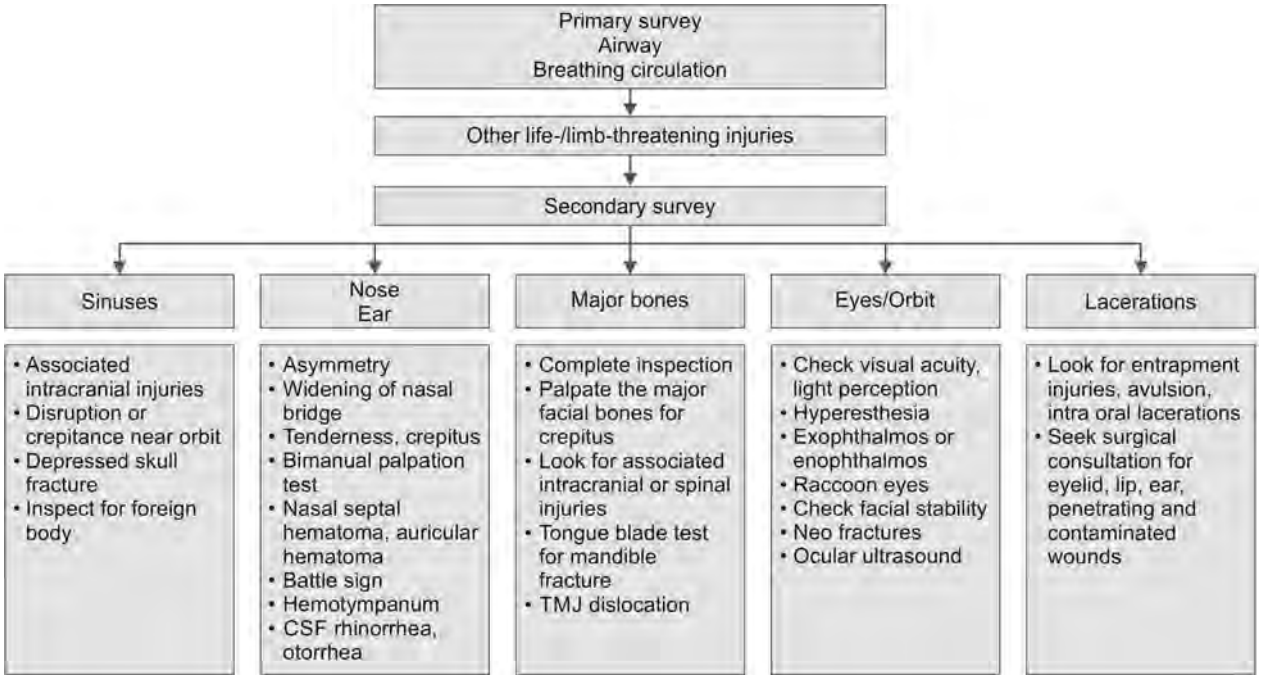


FIGS. 15A AND B: (A) Longitudinal scan of left nasal bone shows depressed fracture. (B) Marked soft-tissue edema and hyperechoic hematoma near depressed fracture lines.



FIGS. 16A TO D: (A) Normal ocular ultrasonography; (B) Scan showing retrobulbar hematoma (guitar pick sign); (C) Ocular scan showing retinal detachment; (D) Scan showing dislocated lens.

hemostasis of active bleeding, and proper evaluation and management of many aspects of trauma. It is vital that emergency physicians recognize associated injuries, including those affecting the brain and cervical spine, as common associations in facial trauma. The emergency physician must always maintain a high degree of suspicion and should evaluate all complaints of facial trauma thoroughly (**Flowchart 3**), because a missed injury can threaten life or vision. A methodical and organized examination is paramount for patient safety and the physician's documentation of the evaluation. CT scans are the most efficient and comprehensive way to evaluate facial trauma and fractures and should be used liberally in patients with any concern for soft tissue or bony injury and especially in those who are unable to provide a reliable examination. CT scans of the head and cervical spine can be life-saving. Many injuries are obscured by swelling or ecchymosis. It is always safer to consult a facial surgeon in the setting of uncertainty. In patients who are safe for discharge, it is the responsibility of the emergency physician to provide clear instructions regarding close follow-up.



(CSF: cerebrospinal fluid; TMJ: temporomandibular)

FLOWCHART 3: Approach to facial trauma.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Head Trauma

Prasad Rajhans, Harshwardhan Singh Pawar, Devendra Richhariya

INTRODUCTION

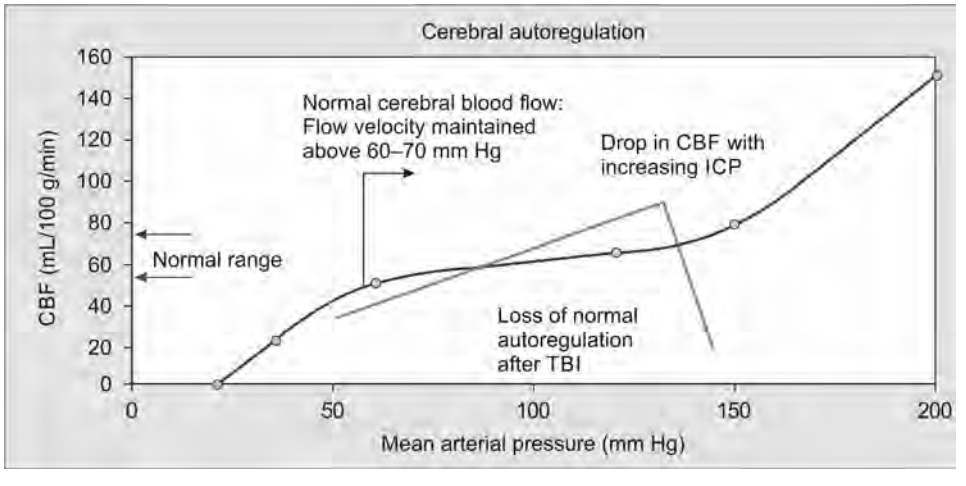
Trauma to the central nervous system (CNS) (the brain and spinal cord) can be classified on the basis of mechanisms of injury, clinical severity, radiological appearance, or anatomic distribution. Education regarding preventive measures of head trauma is important for public, such as the use of helmets and seatbelts. The main objective in the management of patients with head trauma is the prevention of secondary injury such as ischemia and hypoxia. This chapter includes common neurologic injuries related to trauma and their prehospital, in-hospital, and critical care management in patients.

Head trauma is a critical situation and the leading cause of death worldwide. It can be classified based on:

- Mechanism of injury—contact/impact loading and noncontact/inert loading
- Severity of injury—mild, moderate, severe
- Pathoanatomic—based on the location and anatomic feature of injury
- Pathophysiologic—primary injury and/or secondary injury

CEREBRAL BLOOD FLOW AND AUTOREGULATION

The CNS is enclosed in a bony vault. It comprises brain parenchyma, cerebrospinal fluid (CSF), and blood. In normal physiology, these three elements are in homeostasis. An adult brain represents 2% of body weight. It receives 12–15% of total cardiac output. This represents the high metabolic rate of brain parenchyma. Cerebral blood flow (CBF) is 45–55 mL/100 g/min, cerebral metabolic rate of oxygen is 3–3.5 mL/100 g/min/mL, and intracranial pressure (ICP) (supine) is 8–12 mm Hg. Normal CBF is maintained by cerebral blood vessels by its constriction and dilatation ability under various physiological conditions. This is called autoregulation. Factors affecting CBF are temperature, seizures, partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), mean arterial pressure (MAP), and vasoactive agents. Normal functioning of the brain is dependent upon the cerebral perfusion pressure (CPP) which is the difference between the MAP and the ICP: *CPP = MAP – ICP*. CPP roughly denotes CBF. CBF is maintained well when MAP is maintained between 60 and 150 mm (**Fig. 1**).



(CBF: cerebral blood flow; ICP: intracranial pressure; TBI: traumatic brain injury)

FIG. 1: Determinants of cerebral blood flow.

PATHOPHYSIOLOGY OF TRAUMATIC BRAIN INJURY

Knowledge of the Monro–Kellie doctrine is essential to understand brain pathophysiology in injury. In 1783, Alexander Monro deduced that the cranium is a rigid box and is filled with the nearly incompressible brain and that its volume remains constant. In 1824, George Kellie confirmed Monro's observation. The doctrine states that any increase in the volume of the cranial contents raises the ICP and the increase in the volume of the content occurs at the expense of the other two. The initial reaction is to reduce venous blood and CSF. When these compensatory mechanisms get exhausted, the pressure increases drastically, and brain herniation can occur (**Fig. 2**).

Head trauma leads to brain parenchymal injury which is termed traumatic brain injury (TBI). TBI is defined as any disruption in the function of brain due to external force. TBI is due to falls, road traffic accidents, blunt head injury, assault, blast injury, and sometimes child abuse. The ability of autoregulation and maintenance of CBF get disrupted when any TBI occurs. Cerebral vasoconstriction occurs due to hypertension, alkalosis, and hypocarbia and cerebral vasodilation occurs due to hypotension, acidosis, and hypercarbia. After TBI increase in intracranial blood volume (due to vasodilatation) causes brain swelling, it is the compensatory mechanism of the brain to maintain optimal CBF in view of damaging brain tissue. Secondary to TBI, various devastating intracranial and extracranial events occur such as severe intracranial hypertension, seizures and cerebral edema, hypotension, hypoxia, anemia, and hyper- and hypocapnia. These devastating events determine the final outcome in the patient after TBI. Hypotension and hypoxia clearly worsen the patient outcome. In short, pathophysiology of TBI involves alteration in CBF, parenchymal injury, cerebral edema, ICP, and herniation (**Fig. 3**).

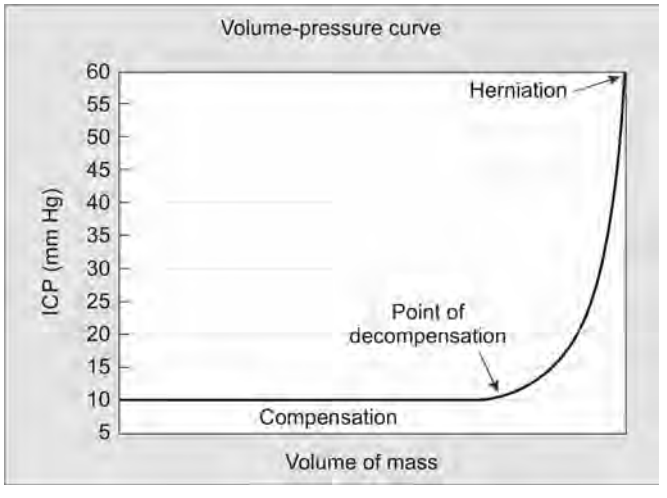


FIG. 2: Intracranial pressure (ICP) versus volume curve.

MECHANISM OF INJURY

Blunt Injuries

Blunt injuries mean acceleration and deceleration of brain after a direct blunt impact to the head.

Blunt impact-induced mechanical forces cause tissue compression, distortion, and shearing, resulting in parenchymal contusions, extra-axial hematomas, and diffuse axonal injury (**Table 1**).

Penetrating Injuries

Penetrating brain injuries are less common than blunt injuries and having high mortality rates. The most frequent penetrating brain injury in the emergency department is a gunshot injury/firearm injury. High-velocity projectile penetrates the brain and damages the parenchyma.

CONSEQUENCES OF TRAUMATIC BRAIN INJURY

Any trauma to brain leads to two different but inter-related consequences: (1) *Primary injury;* and (2) *Secondary injury.* Primary injury to the brain is caused by external mechanical force transferred to the bone, brain parenchyma, blood vessels, and CSF. The mechanism involved is acceleration–deceleration, shear force, direct impact. Consequently, it leads to (1) skull fracture—linear, stellate, nondepressed, depressed; (2) brain parenchymal injury—contusion, diffuse axonal injury; and (3) blood vessel injury—epidural hematoma (EDH), subdural hematoma (SDH), and subarachnoid hemorrhage (SAH). Secondary injury to brain results because of alteration in brain homeostasis. It involves a series of molecular mechanisms as a consequence of inflammation, disruption of the blood–brain barrier, free radicle injury, and cell swelling.

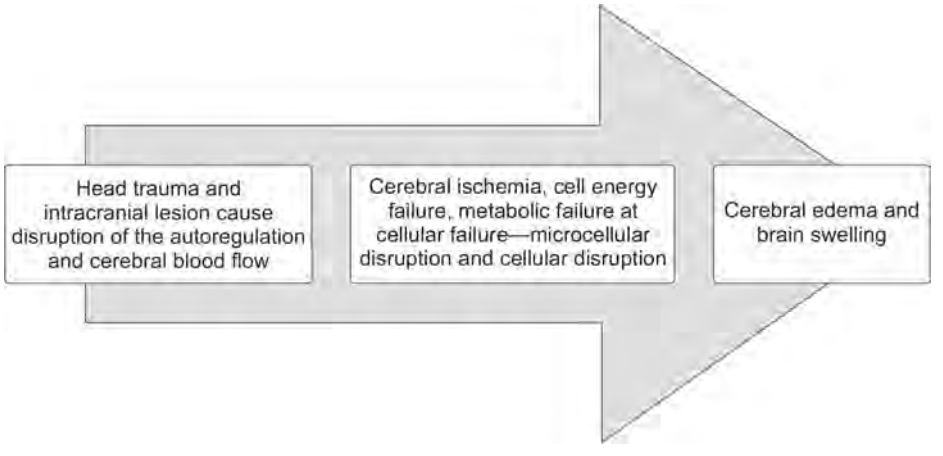

Head trauma and intracranial lesion cause disruption of the autoregulation and cerebral blood flow
Cerebral ischemia, cell energy failure, metabolic failure at cellular failure—microcellular disruption and cellular disruption
Cerebral edema and brain swelling

FIG. 3: Pathophysiologic changes in traumatic brain injury.

TABLE 1: Blunt trauma and pattern of brain injuries.

	Pathophysiology	*Anatomical location*	*Special features*
Parenchymal contusion	Coup/countercoup injury	Frontal or temporal	Can expand within 24 hours
Epidural hematoma	Disruption of middle meningeal vessels, diploic vein, and venous sinuses	Near skull fracture	Lens shaped (convex)
Subdural hematoma	Bridging vein injury	Cerebrum tentorium and falx	Crescent-shaped (concave)
Subarachnoid hemorrhage	Pial vessels injury	Cerebrum basal cistern ventricles	Can be limited to few sulci fissure or diffuse
Diffuse axonal injury	Shear injury of axonal	At cortex and white matter junction	Axonal swelling and axotomy

Cell membrane disruption leads to flux of sodium and calcium that causes activation and release of excitatory neurotransmitters such as glutamate and excessive stimulation of cell. This mechanism is called excitotoxicity. Activation of enzyme due to calcium influx leads to free oxygen radical generation and injury. Also, activation of proteases leads to disruption of cytoskeleton and caspases lead to cell cycle disruption. Cell death occurs via necrosis and pathological apoptosis. There is disruption of cell membrane and blood–brain barrier leading to cytotoxic and vasogenic edema, respectively. Brain edema can lead to raise ICP, which in turn can cause compression-induced ischemia. Secondary injury is accentuated by hypoxemia, hypercapnia/hypocapnia, hypotension/hypertension, hyperthermia, hyperglycemia, and dyselectrolytemia.

Brain herniation is of four types: (1) Uncal transtentorial, (2) central transtentorial, (3) cerebello-tonsillar, and (4) upward posterior fossa.

Uncal transtentorial herniation is the most common. It is seen with a lesion in the temporal lobe or middle fossa. The uncus part of the temporal lobe herniates through the tentorium. It compresses the outer parasympathetic fiber of the oculomotor nerve, which causes fixed mid-dilated pupils on the ipsilateral side and pyramidal tract which causes contralateral hemiparesis. Central transtentorial herniation occurs with the midline lesion present in the frontal occipital or vertex. It causes bilateral pinpoint pupils, bilateral Babinski reflex, and increased muscle tone. Cerebello-tonsillar herniation occurs when the cerebellar tonsil herniates through the foramen magnum. It causes bilateral pinpoint pupil, flaccid paralysis, and sudden death. Upward transtentorial herniation results from a posterior fossa lesion and leads to a conjugate downward gaze with absence of vertical eye movements and pinpoint pupils.

PATTERN OF BRAIN INJURIES

Skull Fracture

Skull fractures occur because of external force. They are of the following types: linear, stellate, depressed, nondepressed, open, closed, basilar, and vault. A CT scan with bone window is required to make a diagnosis of skull bone fractures. Skull fractures are often associated with intracranial injury. Basilar skull fractures cause retro-orbital ecchymosis racoon eyes, retroauricular ecchymosis (Battle's sign), CSF leak from the nose and ear, and injury to VII and VIII cranial nerves. These signs should raise a suspicion of basilar fracture. Sometimes, a fracture can travel to the carotid canal and cause injury to the carotid arteries. A temporal bone fracture can injure the middle meningeal artery (MMA) and cause EDH. Open fractures and CSF leaks can cause infection in the CNS as they provide the portal of entry to microbes.

Intracranial Injuries

These can be classified as diffuse and focal, e.g., diffuse brain injuries and concussion.

Diffuse axonal injury is caused due to shearing force and diffuse injury is caused due to hypoxemia. *Concussion* is a nonfocal transient disturbance in the brain. *Diffuse axonal injury* occurs at the interface of gray and white matter. It results from shearing force on axons. It is usually seen in high-velocity injury and acceleration–deceleration injury. It causes punctate hemorrhage in the brain parenchyma.

Intracranial hemorrhage: It occurs in 46% of cases with TBI. It is associated with an increase in morbidity and mortality. It includes the following:

Epidural hematoma: It occurs in 22.5% of TBI. EDH develops after direct mechanical force over the skull and skull fracture. The most common site for EDH is the temporoparietal region, mostly unilateral and in young individuals. The classic presentation of lucid interval is seen in about 30% of patients. It is an extra-axial intracranial hematoma between the inner table of the skull bone and the dura mater. It causes the lenticular (biconvex) shape hematoma on a noncontract computed tomography (CT) scan (**Fig. 4**). The meningeal arteries lie between the dura mater and the skull in epidural space. The hematoma occurs due to injury to MMA which is in temporal fossa and associated skull fracture. It does not cause the suture line as dura mater is attached at the suture line of the skull. As it is an arterial bleed, it causes rapid intracranial bleed and significant mass effect and midline shift. The classic clinical attribute is the lucid interval which is typically present as an initial loss of consciousness following trauma,then complete transient recovery (lucid interval) followed by rapid progression of neurological deterioration. It is a neuroemergency and may require hematoma evacuation. Antiedema agents should be avoided as they can readily expand the hematoma by intracranial dehydration. The mortality in EDH is approximately 23%.

Subdural hematoma: SDH, developed between the dura mater and brain, is mostly due to a fall from height and acceleration–deceleration injury is due to a road traffic accident. SDH is more common than EDH. It is the most common intracranial injury associated with TBI. The dura mater splits into two leaves and encloses the venous sinuses. The intracranial hematoma

occurs due to disruption of bridging veins that drains blood to venous sinuses from brain parenchyma. This is common in the elderly. The clinical features of an SDH depend upon the patient's age, the presence of polytrauma, or the presence of altered mental status from a nontraumatic cause (e.g., alcohol or drug intoxication).

It appears as concave (crescent) shaped and crosses the suture line on the CT scan of the brain (**Fig. 5**). It is limited by falx cerebri. It is often associated with parenchymal injury. It is associated with 33% mortality in TBI.

Subarachnoid hemorrhage: It occurs in 22% of TBI. The bleeding occurs in the subarachnoid space which lies between the arachnoid mater and the pia mater and filled with CSF. Pia mater is firmly attached to brain parenchyma. SAH results from an injury to corticomeningeal vessels. It is often associated with brain contusion. It generally does not produce mass effect and mile shift and can cause a rise in ICP due to obstructive hydrocephalus (HCP). It can also cause an ischemic injury to cells through vasospasm of the vessel due to extravasation of hemoglobin. It is associated with the highest mortality of 40%.

Intraparenchymal bleed: It occurs in 21% of patients with TBI. The hemorrhage occurs in brain parenchyma. It is associated with brain edema and mass effect. Significant intracranial bleed can cause compression and herniation of brain parenchyma. It can cause compression ischemia in opposite-side brain parenchyma due to raised ICP. It is associated with 31.8% mortality.

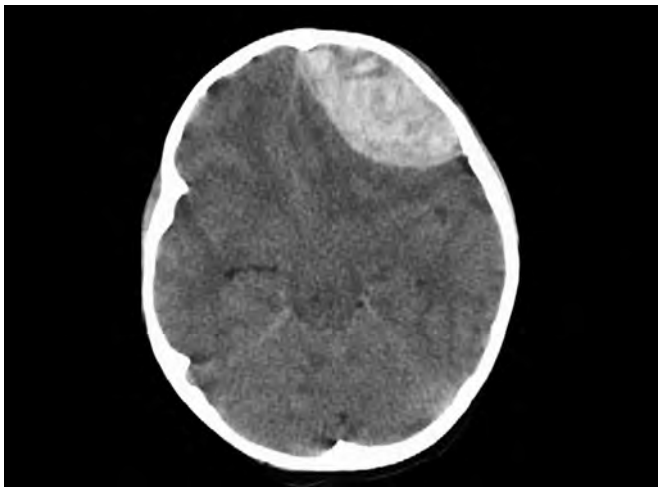


FIG. 4: Noncontrast CT scan image of epidural hematoma.

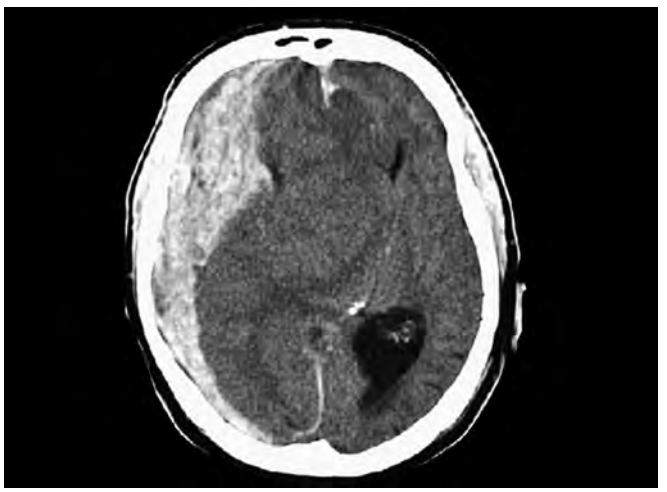


FIG. 5: Noncontrast CT scan image of subdural hematoma.

Contusion: It is a focal heterogeneous lesion that consists of punctate hemorrhage, edema, and necrosis. It is commonly associated with the acceleration–deceleration mechanism of injury. It is mostly seen in inferior frontal and anterior temporal lobes. The contusion can occur at the site of impact, coup and opposite to it, countercoup. So, the part of skull and brain that lies diagonally opposite to the impact should be checked.

TRAUMATIC BRAIN INJURY—ACCORDING TO SEVERITY

Traumatic brain injury can be classified on the basis of Glasgow coma scale (GCS) as mild GCS 14–15, moderate GCS 9–13, and severe GCS < 8.

Mild Traumatic Brain Injury

Concussion

Concussion is a transient, brief disruption of the neurologic function after a minor blunt trauma to the head, with or without a loss of consciousness, usually as a result of acceleration–deceleration forces to the head. Usually, the patient presents with symptoms of headache, confusion, and amnesia. Headaches, sensory sensitivity, memory or concentration difficulties, irritability, sleep disturbances, or depression may persist for a long period after a concussion, termed postconcussion syndrome.

Moderate and Severe Traumatic Brain Injury

A moderate TBI patient has a GCS score of 9–13. Pateint can present with a variety of clinical features such as worsening headache and nausea, confusion, seizure, and loss of consciousness. The patient may present with isolated facial trauma or polytrauma associated with focal neurologic deficits. The emergency physician should be more cautious while managing this type of patient. Initially, patients are able to talk but gradually their GCS score deteriorates significantly and are consistent with severe TBI (talk and deteriorate patient). Most of the patients have extra-axial hematomas, epidural or subdural. These patients have better clinical outcomes if detected early and treated rapidly. Successful management depends upon frequent assessment of GCS score, close observation for minor mental status changes or focal neurologic findings, frequent use of CT scanning, and early neurosurgical intervention.

In the emergency department, if the patient presents with moderate TBI with herniation, immediate interventions such as hyperventilation and osmotic therapy should be initiated and consideration should be given for surgical evacuation of hematoma before transferring to a definitive care unit. All moderate TBI patients should undergo a CT scan and should be admitted to the observation unit for frequent neurological examination and monitoring; a repeat CT scan should be done if required.

Severe TBI is when the patient presents acutely with a GCS score of 8 or less. Any intracranial contusion, hematoma, or brain laceration is considered as severe TBI. A patient with severe TBI and with an increase in ICP presents with symptoms of progressive hypertension, bradycardia, and shallow or

irregular respiration (Cushing's reflex/phenomenon). These features represent the life-threatening raised ICP and require urgent ICP management such as hyperventilation osmotic therapy and surgical decompression.

CLINICAL FEATURES OF TRAUMATIC BRAIN INJURY

Symptoms vary and depending on the severity of the head injury, these may include any of the following: Vomiting, lethargy, headache, confusion, paralysis, coma, loss of consciousness, dilated pupils, vision changes (blurred vision or seeing double, not able to tolerate bright light, loss of eye movement, blindness), CSF (which may be clear or blood-tinged) coming out of the ears or nose, dizziness and balance problems, breathing problems, slow pulse, slow breathing rate, with an increase in blood pressure, ringing in the ears or changes in hearing, cognitive difficulties, inappropriate emotional responses, speech difficulties (slurred speech, inability to understand and/or articulate words); difficulty swallowing, body numbness or tingling, droopy eyelid or facial weakness, and loss of bowel control or bladder control. Signs of herniation include irregular pupil, abnormal flexion or extension, and Cushing triad—hypertension, bradycardia, and irregular breathing.

GUIDELINES FOR MANAGEMENT OF HEAD INJURIES

Guidelines are for effective clinical assessment and management of a patient with head injury. They promote the best and appropriate treatment to the person with head injury and are also for their families and their attendants so that they have the knowledge about what should be done for the betterment of the injured person. Also, include referral guidelines in cases where specialist care is needed.

Prehospital Care

Initial assessment: It should start with the "Glasgow coma scale" and the score should be recorded or communicated properly on every note. *Children with head injury should be assessed and managed according to* advanced pediatric life support. *Adults with head injury should be assessed and managed according to* advanced trauma life support (ATLS) course.

Immediate care at the scene: Cervical collar should be applied in case of suspected head injury:

- GCS < 15 on initial assessment
- Neck pain or tenderness
- Focal neurological deficit
- Paresthesia in the extremities
- Any other clinical suspicion of cervical spine injury

It manages pain effectively, gives assurance to the patient and family, and supports limb fractures and Foley's catheterization.

Emergency Department Care

Assessment of all head injuries of the patients should be done within 15 minutes of arrival:

- Airway, breathing, and circulation (ABC) assessment and management
- Assessment of risk factors
- CT of head and cervical spine imaging and other body areas
- Conscious patient should be assessed immediately
- An anesthetist or critical care physician should provide appropriate airway management and assist with resuscitation in a patient with GCS 8 or less.
- A standard head injury *pro forma* should be used for documentation.

Investigations for Clinically Important Brain Injuries

Acute clinically important brain injuries should be investigated by CT imaging of the head using minimum radiation dose. Magnetic resonance imaging (MRI) should be performed depending on the need but should not be the primary investigation. There is no role of X-ray of skull. *The criteria for performing a CT head scan* are as follows:

- GCS < 13 on initial assessment in the emergency department
- GCS < 15 at 2 hours after the injury on assessment in the emergency department
- Open or depressed skull fracture
- Features of basal skull fracture
- Post-traumatic seizure
- Focal neurological deficit
- Vomiting
- Elderly group
- Any history of bleeding or clotting disorders
- Retrograde amnesia of events immediately before the head injury

In all the above-mentioned cases, a provisional written radiology report should be made available within 1 hour of the scan being performed. The risk stratification of head trauma in the emergency department is helpful in triaging the high-risk patient and prioritize for the management (**Table 2**).

RESUSCITATION AND MANAGEMENT OF HEAD TRAUMA IN THE EMERGENCY DEPARTMENT

Airway, Breathing, Circulation

Head trauma management started with assessment and stabilization of the airway, breathing, and circulation, like any other critically ill patient. Rapid-sequence endotracheal intubation with in-line stabilization of the cervical spine should be considered for airway protection for patients with a GCS < 8. Maintain PaO_2 > 60 mm Hg and saturation > 90%. Hypoxia and hypotension are associated with increased mortality. Maintain normocarbia ($PaCO_2$ around 35 mm Hg) and avoid hyperventilation in a patient with TBI; hyperventilation produces vasoconstriction and further ischemia which decreases cerebral perfusion. Similarly, hypercarbia produces vasodilation and raised intracranial tension and clinical deterioration. Use of hyperventilation should be restricted only to acutely herniating and deteriorating patients while arranging for emergency craniotomy.

Fluid Resuscitation

Choosing the right fluid is an important aspect for head trauma management. Maintain normovolemia by intravenous fluid, blood, and blood products. Ringer's lactate and normal saline

TABLE 2: Risk assessment in a head trauma patient in the emergency department.

High-risk head trauma	*Medium-risk head trauma*	*Low-risk head trauma*
• Focal neurologic deficit • Unequal pupils • Skull fracture • Polytrauma • GCS score of <8 • Unconsciousness • Post-traumatic confusion • Worsening headache • Vomiting • Post-traumatic seizure • Associated intoxication • Unreliable history of injury • Age older than 60 years or younger than 2 years	• Initial GCS score of 13–15 • Brief period of LOC • Post-traumatic amnesia • Vomiting • Headache • Intoxication	• Asymptomatic • Conscious • Well orientation/memory • Accurate history • No other injuries • Normal neurological exam • Normal pupils • GCS score of 15 • Injury of >24 hours' duration • No/mild headache • No vomiting

(GCS: Glasgow coma scale; LOC: loss of consciousness)

are ideal solutions for resuscitation of TBI. Hypotonic and glucose-containing fluid should not be used. A normal serum sodium level should be maintained. Hyponatremia causes brain edema. A vasopressor can be used in neurogenic shock due to spinal cord injury.

Measures to Maintain Intracranial Pressure

It is important to maintain an equal volume of each compartment (brain, blood, CSF) of skull. If the volume of one component is increased [due to space-occupying lesion (SOL), intracranial hemorrhage, edema], then the volume of other components should decrease as a compensatory mechanism. A mismatch in the compensatory mechanism leads to a rise in ICP; a decrease in CPP ultimately causes cerebral ischemia. ICP monitoring is preferred in severe traumatic injury by placing external ventricular drain which is helpful in measuring the global ICP and controlling it by CSF drainage. Mannitol is helpful in reducing the raised ICP. It should not be used in hypotensive patients. It is highly recommended as bolus (1 g/kg) in an acutely deteriorating and herniating patient provided the patient is normovolemic normotensive.

Hypertonic saline is also helpful in reducing the raised ICP. Three percent concentration is frequently used and hypertonic saline can be used in a hypotensive patient. Barbiturates are also helpful in reducing the raised ICP but should not be used in a hypotensive and hypovolemic patient; hence, it is not helpful in an acute resuscitative phase. Hypothermia is also helpful in reducing the raised ICP. Prophylactic hypothermia is neuroprotective and beneficial effects are seen in severe TBI.

Anticonvulsant

The possibility of seizure in head trauma increases with an increase in the severity of head injury. Patients with severe TBI are more prone to seizures. Seizure can be controlled by anticonvulsant such as phenytoin, fosphenytoin, diazepam and lorazepam. Seizures should be controlled as soon as possible to prevent secondary brain injury. In an adult, the loading dose of phenytoin is 1 g and then the maintenance dose is 100 mg every 8 hours.

Antibiotics

There is a high possibility of infection rate in a patient with severe TBI. Prophylactic antibiotics can be used in a patient with basal skull fracture and CSF leak in view of risk of meningitis. The risk of infection also exists in a patient with external ventricular drain.

Scalp Wound

It should be inspected carefully and adequately cleaned. Stop hemorrhage by applying direct pressure or bleeding vessels ligation. Sutures or staples can be applied. CT scan of the head should be performed to exclude or confirm the skull fracture. The advice of a neurosurgeon should be taken for all cases of open/depressed skull fracture.

Penetrating Brain Injuries

A CT scan is appropriate in locating the bullet foreign bodies and intracranial air. Angiography is helpful in identifying the traumatic aneurysm and arteriovenous fistula. In these cases, endovascular management is helpful. Start prophylactic antibiotics and early ICP monitoring.

Do not remove any penetrating objects such as knife arrow before vascular injury assessment or definitive surgical management, otherwise fatal hemorrhage may occur.

Neurosurgical Consult

A neurosurgeon should be consulted in each and every case of head injury and for further follow-up. The most important indications for urgent neurologic consult are coma, confusion, focal neurological deficit, seizure, penetrating injury, And skull base fracture with CSF leak.

Communication with Families and Attendants

The attending and admitting physician should brief the families about the overall condition and explain what they are doing. The team of doctors managing the patient should share information about possible complex changes in the patient with family members.

Transfer of Child or Adult from a Hospital to a Neuroscience Unit

- Patient should be transferred to a neuroscience unit oy after completing the initial resuscitation and stabilization and establishing comprehensive monitoring.
- Use intubation and ventilation before transfer.
- Patient should be accompanied by a trained and experienced doctor and assistant in emergency cases and by clinical staff in a nonemergency condition.

During transfer, family members must be given full access to the patient as is practical.

Admission and Observation

Head injury should be admitted under the care of a trained neurosurgery team

- Patients with clinically significant abnormalities on neuroimaging
- Patients with low GCS regardless of the neuroimaging results
- CT scanning could not be done due to patient irritability
- Persistent vomiting and severe headaches
- Drug or alcohol intoxication, suspected nonaccidental injury, meningism, CSF leak

Observation of Admitted Patients

A patient admitted with head injury should be observed only by trained clinicians for neurological observations such as GCS, pupil size and reactivity, limb movements, respiratory rate, heart rate, blood pressure, temperature, and blood oxygen saturation. These should be performed and recorded on a half-hourly basis until GCS of 15 has been achieved. After that, it should be done half-hourly for 2 hours, then 1-hourly for 4 hours, and then 2-hourly thereafter.

Any deterioration should be informed to the supervising team:

- New development of agitation
- Decrease of even 1 point in GCS score
- Severe or increasing headache or persisting vomiting
- New development such as pupil inequality or asymmetry of limb or facial movement
- In all the above cases, an immediate CT scan should be considered.

Discharge and Follow-up

Patients can be discharged, if there is no indication for a CT scan of the head and no other factors (such as drug or alcohol intoxication, other injuries, shock) are present. Patient can be discharged if CT head and cervical spine is normal and GCS 15 with normal clinical examination. Patients admitted following a head injury may be discharged after resolution of all significant symptoms and signs.

Advice on discharge and follow-up: Provide a printed discharge summary to all patients with any kind of head injury and to their families. A printed summary should focus on:

- Details about head injury and recovery process
- List of dangerous symptoms when they need to contact the emergency department
- Contact details of the hospital services treating team
- Medication chart

Any patient who has residual problems should be managed as outpatient by a team of neurologist, neurosurgeon, clinical psychologist, and rehabilitation medicine specialist.

SUMMARY

Head trauma leads to brain parenchymal injury which is termed traumatic brain injury. TBI is due to falls, road traffic accident, blunt head injury, assault, blast injury, and sometimes child abuse. TBI involves alteration in CBF, parenchymal injury, cerebral edema, ICP, and herniation. Head trauma is a critical situation and leading cause of death worldwide. Education regarding preventive measures of head trauma is important for public, such as the use of helmets and seatbelts. An emergency physician should have in-depth knowledge of common neurologic injuries related to trauma and their prehospital, in-hospital, and critical care management in patients (**Table 3**).

TABLE 3: Management of traumatic brain injury (TBI).

Severity of TBI	*Mild TBI*		*Moderate TBI*	*Severe TBI*
Initial management	AMPLE history and neurological exam: Ask particularly about use of anticoagulants		Neurosurgery evaluation or transfer required	Urgent neurosurgery consultation or transfer required
	May discharge if admission criteria not met	Admit for indications below:	Primary survey and resuscitation	Primary survey and resuscitation
	• Determine mechanism, time of injury, initial GCS, confusion, amnestic interval, seizure, headache severity, etc. • Secondary survey including focused neurological exam	• No CT available • CT abnormal, skull fracture, CSF leak • Focal neurological deficit • GCS does not return to 15 within 2 hours	• Arrange for transfer to definitive neurosurgical evaluation and management • Focused neurological exam • Secondary survey and AMPLE history	• Intubation and ventilation for airway protection • Treat hypotension, hypovolemia, and hypoxia • Focused neurological exam • Secondary survey and AMPLE history

Continued

Continued

Severity of TBI	*Mild TBI*		*Moderate TBI*	*Severe TBI*
Diagnostic	• CT scanning as determined by head CT rules • Blood/Urine EtOH and toxicology screens	• CT not available, CT abnormal, skull fracture • Significant intoxication (admit or observe)	• CT scan in all cases • Evaluate carefully for other injuries • Type and crossmatch, coagulation studies	• CT scan in all cases • Evaluate carefully for other injuries • Type and crossmatch, coagulation studies
Secondary management	• Serial examination until GCS is 15 and patient has no perseveration or memory deficit • Rule out indication for CT	• Serial examination Perform follow-up CT scan if first is abnormal or GCS remains <15 • Repeat CT (or transfer) if neurological status deteriorates	• Serial examination • Consider follow-up CT in 12–18 hours	• Serial examination • $PaCO_2$ 35–40 mm Hg • Mannitol • Brief hyperventilation $PaCO_2$ no <25 mm Hg • $PaCO_2$ no <25 mm Hg, except with signs of cerebral herniation. Avoid hyperventilation in the first 24 hours after injury when cerebral blood flow can be critically reduced. Emergent neurosurgical care
Disposition	Home if patient does not meet criteria for admission	• Obtain neurosurgical evaluation if CT or neurological exam is abnormal or patient status deteriorates • Arrange for medical follow-up and neuropsychological evaluation	Repeat CT immediately for deterioration and manage as in severe brain injury	
Perform ABCDEs in all patients with special attention to hypoxia and hypotension.				

(ABCDE: airway, breathing, circulation, disability, exposure; AMPLE: allergies, medications, past medical history, last eaten, events leading; CSF: cerebrospinal fluid; CT: computed tomography; EtOH: ethyl alcohol; GCS: Glasgow coma scale; $PaCO_2$: partial pressure of carbon dioxide; TBI: traumatic brain injury)

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Neck Trauma

Lokendra Gupta, Atul Singh Tomar

INTRODUCTION

Neck trauma management in emergency is a challenging and arduous task. Traumatic neck injuries account for 5–10% of all traumatic injuries and carry a high rate of morbidity and mortality because several vital structures can be damaged as this anatomical region contains many vital structures (complex network of neurovascular and muscular structures supported by various fascial planes). In the neck, multiple vital structures are vulnerable to injury in a small anatomic area and not protected by bones. These patients will require urgent initial assessment as per the advanced trauma life support (ATLS) protocol. The mortality rate for penetrating neck injuries is as high as 10%. The most common cause of death from penetrating neck trauma is a vascular injury. The area of highest risk is to injuries at the base of the neck, in zone 1. Beware that up to 50% of gunshot wounds are accompanied by significant injuries. These carry a mortality rate of 10–15%. Stab wounds cause serious injury in 20–30% of cases, with an overall mortality rate of 5%. The most common cause of delayed mortality is due to esophageal injury, which may not be readily apparent on initial presentation.

ETIOLOGY

Blunt: Motor vehicle accidents, sports injuries, strangulation blows

Penetrating: Stab injuries (knife, razor, blade, glass, etc.), projectile injuries (handgun, rifle, shotgun)

Note: Children may sustain penetrating injuries after falls onto objects in their environment (e.g., fence posts) or objects held in their mouth (e.g., toothbrushes or pencils).

ANATOMY

The neck is divided into three zones: (1) Zone 1, (2) Zone 2, and (3) Zone 3 (**Table 1**). In penetrating trauma, zone designations have anatomic, diagnostic, and management implications. Since the zone system is helpful in guiding management decisions, it is preferable to employ the zone system when describing traumatic injuries. Understanding the anatomy of the neck, especially the location of important structures, is essential to providing optimal care (**Fig. 1**).

TABLE 1: Anatomical zones of the neck and their structures.

	Zone 1	***Zone 2***	***Zone 3***
Anatomic landmarks	Clavicle/sternum to cricoid cartilage	Cricoid cartilage to the mandible	Superior angle of the mandible
• Anatomic structures in zone	• Proximal common carotid artery • Subclavian artery • Vertebral artery • Lung apices • Trachea • Thyroid • Esophagus • Thoracic duct • Spinal cord	• Carotid artery • Vertebral artery • Jugular vein • Pharynx • Trachea • Esophagus • Larynx • Vagus nerve • Recurrent laryngeal nerve • Spinal cord	• Vertebral artery • Distal carotid artery • Distal jugular vein • Salivary and parotid glands • Cranial nerves IX–XII • Spinal cord

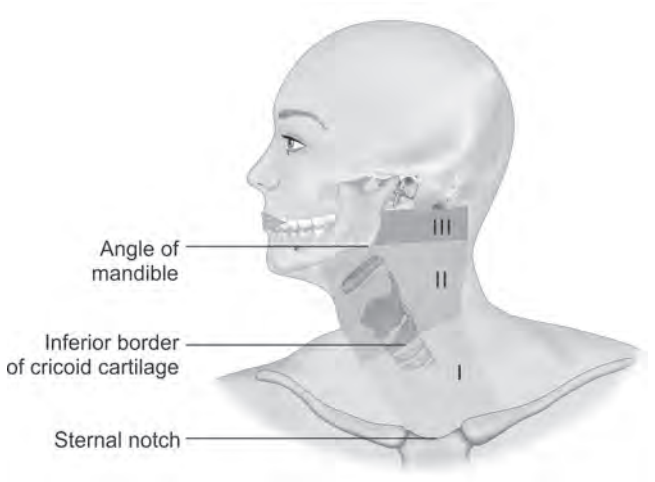


FIG. 1: Anatomical zones of the neck.

Zone 1: This is the area between the clavicles and the cricoid cartilage. This zone contains vital structures which include the innominate vessels, the origin of the common carotid artery, the subclavian vessels and the vertebral artery, the brachial plexus, the trachea, the esophagus, the apex of the lung, and the thoracic duct. Furthermore, surgical exposure and access can be difficult in this zone, because of the presence of the clavicle and bony structures of the thoracic inlet.

Zone 2: This is the area between the cricoid cartilage and the angle of the mandible. The following structures are located here: The carotid and vertebral arteries, the internal jugular veins, the trachea, and the esophagus. This zone has comparatively easy access for clinical examination and surgical exploration. It is the largest zone and the most commonly injured in the neck.

Zone 3: This is the area between the angle of the mandible and the base of the skull. This area contains the distal carotid and vertebral arteries and the pharynx. Since it is very close to the base of the skull, this area is less amenable to physical examination and difficult to explore during surgical evaluation.

Other important anatomic features are as follows:

- There is anatomic continuity in the fascial layers between the neck and the anterior mediastinum.
- The *platysma muscle* sits between the superficial and the deep cervical fascia: Violation of the platysma increases the likelihood of deep structure injury and should be explored in the operating room immediately.

Anatomically, the neck is also described in triangles. The sternocleidomastoid muscle separates the neck into two triangles: (1) The anterior triangle contains most of the major anatomic structures of the neck including larynx, trachea, pharynx, esophagus, and major vascular structures and (2) the posterior triangle contains muscles, the spinal accessory nerve, and the spinal column.

PATHOPHYSIOLOGY

The pathophysiology of neck injury depends on the mechanism of injury. The neck contains many critical organ systems adjacent to one another. It is for this reason that even innocuous-appearing wounds have the potential to cause either immediate or delayed life-threatening injuries or complications. It is rare to have a cervical injury without a neurological deficit in patients with penetrating neck trauma. With a low-risk National Emergency X-radiography Utilization Study I (NEXUS I) criteria, spinal cord injuries are unlikely to occur. These criteria obtain only if the patient is:

- Alert and awake
- Not intoxicated
- Has no signs or symptoms of neurologic injury
- Has no spinous process tenderness

Vascular injuries are the most common of cervical injuries and occur in up to 40% of patients with penetrating neck trauma.

CLINICAL PRESENTATION

Clinical presentations related to neck trauma are given below. An emergency medicine clinician must be familiar with hard and soft signs (**Table 2**). In pediatrics, it is prudent to consider *stridor* as an additional *"hard"* sign as it may indicate impending airway loss secondary to bleeding into the airway or from swelling encroaching on the patency of the airway. A patient with an apparently stable airway, in the first few hours, may deteriorate quickly due to edema. Even minor signs should still lead to very careful observation.

- ***Airway*:**
  - Respiratory distress
  - Stridor hoarseness
  - Hemoptysis
  - Subcutaneous emphysema
  - Sucking wound
- ***Vascular:***
  - Hematoma
  - Change of sensorium
  - Persistent bleeding
  - Bruit

TABLE 2: Clinical features of concern in neck trauma.

Hard signs	• Airway compromise • Expanding and pulsatile hematoma • Active, brisk bleeding • Hemorrhagic shock • Hematemesis • Neurologic deficit • Massive subcutaneous emphysema • Air bubbling through wound
Soft signs	• Hemoptysis • Oropharyngeal blood • Dyspnea • Dysphagia • Dysphonia • Nonexpanding hematoma • Chest tube air leak • Subcutaneous or mediastinal air • Vascular bruit or thrill • Crepitus

- Thrill
- Hypovolemic shock

- ***Neurological*:**
  - Hemiplegia
  - Quadriplegia
  - Coma
  - Cranial nerve deficit
  - Change of sensorium
- ***Esophageal*:**
  - Dysphagia
  - Odynophagia
  - Hematemesis
  - Hemoptysis
  - Tachycardia
  - Fever

EVALUATION OF NECK TRAUMA

Evaluation of neck injuries warrants notification of a trauma team or surgeon, if either is available. Since physical examination may not be reliable in ruling out injuries in patients with neck trauma, one should consider a low threshold for obtaining additional imaging studies and/or a surgical consultation. Periodic examination is required to identify deterioration in clinical status as well as any ongoing. The value of a thorough secondary survey to evaluate for additional injuries cannot be overemphasized in such patients. Diagnostic testing is performed for stable patients manifesting soft signs of injury and sometimes even for those who are asymptomatic at initial presentation.

A plain chest X-ray may show pneumomediastinum/pleural effusion/hydrothorax/subcutaneous emphysema in the event of esophageal perforation. *A plain X-ray of neck* (*soft tissue views*) may show surgical emphysema and soft-tissue swelling but are unreliable in demonstrating laryngeal injury.

Computed tomography (CT) angiogram of neck shows that the role of screening for associated cerebrovascular injury to carotid or vertebral arteries is limited in the pediatric population. *Indication for CT angiogram of neck in trauma includes*: Lateralizing neurological deficit (not explained by CT of head), infarct on CT of head, cervical hematoma, massive epistaxis, anisocoria/Horner's syndrome, Glasgow Coma Scale (GCS) < 8 without significant CT head findings, and cervical spine fracture. Base of skull fracture (particulary fracture extending through petrous temporal bone and involving carotid canal). Facial fractures (particularly LeFort I or III). A plain CT scan of neck, i.e., without contrast, may be better able to identify laryngeal fracture but should not be performed in unstable patients.

Contrast Swallow

Ear, nose, and throat (ENT) may advise a contrast study, but this investigation should not be ordered without ENT consultation. Water-soluble contrast, if swallowed prior to X-ray, may reveal a contrast leak. Barium contrast can cause mediastinal and/or pulmonary inflammation if aspirated, so it is better avoided if there is an aspiration risk.

All patients with signs/symptoms of injury to the neck should be discussed with ENT for consideration of a fiberoptic laryngoscope.

Evaluation of Aerodigestive Tract Injuries

Aerodigestive tract injuries, especially those involving the cervical esophagus, should be identified and repaired within 12–24 hours after injury to minimize associated morbidity and mortality. Evaluation of asymptomatic aerodigestive tract injuries includes contrast swallow studies and endoscopy (rigid and flexible esophagoscopy, bronchoscopy, and laryngoscopy).

- ***Endoscopy*:** It is more reliable than contrast swallow studies to identify injuries to the hypopharynx and cervical esophagus. Several authors have demonstrated that endoscopy will identify 100% of digestive tract injuries, whereas contrast swallow studies are less sensitive, especially for hypopharyngeal injuries.
- ***Rigid and flexible esophagoscopy, rigid and flexible bronchoscopy, and rigid direct laryngoscopy*:** These are performed in the operating room under general anesthesia. It is recommended that both rigid and flexible esophagoscopy be performed to rule out occult esophageal injuries.
- ***Rigid and flexible esophagoscopy*:** Rigid esophagoscopy may provide a better view of the proximal esophagus near the cricopharyngeal muscle, while flexible esophagoscopy, with its magnification on the viewing screen and ability to insufflate, gives excellent visualization of more distal esophageal anatomy.
- ***Swallow studies*:** Finally, swallow studies with either gastrografin or barium may not be available in austere environments to rule out occult esophageal injuries and, as noted above, are less accurate than endoscopy. Missed esophageal injuries, which may be occult in 25% of patients, can be devastating, with mortality rates ranging up to 25%.

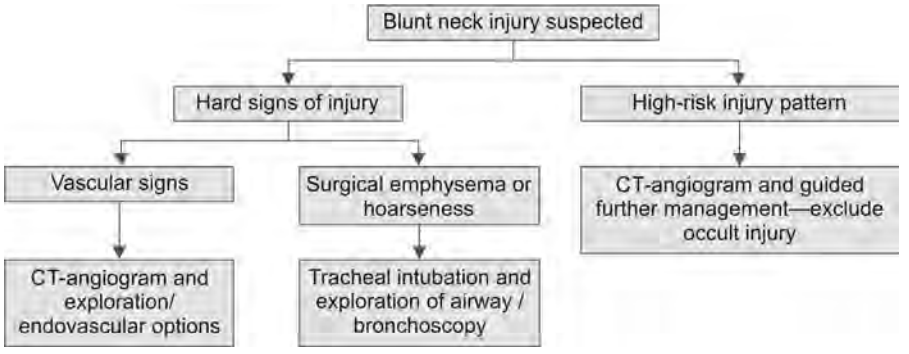
MANAGEMENT

Since the neck contains vital structures, prompt evaluation and rapid intervention are required. The initial assessment should be performed according to the ATLS protocols. An immediate trauma service consultation should be obtained for patients with suspicion of vascular, tracheal, or esophageal injury.

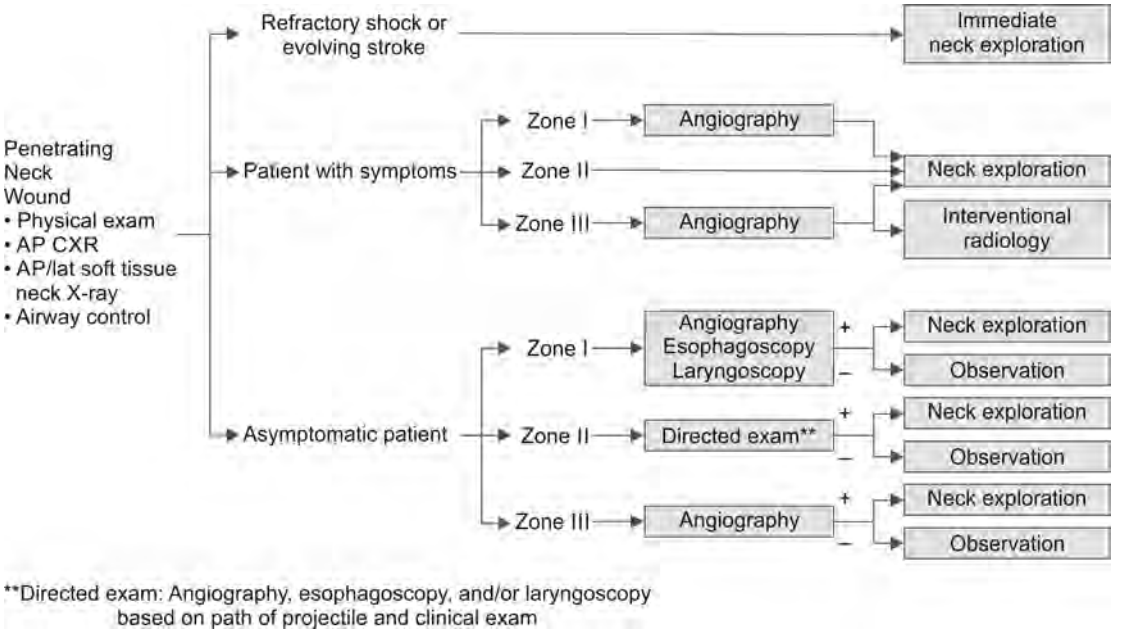
Priorities in the management of patients with neck trauma are like those for any other patient with a life-threatening condition. The primary priorities are securing the airway, maintaining ventilation, controlling hemorrhage, and treating shock. At the same time, check vital signs and determine the stability of the patient. Patients with neck may have other life-threatening injuries that may take precedence. Further management of blunt neck trauma and penetrating neck trauma is described in **Flowcharts 1** and **2**, respectively.

Airway

As always, the priority is airway stabilization, particularly in patients with neck trauma, while maintaining cervical spine immobilization. Remember that in-line stabilization should always be maintained when there is a concern for a cervical spine injury. Up to 10% of patients with penetrating neck injuries may present with airway compromise. Be aware that despite a stable initial appearance, airway compromise can ensue rapidly.


Blunt neck injury suspected
Hard signs of injury
High-risk injury pattern
Vascular signs
Surgical emphysema or hoarseness
CT-angiogram and guided further management—exclude occult injury
CT-angiogram and exploration/ endovascular options
Tracheal intubation and exploration of airway / bronchoscopy

FLOWCHART 1: Management of blunt neck trauma.



(AP: anteroposterior; CXR: chest X-ray)

FLOWCHART 2: Management of penetrating neck trauma.

Beware that swelling, distorted anatomy, and hematoma formation may contribute to impending airway obstruction in facial or neck trauma. Therefore, early airway control should be considered as the conditions may rapidly worsen.

Breathing

Evaluate the breathing and assess for any hemothorax or pneumothorax, particularly with penetrating zone 1 injuries.

Circulation

Direct simple pressure on the open wounds should be used to control bleeding in the emergency department. Wounds that have air sucking or bubbling should be covered with Vaseline gauze. No blind probing of the wound and no clamping of the vessels should occur in the emergency department. It is important not to occlude both carotid arteries or obstruct the patient's airway. Avoid nasogastric tube placement in patients with penetrating neck injury because of the risk of hematoma rupture. The agitation of the patient during tube insertion may precipitate bleeding. Further management of the patient with penetrating neck trauma depends on the anatomic zone of injury, clinical presentation, and hemodynamic stability. Determine the zone of injury, as this will determine evaluation and management strategy.

Zone 1: Since up to one-third of patients with a clinically significant zone 1 injury may have no symptoms at their initial presentation, many centers advocate vascular evaluation of the aortic arch and great vessels, with an esophageal evaluation.

Zone 2: This area has easier surgical access and poses a low risk for adverse sequelae from exploration. The decision for surgical exploration depends on the symptoms. Symptomatic penetrating zone 2 injuries should undergo neck exploration. Asymptomatic patients with penetrating zone 2 injuries may be treated with either mandatory exploration or directed evaluation and serial examinations. *Indications for an angiogram:* A stable patient with persistent hemorrhage or neurologic deficits, the presence of Horner syndrome (sympathetic nerve plexus injury), and hoarseness (recurrent laryngeal nerve injury). This suggests a violation of the carotid sheath.

Zone 3: In this zone, there is potential for injury to major blood vessels and the cranial nerves close to the skull base. Beware that patients with arterial injuries may be asymptomatic at their initial presentation, and surgical exposure and control of bleeding in this location may be quite difficult. In addition, many vascular injuries are amenable to definitive treatment by an interventional radiologist. Therefore, the injury can be potentially treated in the same setting like the one in which the diagnostic angiogram is done.

SUMMARY

Initial management of these patients is established according to ATLS criteria. Urgent surgical examination is indicated in unstable patients and patients with severe signs. Later, they may benefit from previous CT angiography. If hemodynamic instability is caused by hemorrhage, tamponade with a Foley catheter can assist in the initial stabilization of the patient, providing the necessary time to perform a CT angiogram and diagnose the injury type. It is advisable to perform CT angiogram in all symptomatic patients (reducing the need for surgical examinations, as well as their complications) and also in asymptomatic patients with a high-speed mechanism of injury. Observation is safe in asymptomatic patients; those with a negative CT angiogram do not require treatment. Angiography and interventional radiology can be diagnostic and therapeutic tools in patients with vascular trauma, thereby avoiding unnecessary surgical interventions.

Overall, injuries to zone 1 have the highest morbidity and mortality. Zone 2 injuries are the most common after penetrating trauma, but because they can be readily accessible, they also have the best prognosis. Injuries to Zone 2 can be challenging, because access to some structures may not be easy. The prognosis of these injuries is guarded. In individuals who suffer complete transection of the spinal cord, the injury is almost always fatal. Individuals who do retain neurological function, including preservation of rectal tone, usually have a good outcome. However, if the neurological deficits persist, the outcomes are poor. When the vasculature structures are injured by blunt trauma, the outcomes are worse compared to penetrating injuries. In many neck injuries, one also has to search for airway and esophageal injuries as they may not always be apparent. Overall, the mortality rate for patients suffering penetrating trauma to the neck varies from 2 to 5%, but if a major blood vessel has ruptured, this is often fatal in about 70% of cases.

The *laryngotracheal airway* and the *cervical spine* are the two most integral structures that can be damaged in blunt trauma to the neck. Prior to any intervention, such as flexible fiberoptic evaluation of the airway, the neck must be stabilized securely in line. The status of the cervical spine takes evaluative precedence after the airway has been secured in a manner that does not compromise a potential cervical spine injury. Hemodynamic stability or instability will be an important guide to the urgency of intervention, including diagnostic computed tomography angiography (CTA) prior to exploration of the neck to control bleeding and secure the vascular elements. An excellent physical examination must always be performed and will be the clinical guide to the next steps in evaluation and treatment.

IMPORTANT POINTS

- Penetrating injuries to the neck can damage a host of structures. Understanding the zones of the neck and the structures within them can help predict injuries.
- If the platysma is violated, it should be assumed that deeper structures have been injured until proven otherwise.
- Early airway management is crucial as injuries can lead to dynamic airway obstruction. Always be prepared for a surgical airway.
- The presence of any hard signs of aerodigestive/neurovascular injuries (expanding/pulsatile hematoma, active brisk bleeding, hemorrhagic shock, massive subcutaneous emphysema, air bubbling through the wound, neurologic deficit) or violation of platysma mandates an immediate operation theater (OT) trip. Do not delay the patient in getting to the OT for additional studies.
- Attempt to control vascular injuries with direct pressure and consider balloon tamponade with a Foley catheter.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Spinal Trauma

Winston Noronha

INTRODUCTION

Spinal cord injuries (SCIs) are seen in high-speed vehicle crashes and falls from heights. The victims are usually young, healthy adult males. Up to 10–15% of head injury cases have a coexisting cervical spinal injury, so radiological evaluation of the cervical spine is necessary along with head injury. During the evaluation of head injury, there should be high suspicion of spinal injury and adequate immobilization of spine should be maintained. Proper evaluation and management of spinal injurers are important because if missed or not treated, they can lead to permanent neurological deficit. There is often injury to the brain, chest, abdomen, pelvis, and extremities. SCI can occur at any level and it can be complete or incomplete. The most common level of SCI in adults is C5, followed by C4, C6, C7, T12, and L1. In children, fractures of C1 and C2 are more common. SCI primarily affects young, healthy adults—mostly young, adult males (80.7% male predominance)—and thus is a devastating and life-altering injury. SCI can present in the form of minor symptoms such as pain, numbness to severe symptoms such as paralysis and incontinence. Injury to any one of the seven cervical vertebrae can cause quadriplegia (injury at the level of neck) (**Fig. 1**). Quadriplegia and paraplegia have high mortality and morbidity due to bedsores, respiratory and urinary infection, contractures, etc. SCIs do not only damage the sensory and motor systems but also cause muscle atrophy, pressure sore, kidney, bladder and bowel problems, and cardiac and respiratory dysfunctions. These patients need constant long-term care which throws a great burden on the family financially, psychologically, and physically.

APPLIED ANATOMY OF SPINE

The vertebral column has 33 vertebrae extending from the skull base to the coccyx. There are 7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and 4–5 coccygeal vertebrae. The vertebrae are separated by disks. The spinal canal contains the spinal cord, which is protected in front by the vertebral body and behind by the laminae, pedicles, transverse and spinous processes, and strong ligaments and muscles. The spinal canal is widest at the level of second cervical vertebra and narrows below. Various nerve roots exit the spinal cord at each vertebral level through fenestrations. The vertebral column is strong enough to protect the delicate spine but has enough flexibility to allow full range of spinal movement (flexion-extension, lateral flexion, and rotation). The cervical spine by its location and greater mobility makes it most

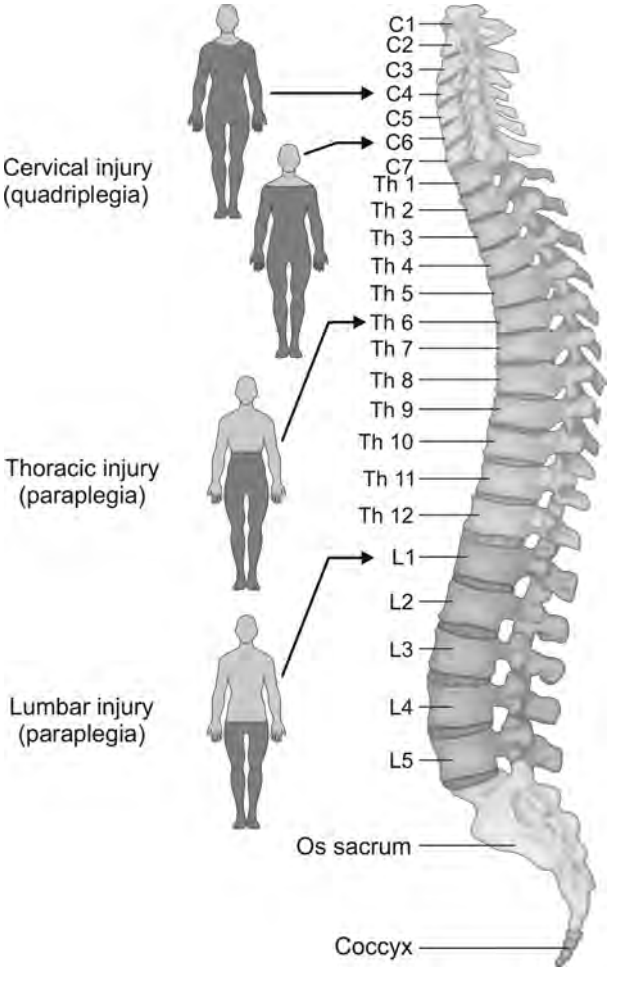


FIG. 1: Level of spinal injury and manifestation.

vulnerable to injury. Thoracic vertebrae have limited mobility and these are supported by the rib cage which makes them less vulnerable to injuries. The thoracolumbar junction between the less mobile thoracic and more mobile lumbar vertebrae is more prone to injuries. A typical vertebra consists of: Body, pedicles, laminae, transverse and spinous processes, and four articular surfaces (**Fig. 2**). The bones are held by tough ligaments, i.e., anterior and posterior longitudinal ligaments (PLLs) and the posterior ligamentous complex (PLC) which includes supraspinous and interspinous ligaments, ligamentum flavum (LF), and capsules of the facet joints. In children, the spinal cord can be injured without vertebral fracture. This is called *SCIWORA* (Spinal Cord Injury without Radiological Abnormality). Ligamentous injuries can also cause spinal cord damage without vertebral fractures. In the spinal tract, the nerve fibers are arranged in columns or tracts (**Fig. 3**). The important ones are mentioned in **Table 1**.

MECHANISMS OF INJURY

Various mechanisms of hyperflexion, hyperextension, flexion rotation, and penetration give rise to various injuries to the spine (**Fig. 4**):

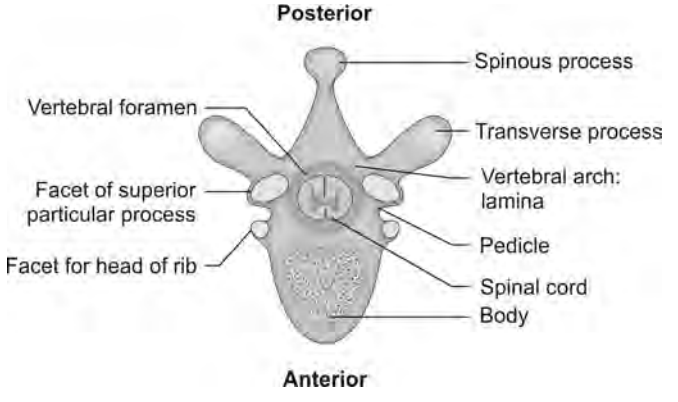


FIG. 2: Typical vertebra.

- Compressive force in a craniocaudal direction (axial loading)
- Acute flexion causing anterior wedge compression of the vertebra
- Flexion around an axis anterior to the vertebral column—transverse vertebral chance fracture
- Disruption of the posterior spinal elements (pedicles, facets, and lamina)—fracture-dislocation

CLASSIFICATION OF SPINAL INJURIES

Level of Injury

The level of injury is documented by the vertebral level and neurological level. More important is the neurological level which may not correspond to the bony level as the nerves ascend to join the cord higher up.

Severity of Neurological Deficit

Neurological deficit leads to complete or incomplete quadriplegia/tetraplegia and complete or incomplete paraplegia. Incomplete refers to the presence of some voluntary motor activity such as toe movement, sacral sparing, or sensation below the level of the lesion.

Morphology

It is categorized as fractures, fracture-dislocations, SCIWORA, and penetrating injuries. It is further classified as stable and unstable.

Specific Syndromes

Anterior cord syndrome results from an ischemic injury to the anterior part of the cord and has a poor prognosis. Motor pathway damage leads to paraplegia with loss of pain and temperature bilaterally due to damage to the anterior spinothalamic tract. Position and vibration sense are preserved. *Central cord syndrome* occurs in the elderly due to falling forward and striking the face or chin. There is flexion followed by hyperextension. The deficit is more in the upper limbs than

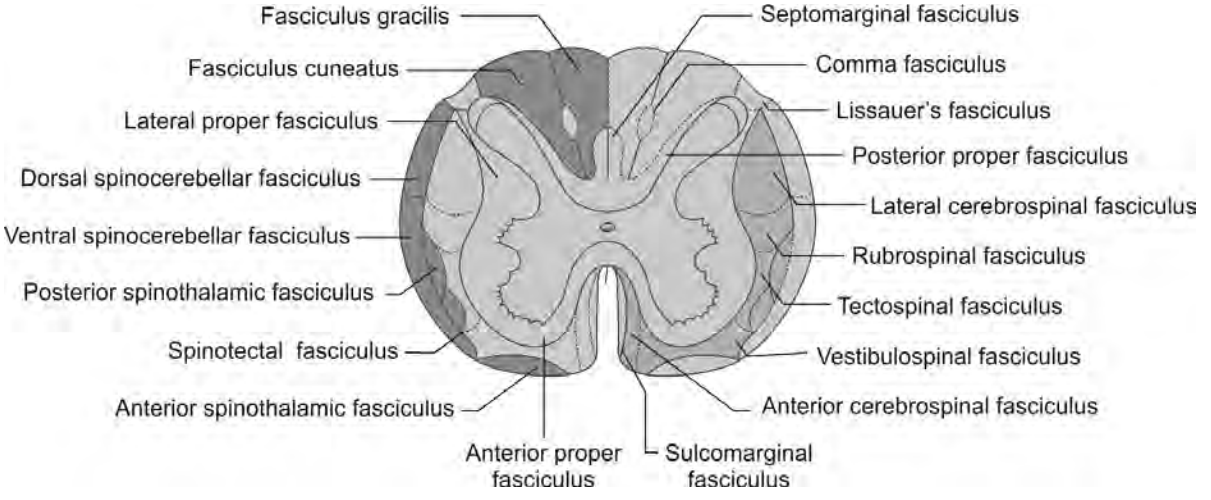


FIG. 3: Spinal tract (transverse section).

the lower limbs. Prognosis is good and recovery occurs first in the lower limbs, then the bladder, and finally the upper limbs. *Brown-Sequard syndrome* is rare and occurs due to the hemisection of the cord. It most commonly occurs following penetrating injury. There is loss of motor power and position and vibration sense on the same side and contralateral to the loss of pain and temperature.

TABLE 1: Spinal tract (location, function, testing).

Tract	*Location*	*Function*	*Testing*
Corticospinal	Anterolateral	Motor power on the same side	Voluntary muscle contraction/ involuntary response to pain
Spinothalamic	Anterior and lateral	Pain and temperature from the opposite side	Pinprick
Posterior columns	Posteromedial	Position sense and vibration sense from the same side	Position of finger and toes Tuning fork

Primary and Secondary Spinal Cord Injury

Primary injury occurs due to the initial mechanical forces and fractured bone fragments, disk materials, and/or ligaments which injure the cord. *Secondary injury* occurs due to movement of the spine, hypotension, and hypoxia. There are physiologic, extracellular biochemical, and intracellular changes. Ischemia can be the result of either capillary or arterial occlusion. The blood–spinal cord barrier integrity is lost leading to an influx of cytokines, vasoactive peptides, and peripheral inflammatory cells leading to cord edema and the proinflammatory state. Neurons are disrupted, and there is excess of extracellular glutamate concentration leading to excitotoxic cell death. Cells die leading to numerous cytotoxic byproducts [e.g., adenosine triphosphate (ATP), potassium ions, deoxyribonucleic acid (DNA), free radicals] released into the local microenvironment which further propagate cell death.

CLINICAL GRADING

Spinal cord injuries are graded according to the *American Spinal Injury Association (ASIA)* scale. The likelihood of recovery increases from category A to D; complete injury carries the worst prognosis.

ASIA A: Injury is complete with no sensory or motor function.

ASIA B: A sensory incomplete injury with complete motor function loss.

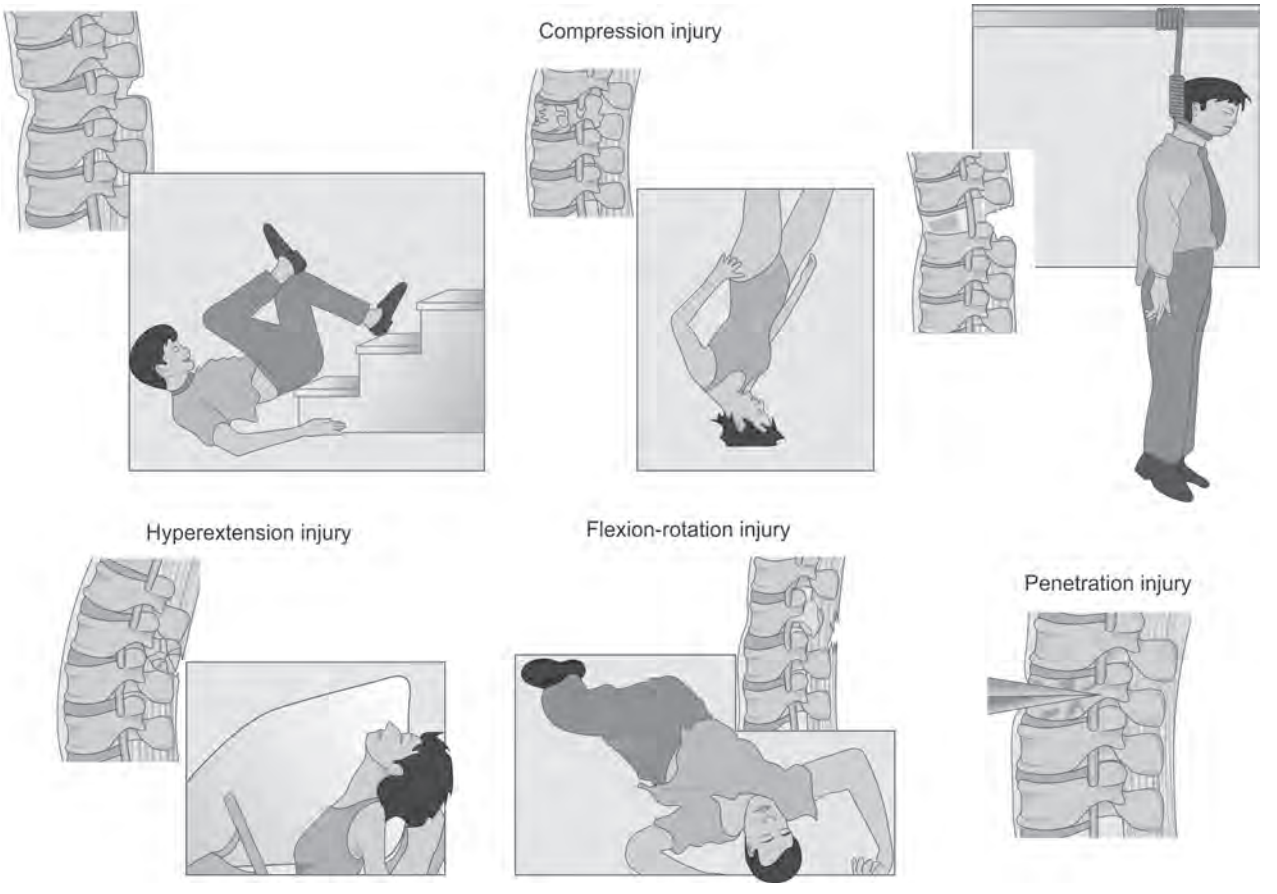


FIG. 4: Mechanism of spinal cord injury.

ASIA C: A motor incomplete injury, where there is some movement, but less than half the muscle groups are antigravity.

ASIA D: A motor incomplete injury with more than half of the muscle groups being antigravity.

ASIA E: Normal

SPECIFIC INJURIES

Upper Cervical Injuries

This type of injury includes injuries to the base of the skull, C1 and C2. Cervical spine injuries are less common in children, but the upper levels are more likely. Mechanisms can be flexion, extension, lateral bending, rotation, and axial loading. *Atlanto-occipital dislocation* is seen in shaken baby syndrome, which occurs due to distraction and extension. It is highly unstable with high mortality as ligaments holding the skull to C1 and C2 are torn. On lateral radiographs, the distance between the clivus and the odontoid is >5 mm. Traction is avoided and treated by occipital cervical fusion. *Disruption of the transverse ligament* of C1 is seen in the elderly due to flexion injury. In complete disruption, the atlanto dens distance is >5 mm and C1/C2 fusion is indicated. *Atlas (C1)* bilateral posterior arch fractures are stable and treated with orthosis. They occur due to compression and extension. They can be associated with fracture of Dens. Fractures on one side of the lateral mass involve anterior and posterior arches due to compression with lateral bending. *Jefferson's fractures* occur due to axial compression and are four-part fractures, i.e., bilateral anterior and posterior arch fractures (**Fig. 5**). Lateral mass and Jefferson's fractures can produce retropharyngeal swelling and respiratory obstruction and may need prophylactic intubation. If there is no lateral widening, an orthosis is used. If the intermass widening is <6.9 mm, a halo can be used, but if it is >6.9 mm, then traction for reduction is followed by halo. *The odontoid process* is the peg-shaped protuberance from the atlas which projects through the ring of the axis. It is commonly fractured and seen on open-mouth views and computed tomography (CT) scans. *Anderson and D'Alonzo* have classified odontoid fractures into three types (**Fig. 6**). (1) Type I fractures are through the dens above the waist and are treated conservatively. (2) Type II fractures at the junction of the dens and body are unstable. If there is <5 mm displacement or <10° of tilt, then halo is enough, but if displacement is >5 mm or tilt is >10°, fixation with a screw or C1/C2 fusion is needed. (3) Type III extends from the dens to the body, heal spontaneously, and do not need surgery. *Hangman's fracture* is a fracture of the posterior elements of C2 and occurs due to sudden extension. *Levine and Edwards* classified the fractures into Types I, II, IIA, and III.

Type I fractures are stable since only the posterior arch is broken with minimal displacement and treated by orthosis. Type II fractures cause anterior displacement of C2 over C3 through the disk, the PLL being intact, and are treated by traction and halo. In Type IIA, the PLL is also disrupted. These are unstable and traction is contraindicated, treated by halo. Uncommon are Type III fractures with the arch fractured and facets remaining attached to the body. There is bilateral facet dislocation, they have no neurological deficit, but need fixation to maintain stability. *C1 rotary subluxation* occurs in children and presents as torticollis. It occurs following trauma, respiratory infection, or rheumatoid arthritis.

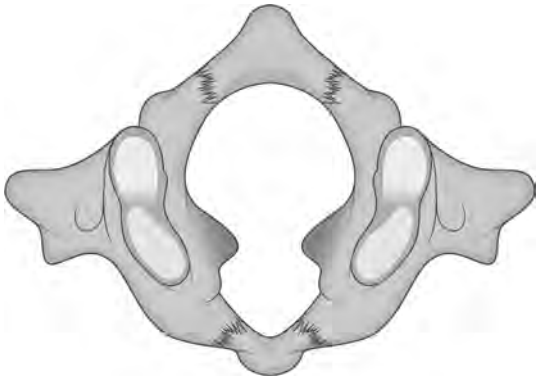


FIG. 5: Jefferson fracture.

Lower Cervical Spine Injuries

Neurological deficit is common as the canal is narrow. The diaphragm may also be paralyzed leading to respiratory distress. *Facet dislocation:* Unilateral dislocations may cause nerve root compression while bilateral dislocations present with neurological deficits and need early magnetic resonance imaging (MRI). Reduction with traction is done followed by fusion. *Compression fractures* are stable when PLC is intact and treated by orthosis; otherwise, fusion is done. Burst *fractures* occur due to flexion with compression. Stable fracture with intact neurology can be managed nonoperatively by applying halo vest for immobilization of spine. Unstable fracture can be managed by posterior fusion with halo vest. If there is neurological damage, then anterior corpectomy with fusion and halo is done, whether stable or not. If it is unstable, then posterior fusion is added. *Teardrop fractures* are unstable, arise due to flexion with rotation and compression, and treated with posterior fusion and halo application. Where neurologic injury exists, anterior corpectomy and fusion are added.

FIG. 6: Anderson and D'Alonzo classification of odontoid fractures: Type I, Type II, Type III.

Thoracolumbar Spine

Thoracolumbar spine prone for wedge compression, burst fracture, Chance fracture, and fracture with dislocation (**Table 2**). *Major injuries* include compression fractures, burst fractures, flexion-distraction injuries, and fracture-dislocations. *Minor injuries* include fractures of transverse, spinous, and articular processes and of pars interarticularis. Transverse process injuries may have brachial or lumbosacral plexus injuries associated with them. *Compression fractures* can be anterior or lateral and are seen on lateral and antero-posterior (AP) views, respectively, due to anterior and lateral flexion forces (**Fig. 7**). These are stable injuries, rarely present with neurological deficits, and are treated with a hyperextension brace. Regular radiographs are essential to monitor for loss of height and angulation. >50% compression may indicate injury to PLC and instability. Nowadays, minimally invasive kyphoplasty can be done by injecting methyl methacrylate. *Burst fractures* caused by vertical and axial compression can impinge on the cord producing neurological deficits (**Fig. 8**). When the posterior ligaments are intact and there is no neurological deficit, they can be managed with a brace. But when there are signs of neurological deficit or PLC is affected, decompression and internal fixation are done. *Chance fractures* are transverse fractures through the body and occur due to flexion most commonly with an incorrectly placed seatbelt (**Fig. 9**). These fractures are commonly associated with other injuries to the retroperitoneum or intra-abdominal viscera. *Fractures with dislocations* are uncommon and occur due to a combination of flexion, rotation, and distraction forces. Since the canal is narrow, they present with neurological deficits. All three columns are affected, and these fractures are unstable. Treatment is reduction followed by stabilization by a posterior approach. An anterior approach may be added if thecal sac compression is persistent.

TABLE 2: Types of spine fracture.

Fracture	*Column affected*	*Stable/Unstable*
Wedge	Anterior only	Stable
Burst	Anterior and middle	Unstable
Fracture dislocation	Anterior, middle and posterior	Unstable
Seat belt	Anterior, middle and posterior	Unstable

Denis Three-column Concept of Spinal Fracture

Three-column concepts are applied mainly for the classification of thoracolumbar spinal fracture but can also be

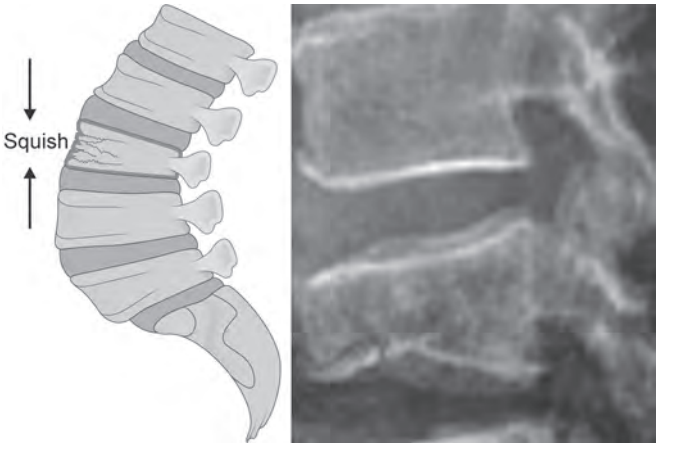


FIG. 7: Compression fracture.

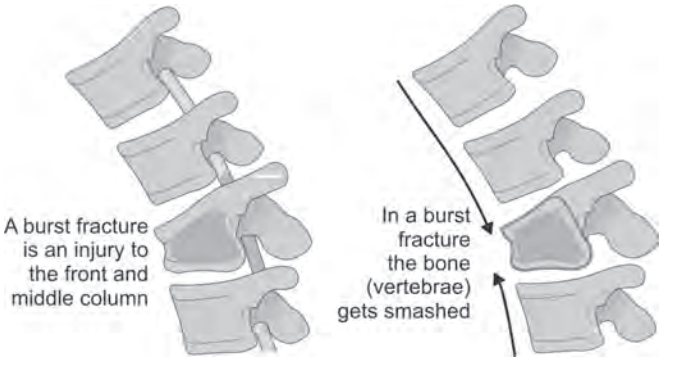
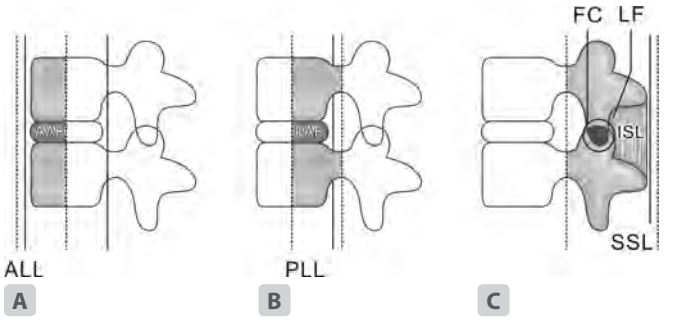


FIG. 8: Burst fracture.

FIG. 9: Chance fracture occurring due to an incorrectly placed seatbelt.



(AAF: anterior annulus fibrosus; ALL: anterior longitudinal ligament; FC: facet capsule; ISL: interspinous ligament; LF: ligamentum flavum; PAF: posterior annulus fibrosus; PLL: posterior longitudinal ligament; SSL: supraspinous ligament)

FIGS. 10A TO C: Denis three-column concept of spinal fracture. (A) Anterior; (B) Middle; (C) Posterior.

applied to the lower cervical spine. These are widely used in clinical practice and for reporting due to their simplicity (**Figs. 10A** to **C**).

Anterior column—anterior longitudinal ligament (ALL), anterior two-thirds of the vertebral body, and annulus fibrosis or disk

Middle column—posterior third of the vertebral body and annulus fibrosis and PLL

Posterior column—pedicles, facet joints, capsules, laminae, supraspinous and interspinous ligaments, joint capsule, and LF

For instability, there should be a compromise of two columns, i.e., middle + anterior or middle + posterior.

RADIOLOGY IN SPINAL TRAUMA

Canadian C-spine rule and National Emergency X-Radiography Utilization Study (NEXUS) criteria are used for cervical spine radiology.

Canadian C-spine rule consists of the following:
- Age ≥ 65 years
- Paresthesias in extremities
- Dangerous mechanism of injury:
  - Fall from an elevation ≥3 ft or five stairs
  - Axial load to the head (e.g., diving)
  - Motor vehicle collision at high speed (>100 km/h) or with rollover or ejection
  - Bicycle collision
  - Collision involving a motorized recreational vehicle

  If any of these are present, imaging is done.

Nexus criteria: Spine imaging is recommended if one of the following criteria is present:
- Focal neurologic deficit
- Midline spinal tenderness
- Altered level of consciousness
- Intoxication
- Distracting injury

NEXUS Mnemonic: *N*—neurodeficit/*E*—ethanol (alcohol) intoxication/*X*—eXtreme distracting injury/*U*—unable to provide history (altered level of consciousness)/*S*—spinal tenderness (midline). Radiographs with AP and lateral views of the cervical spine will detect 90–95% of lesions. For C1, open-mouth view and for C7, swimmer's views are taken. The thoracic and lumbar spine can be preliminarily studied by radiographs and are taken in AP, lateral, and sometimes oblique views.

Computed tomography: Multiplanar CT scans with 3-mm fine cuts and sagittal 3D reconstruction are very useful for determining the bony injury, especially in lateral mass fractures, facet fractures, and fractures causing bony fragments to impinge on the spinal canal.

Magnetic resonance imaging: MRI is not usually done in the acute setting. It is useful to study the soft tissues, ligamentous injuries, hematomyelia, and cord contusions.

INITIAL ASSESSMENT AND MANAGEMENT

Patients are shifted with cervical collar and placed on a long spine board. They are logrolled during shifting without unnecessary movement to the spine. Two sandbags are placed on either side of the head to prevent neck rotation. First is *airway, breathing, and circulation.* During intubation, care should be taken to maintain in-line stabilization manually. The important aspect is to maintain oxygenation and blood pressure. Low blood pressure with tachycardia indicates hypovolemic shock, and radiographs of chest and pelvis and extended focused assessment with sonography for trauma (eFAST) are done to rule out sources of bleed.

Cervical Collar and Spine Board

After resuscitation, if the cervical spine has no injury, then the cervical collar is removed (**Fig. 11**). Traditionally, when any spinal injury has been suspected, the entire spine is immobilized onto a longboard, along with the placement of a rigid collar to immobilize the cervical spine. Spine boards (**Fig. 12**) can cause significant discomfort to the patient, skin breakdown, and decubitus ulcers in a relatively short amount of time. It can compromise ventilatory status in some patients. Thus, for all of these reasons, patients who are placed on a backboard initially should be removed from them as soon as possible. The backboard should continue to be used for specific purposes. It is an excellent device to help extricate patients or when patients need to be carried over large distances. The spine board is removed as early as possible or within 2 hours

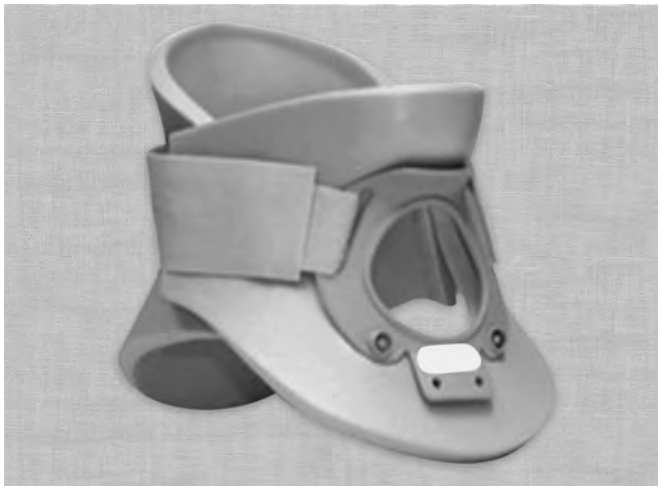


FIG. 11: Philadelphia cervical collar.

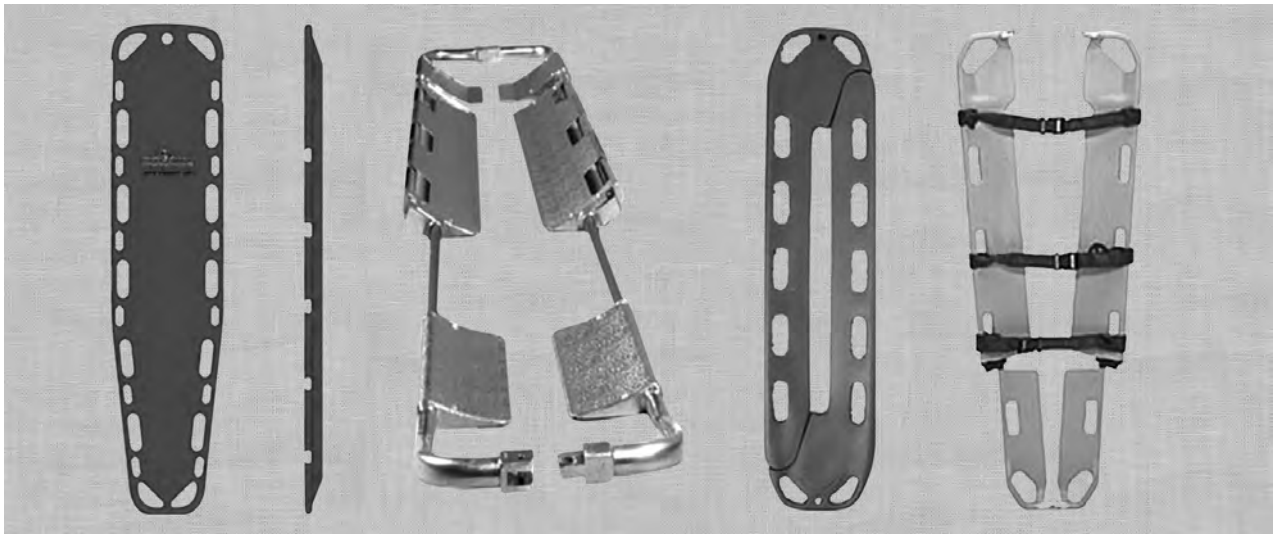


FIG. 12: Spine board, scoops, Combi-carrier, ortho-stretcher.

to prevent pressure sores. Neurological assessment is possible only in a conscious patient. Simultaneously, radiological assessment is also done.

Technique of Removal of Helmet

Two rescuers are involved in this process. The first rescuer maintains the in-line stabilization by placing both sides of the mandible and applying pressure on the jaw. The second rescuer slides the helmet backward if the helmet is covering the full face; glasses should be removed first and the helmet should be expanded laterally to clear the ears and moved backward and raised over the nose for soft removal (**Fig. 13**).

Technique of Logroll in Shifting Suspected Spinal Trauma

Logroll is the procedure used to put the injured on a stretcher. Four persons are required for this technique. Maximum care must be taken to avoid worsening an unstable trauma. The head-neck-chest axis must be kept straight to protect the spine, and the first responders must keep the patient's body stable (no movement of the feet) during the lift (**Fig. 14**).

Neurogenic Shock and Spinal Shock

Maintaining mean arterial pressure (MAP) at 85–90 mm Hg for 7 days has been found to improve outcomes. The presence of bradycardia with hypotension can be due to neurogenic shock while head injury produces hypertension and bradycardia. In SCI, there are two conditions: (1) *Neurogenic shock and* (2) *spinal shock*. Neurogenic shock is a cardiovascular event. It occurs when there is a cord injury above the T6 level. The sympathetic nerve gets affected and due to peripheral vasodilatation, there is hypotension. Patients cannot develop tachycardia as the sympathetic nerves to the heart are affected. This is treated with fluids followed by vasopressors, if necessary. *Spinal shock* is the state of complete paralysis due to spinal cord injury. There is flaccid paralysis with loss of reflexes including anal wink and bulbocavernosus reflex. This will recover as the neurological condition improves. SCI is often overlooked in (1) head injury, (2) intoxication, and (3) polytrauma initial.

FIG. 13: Helmet removal in suspected spine trauma.

Use of Steroids

The 2016 Cochrane review is recommended against the use of steroids. But the AO Spine 2017 guidelines recommend steroids, i.e., methylprednisolone intravenously within 8 hours of cervical spine injury and continued for 24 hours. The dose should be 30 mg/kg bolus followed by 5.4 mg/kg/h for 23 hours. An increased risk of sepsis (pneumonia, septicemia) was noted within 48 hours of steroid administration.

Evaluation of Neurological Status

Neurological assessment consists of (1) Glasgow coma scale, (2) pupils, and (3) localizing signs. The spine is examined during the secondary survey for deformity, bruising, and lacerations on inspection and tenderness, spasm, and step on palpation. Sensory level, motor level, and reflexes are examined.

Cranial nerve examination and reflexes: The lower four cranial nerves may be involved in high cervical spine injuries and should be tested. The reflexes which are assessed include

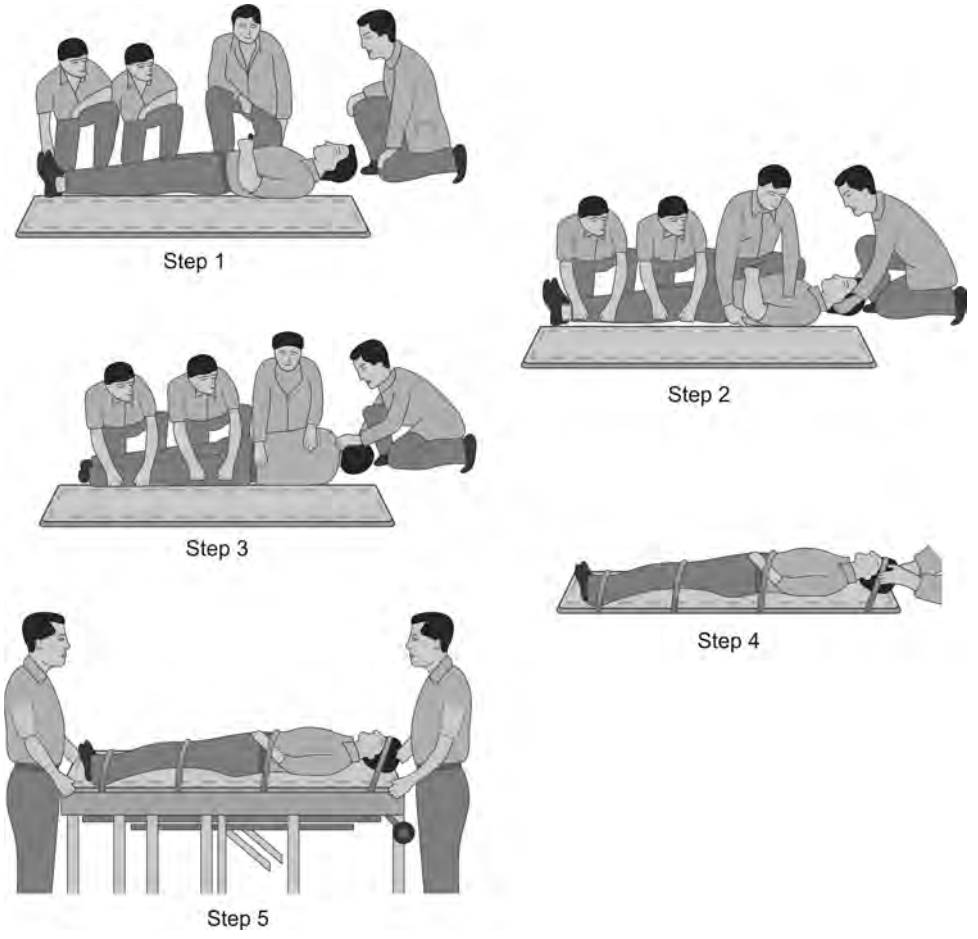


FIG. 14: Logroll techniques.

biceps (C5), triceps (C7), knee (L4), and ankle (S1) jerks. *Reflex grading (0–4) is as follows:* 0—absent reflex, 1—decreased, 2—normal**,** 3—exaggerated reflex, 4—sustained clonus. In addition, sacral reflexes (bulbocavernosus/clitorocavernosus and anal wink) and plantar reflex are also tested.

Determination of sensory level: This is the most caudal, intact dermatome having a score of "2" for both light touch with a cotton swab and pinprick sensation with a needle. Important dermatomes from C2 to S4–5 are examined on either side. Sensory grading is: 0—total sensory loss, 1—some sensation present, 2—normal sensation. *Dermatome* is the area of skin supplied by a single nerve root. *Important dermatomes are:* C5—deltoid region, C6—thumb, C7—middle finger, C8—little finger, T4—nipple, T8—epigastrium, T10—umbilicus, T12—groin, L3/4—medial aspect of thigh above knee, L5—first web space, S1—lateral border of foot, S2—ischial tuberosity, S3/4—perianal. *Determination of motor level:* Grade 0—complete paralysis, Grade 1—flicker of contraction, Grade 2—movement with gravity eliminated, Grade 3—movement with gravity but not against resistance, Grade 4—against resistance but less than normal power, Grade 5—normal power. The motor level is the lowest muscle group with 3/5 grade of power.

Myotome is a group of muscles innervated by a single nerve root. The important myotomes are as follows:
Upper limb: C5—shoulder abduction, C6—elbow flexion, C7—elbow extension, C8—finger flexion T1—finger abduction. *Lower limb*: L2—hip flexion, L3—knee extension, L4—ankle dorsiflexion, L5—great toe extension, S1—ankle plantar flexion.

The neurological level is the most caudal level of the spinal cord with intact sensation (at least grade 2) and muscle power of at least 3/5. Absent reflexes represent lower motor neuron (LMN) paralysis whereas exaggerated reflexes represent upper motor neuron (UMN) paralysis. The appearance of spinal reflexes indicates recovery from spinal shock. The most sensitive predictor for recovery is the completeness or incompleteness of injury.

MANAGEMENT

Nonoperative Management of Spinal Cord Injury

Traditionally, all SCIs were treated nonoperatively with a spinal brace for a period of 6–8 weeks combined with bed rest. With advances in radiology and surgical techniques, many patients are being operated.

Operative Intervention

Indication, Principle, and Timing of Surgery

The indications of operative intervention are: (1) neurological deficit and (2) unstable spine. The goals of surgery are decompression to relieve pressure, ensuring an adequately sized canal, and fixing the vertebral column after aligning the bones. Surgery entails removal of the fragments in the canal, thereby relieving cord pressure. Fixation is done with rods,

plates, and screws to one to two levels above and below the fractured.

Timing of decompression: Many studies have showed improvement in neurology with grade improvement by 2 or more over 3–6 months after early, i.e., <24 hours, decompression. The results have been better mainly in cervical spine injury.

Spinal instability: White and Panjabi described three subsystems for stability: (1) Passive—spinal column, (2) active—spinal muscles and tendons, (3) control—neural feedback.

ADJUNCT THERAPY

Pressure Sores

Patients are prone to develop bedsores due to immobility. Vulnerable areas are the sacrum, trochanteric regions, heels, elbows, and occiput. Measures to prevent bedsores are: (1) Early removal of spine board, (2) Water bed or alpha bed, (3) Change of position after 2 hours, (4) Smoothening the sheets, (5) Lotions for the back, and (6) Improvement of nutrition. Early aggressive treatment is needed to prevent fatal sepsis. Once pressure sores develop, debridement is followed by vacuum-assisted closure (VAC) therapy and flap cover.

Prophylaxis against Deep Venous Thrombosis

Pneumatic compression stockings should be used early. When there is no intracranial, abdominal, or pelvic injury where hemorrhage is likely, low-molecular-weight heparin should be used. Calf pumps can also be used.

Chest Physiotherapy

Patients are prone to retaining tracheobronchial secretions and developing atelectasis and other pulmonary complications. Steam inhalation, saline nebulization, deep breathing maneuvers, chest physiotherapy, and incentive spirometry are preventive.

Urinary Tract Infection

With immobilization and bladder denervation, patients develop retention leading to urinary infection. Foley's catheterization is initially followed by condom drainage or clean self-intermittent catheterization (CSIC) in the long term.

Neurorehabilitation

This is done to strengthen the muscles and improve range of *movement. Functional electrical stimulation and epidural spinal cord stimulation* are done to reduce pain and improve muscle power and bladder function. *Exoskeletons* which are external motorized orthoses improve activity.

EMERGING THERAPIES

Riluzole, a sodium channel antagonist; *minocycline,* a tetracycline group antibiotic; *granulocyte colony-stimulating factor* (G-CSF); *systemic hypothermia*; *stem cell therapy*; *biodegradable polymer scaffolds and hydrogels*; and cethrin inhibitor (Rho) have shown promise to reduce damage and promote axonal growth.

SUMMARY

Adequate safety measures will reduce spine trauma. Cervical collar and spine board are mandatory. The spine board should be removed as early as possible. The cervical collar is removed after clinical examination and radiology. The patient should be carefully logrolled while shifting. Initial management is always airway, breathing, circulation, disability (ABCD). Treatment of other life-threatening injuries takes precedence over the spine. Hemorrhage should always be ruled out in every case of hypotension. Maintain blood pressure and oxygenation. Neurological level of injury helps in severity and prognosis. CT scan is the investigation of choice. MRI is not done often but it is referred especially for cord compression and neurodeficiencies. An unstable spine injury should be operated early ideally within 24 hours. Newer therapies for spinal regeneration are showing promise.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Cardiothoracic Trauma

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INTRODUCTION

Direct thoracic trauma leads to one fourth of all deaths from trauma. Usually, it is caused by motor vehicle crash (MVC) leading to immediate death. This includes myocardial wall rupture and thoracic aorta rupture. Myriad causes of early deaths, 30 minutes to 3 hours from thoracic trauma, are preventable. These include tension pneumothorax, cardiac tamponade, airway obstruction, and uncontrolled exsanguination. Three fourths of thoracic trauma can be managed expectantly with simple tube thoracotomy and blood. We need an efficient trauma system to do well post emergency department (ED) resuscitation. As computed tomography (CT) scans are getting ubiquitous, missed injuries are becoming uncommon. Disruption of these structures can cause catastrophic consequences since the chest wall is critical for ventilation and oxygenation. As the thorax expands outward, the diaphragm expands down and creates negative pressure. Injuries to this region can disrupt this physiology and with significant consequences. Common cardiothoracic injuries are given in **Table 1**.

CHEST WALL INJURY

Chest wall injury (CWI) is a comprehensive term, including soft-tissue injury, rib fracture, flail chest, and sternal fracture, costochondral separation. Approximately 50% of thoracic trauma have a CWI. It is often not obvious and can be overlooked in a secondary survey. An intact chest wall is essential to normal ventilation for the inspiration and expiration cycles. Those with limited reserves have more difficulty; for example, elderly patients with a preexisting pulmonary disease cannot tolerate even a minor injury. We can miss many CWIs if we do not fully disrobe the patient and observe respiratory rate, adequacy of tidal volumes, respiratory effort, palpation for tenderness, deformity, and crepitus.

RIB FRACTURE

Most injuries are simple rib fractures. The susceptibility of rib fractures increases with age. More than the rib fractures, their potential complications need management, i.e., pneumothorax, hemothorax, pulmonary contusion, post-traumatic pneumonia, and liver/spleen injury. In children, rib fractures are correlated with an underlying pulmonary injury. Ribs break at the point of impact or the weakest area, which is commonly the posterior angle/posterolateral area. Usually, 4th to 9th ribs break, 1st to 3rd are protected, and 9th to 12th are mobile and can penetrate intra-abdominally. Suspect spleen and liver injuries in lower rib fractures. Suspect intrathoracic injuries for 1st to 3rd ribs; if more than two ribs fracture, there is a risk for internal injuries.

Clinical Features

Tenderness, bony crepitus, ecchymosis, and muscle spasm are present. The barrel compression test is done to assess pain at the fracture site. Clinical impression and physical findings are not specific to rib fractures. Chest X-ray (CXR) often misses rib fractures but it can find the intrathoracic injuries. Rib-specific views should be ordered in general: Rib series, expiratory, oblique, and cone-down views. The only reason to get an X-ray

TABLE 1: Common cardiothoracic injuries.

Structures involved	***Injuries***		
Airway	Tracheobronchial injury	Traumatic asphyxia	
Lung	Pulmonary contusion	Pneumothorax, hemothorax	Bronchopleural injury
Cardiac	Tamponade	Commotio cordis	Myocardial contusion
Vascular	Intercostal/great vessel disruption	Blunt aortic dissection	
Gastrointestinal	Esophageal perforation	Esophageal disruption	
Chest wall	Rib fracture	Flail chest	

in addition to clinical suspicion of rib fractures is to look into intrathoracic pathology 50% of isolated single rib fractures are missed. CT scans are much more sensitive. Order a CT scan if the following are present: dangerous mechanism of injury, physical examination findings of multiple rib fractures, elderly patient, lower rib fractures, and hemodynamic or respiratory compromise.

Management

Rib fractures can be managed by controlling the pain, and maintaining pulmonary function, and continuing with daily activities and deep breathing. Chest wall binders should be avoided because they promote hypoventilation and atelectasis. This has never been supported with research or science though. Generally, people with more than three rib fractures may need hospitalization for pulmonary therapy and analgesia. Especially in elderly, intercostal nerve block should be given by using 1% lidocain and 0.25% bupivacaine along the inferior rib margin several centimeter posterior to site of fracture, which block one rib above and one rib below. Most rib fractures heal within 3–6 weeks. Analgesia is usually needed for 1–2 weeks.

Complications

Pneumothorax, hemothorax, pulmonary contusion, post-traumatic pneumonia, liver/spleen injury, post-traumatic neuroma, costochondral separation, and separated rib fractures can lead to delayed hemorrhage due to torn intercostal artery that can rebleed.

FLAIL CHEST

Flail chest can be a life-threatening injury due to high energy injury. It is usually associated with lung parenchymal injury. Flail chest is defined as three or more ribs fractured at two points leading to paradoxical chest wall motion. It can also occur with a vertical sternal fracture/costochondral injury. This is one of the most serious chest wall injuries with 8–36% mortality rate, especially in those with bilateral flail segments. The lung contusion/parenchymal injury leads to altered ventilation/oxygenation. The pain from the fractures leads to hypoventilation, hypoxia, atelectasis, etc. Physical examination requires a thorough examination of the entire chest for asymmetrical movement. Specific visual inspection can be guided by pain/crepitus. Endotracheal intubation will mask the paradoxical movement. The exact rib fracture and pulmonary contusion will be found best on CT scan which can be easily missed on chest X-ray.

Management

There is no ideal prehospital management. It is important to watch and deal with pain and hemopneumothorax expeditiously. These should be related before considering intubation. Continuous positive airway pressure (CPAP)/noninvasive oxygenation strategies should be attempted first. Consider continuous cardiac monitoring and also serial cardiac enzyme estimation given the risk for cardiac injury and dysrhythmias. Intubation is done only for ventilatory failure despite chest physiotherapy, oxygen/noninvasive positive-pressure ventilation (NIPPV), analgesia, high-nerve blocks, and epidural analgesia. People treated with these have much fewer complications. Consider open reduction and fixation of the rib fractures for patients in whom multiple ribs are involved, leading to decreased respiratory function, requirement of ventilation, and incessant pain (**Figs. 1A** to **F**). There evidence to support that they have improved recovery, better cosmetics, and improved function in those getting surgery. Long-term complications are chronic pain, dyspnea, and chest wall deformities.

COSTOCHONDRAL SEPARATION

Due to blunt trauma to the chest, i.e., an injury to the cartilage, patients have a snapping sensation with deep inspiration. Poorly detected on X-ray, it takes many weeks to heal fully.

NONPENETRATING BALLISTIC INJURY

The kinetic energy is so high during trauma that in spite of an intact chest wall cavity, the energy is enough to damage the liver, lung, kidney, heart, and spinal cord. *Situations*: Trauma caused by people wearing bullet-resistant/bulletproof vests, due to rubber bullets, and due to bean bags. Clinical findings are pain, areas of bruising, and tenderness. Key features not to be missed are crepitus, subcutaneous air, retained foreign bodies, and bony step-offs. Basic radiography should be performed to exclude foreign bodies and associated pneumothorax/hemothorax. CT scan should be considered. Most of the patients should be admitted for overnight observation and serial examination. Consider serial abdominal examinations or CT of abdomen if available. Do not underestimate the risk and extent of injuries in the absence of penetration.

STERNAL FRACTURE

Sternal fracture occurs due to anterior blunt chest wall trauma, more likely in restrained passengers. It is usually due to the diagonal strap running across the sternum. A sternal fracture can mean that less energy was dissipated to the internal organs. This may be associated in 10% of cases with rib and lung contusions.

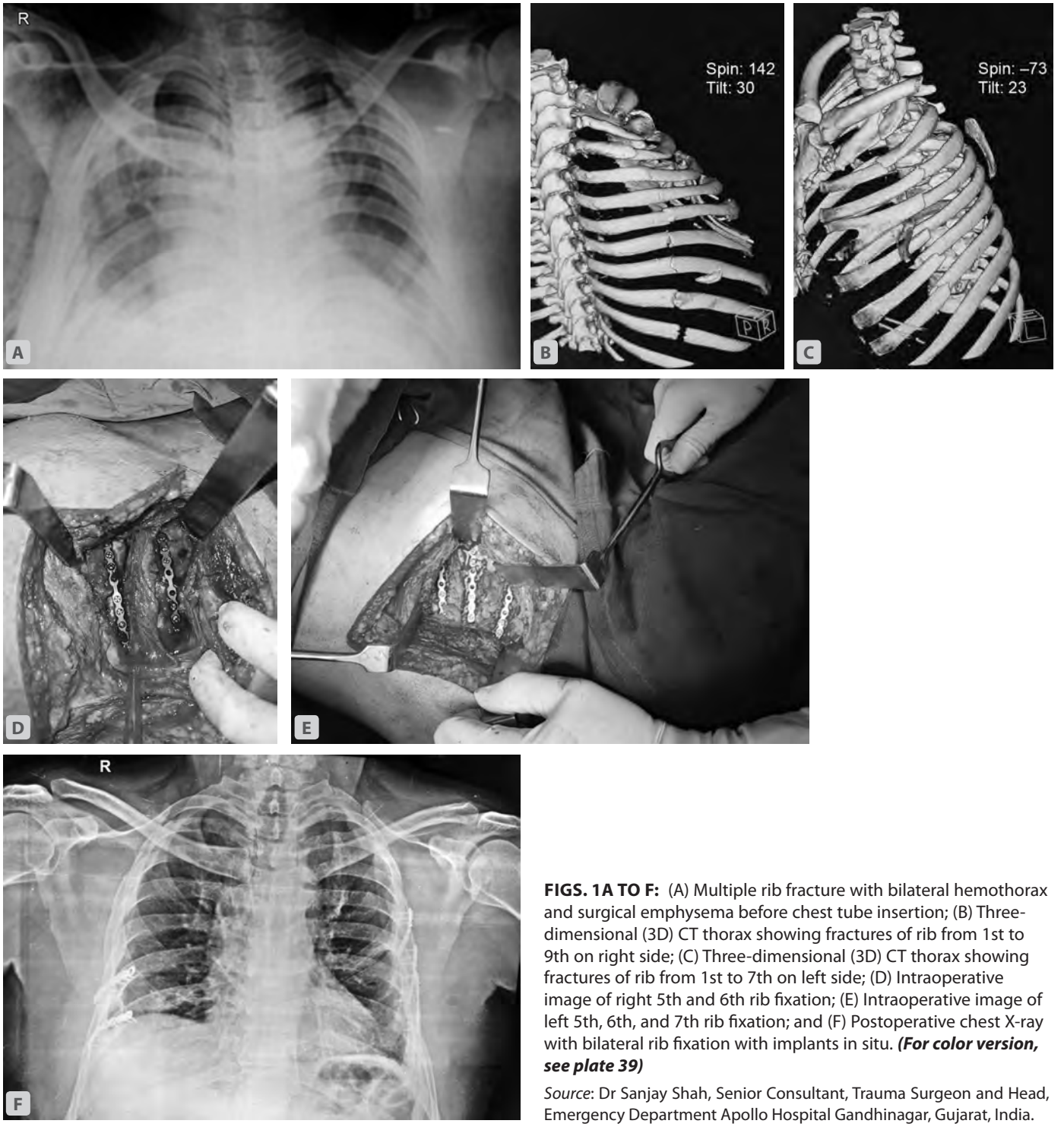
Nondisplaced sternal fractures: Benign, <1% mortality, and low intrathoracic morbidity, although mediastinal injuries should be considered. Cardiac complications are rare, 1–6%. There is no association with aortic rupture. The main complications are mediastinal hematomas, which can lead to blood loss. Clinical features are anterior chest pain with point tenderness, swelling, ecchymosis, and deformity.

Diagnosis: Anyone with a suspected sternal fracture should get a CT scan. CT chest is preferred investigation over ultrasound chest and X-ray.

Everyone should get an electrocardiogram (ECG) done. Sternal fracture can be managed by analgesia. Discharge home if there are no other injuries. Rarely surgery is required, only in cases of displaced sternal fracture or if lung parenchymal injury is present.

SUBCUTANEOUS EMPHYSEMA

In the presence of thoracic trauma, free air in the subcutaneous tissue represents an injury to air-containing structures: Sub-



FIGS. 1A TO F: (A) Multiple rib fracture with bilateral hemothorax and surgical emphysema before chest tube insertion; (B) Three-dimensional (3D) CT thorax showing fractures of rib from 1st to 9th on right side; (C) Three-dimensional (3D) CT thorax showing fractures of rib from 1st to 7th on left side; (D) Intraoperative image of right 5th and 6th rib fixation; (E) Intraoperative image of left 5th, 6th, and 7th rib fixation; and (F) Postoperative chest X-ray with bilateral rib fixation with implants in situ. ***(For color version, see plate 39)***

Source: Dr Sanjay Shah, Senior Consultant, Trauma Surgeon and Head, Emergency Department Apollo Hospital Gandhinagar, Gujarat, India.

cutaneous air in the supraclavicular and anterior neck areas is due to pneumomediastinum. Subcutaneous air in the chest wall is due to an intrapleural injury or penetrating trauma.

Extrapleural injury: From the tracheobronchial tree air leaks in to the mediastinum and neck but it rarely leads to tension pneumomediastinum. It rarely leads to tension pneumomediastinum. It may have Hamman's crunch on heart auscultation. It is worsened by positive pressure ventilation.

Intrapleural injury: It occurs due to a break in the visceral and parietal pleura. Air then tracks into the subcutaneous tissue. Other etiologies are Boerhaave's syndrome—air in the neck and supraclavicular area. Blunt or penetrating chest trauma occurs with or without an intrapleural injury.

Management

Tension pneumothorax or tension pneumomediastinum, all need drainage urgently, with chest tube or pericardiocentesis. Smaller accumulations are treated on the basis of an underlying injury: Bronchial wall rupture, pneumothorax, and esophageal injury. Patients with isolated subcutaneous air should receive high-flow oxygen to help absorb the nitrogen-rich subcutaneous air which causes discomfort.

PULMONARY CONTUSION

The most common significant injury in blunt chest trauma in 30–70% of cases is pulmonary contusion.

High-risk populations for pulmonary contusion are: MVCs, pedestrian struck by motor vehicle, shock-wave-induced injury from a bomb blast in air or water, and ballistic or missile injuries. These are very common in children. *Pulmonary contusion is defined as*: Bruise to lung parenchyma tissue leading to alveolar hemorrhage and edema. It must be suspected clinically; the onset may be insidious and quickly become life-threatening. There are no clear signs to suggest pulmonary contusion. It may commonly present with rib fractures and flail segments. But the most severe contusions may present as dyspnea, absent breath sounds, rales, hypotension, hypoxia, hemoptysis, tachycardia, and cyanosis. An emergency physician must be careful not to miss the diagnosis. Clinical suspicion may arise in the presence of other injuries such as rib fracture, subcutaneous air, and pneumonitis. The X-ray may show frank consolidation or patchy, irregular, alveolar infiltrates.

Acute respiratory distress syndrome (ARDS) versus pulmonary contusion: Pulmonary contusion appears in the first minutes to 6 hours and lasts for 24–48 hours. ARDS is diffuse and bilateral, has a slow onset, and comes on after 24–72 hours. X-ray is much more effective at diagnosing clinically significant pulmonary contusions. CT scan of the chest is more sensitive (2×) than X-ray, especially in the acute phase, and will find other potential injuries/issues. However, many of the contusions may be occult and not as clinically important. Arterial blood gas (ABG) is probably the best means of assessing progression in the contusion (increasing A-a gradient). If the pulmonary contusion can only be seen on CT, it is probably not clinically significant enough to change outcomes (handle it like any other blunt trauma to the chest). But if it is seen on CXR and CT, these carry a high morbidity.

Management

Avoid over administration of intravenous (IV) fluids and follow good pulmonary toileting, good pain control, no colloids, no prophylactic antibiotics. Avoid intubation and mechanical ventilation, especially in the context of flail chest (shown to increase morbidity). If intubation is needed, use a double-lumen tube so that ventilation strategies can differ between the lungs; lung protective strategies. Consider using CPAP and bilevel positive airway pressure (BiPAP). Also consider extracorporeal membrane oxygenation (ECMO) in severe cases.

PULMONARY LACERATION

It is not commonly seen. But it can be found due to penetrating trauma, rib segment tearing the lung, or a torn pulmonary adhesion. It can lead to persistent bleeding and hemopneumothorax. Management consists of oxygen therapy, observation, and if required thoracostomy or operative repair.

PNEUMOTHORAX

Pneumothorax occurs due to an injury in the parietal pleura. It leads to paradoxical lung movement, collapse with inspiration due to negative intrapleural pressure, and expansion with expiration. Different types of pneumothoraces are as follows:

Simple pneumothorax has no communication with the atmosphere and no mediastinal or diaphragm shift. It can be small, moderate—15–60% of lung collapsed, and large. It is often due to rib fracture/penetrating trauma tearing the parietal pleura. It may be due to blunt chest trauma with a full breath and closed glottis leading to an alveoli rupture.

Communicating pneumothorax is due to an open connection with the outside atmosphere, creating a sucking chest wound. It is common in shotgun trauma and leads to paradoxical chest wall and lung movement.

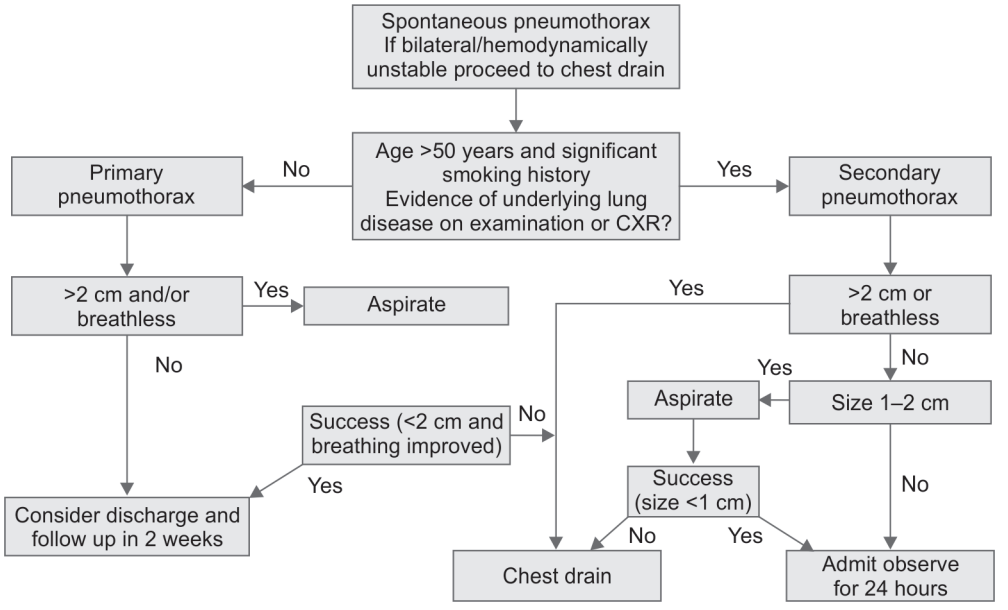
Tension pneumothorax is a life-threatening chest wound leading to a one-way valve, drawing more and more air into the chest without an escape, leading to lung collapse and contralateral compression of the lung, great vessels, and venocaval structures. This leads to shock, hypoxia, decreased cardiac output, and death.

Clinical features of pneumothorax are dyspnea, chest pain, subcutaneous air, and wide spectrum based on severity, from cyanosis to no symptoms. This may have tachypnea, tachycardia, altered mental status, hypotension, tracheal deviation away from the side of the injury, unilateral absence of breath sounds, and neck vein distension. In ventilated patients, early reliable signs are decreasing saturation and blood pressure (BP) and tachycardia. Look for raised ventilation pressure (>40 mm Hg) and ensure that the ventilator pressure alarm settings are set appropriately. The triad of tension pneumothorax is jugular venous distension, absent breath sounds (hyperresonance), and tachycardia; hypoxia occurs first and hypotension is a preterminal state.

Diagnosis: This can be very accurately differentiated on extended focused assessment with sonography in trauma (eFAST) ultrasound during the primary survey. It is found to be more accurate than X-ray. Chest X-ray should be done in upright position and on maximum inspiration. This may miss 30% of pneumothoraces initially; if still suspected, do another film on expiration. CT scan is much more sensitive and may detect "occult" pneumothorax that was not found on X-ray. Tension pneumothorax is a clinical diagnosis and X-ray rarely should delay treatment, although findings may be subtle at times. The approach to pneumothorax is shown in **Flowchart 1**.

Management

Management depends on the size and clinical condition of the patient. In case of blunt trauma, if the initial CXR is negative, then a repeat should be done at 6 hours. If no pneumothorax is found on the CT scan of the chest, the patient may be discharged after appropriate treatment. If CXR is performed and is negative, then repeat CXR should be done at 3 hours. Simple pneumothorax size and symptoms usually guide treatment: If <15%, whether blunt or penetrating or spontaneous or traumatic, usual observation is adequate. If >15% and/or symptomatic: Tube thoracostomy is the best option. It is safer and less scarring than going anteriorly in the second intercostal space in the midclavicular line (**Box 1**). Size depends on age. Ensure that it is placed apical-posteriorly and that radiographic lines are inserted fully into the chest. If there are apical pneumothoraces, due to penetrating trauma, stable patients with <25% involvement may be followed conservatively. In the setting of multisystem trauma,



(CXR: chest X-ray)

FLOWCHART 1: Approach to pneumothorax.

conservative observation is rarely safe or indicated, but this is based on clinical judgment.

Communicating pneumothorax: Three-side occlusive dressing is applied that allows air to escape. Tube thoracostomy can be placed in the ED.

Tension pneumothorax: Emergent needle thoracocentesis—it must be decompressed with needle thoracostomy or by at least a 5-cm 14G angiocatheter; common site of insertion is in the 2nd intercostal space at the midclavicular line or the lateral chest 4–5th interspace anterior axillary line. The chest tube must be performed immediately after needle decompression. It is inserted over the top of the fifth rib in the midaxillary line. The most common cause of serious injury as a result of chest drain insertion is incorrect site of placement. Confirm that the drain lies within the chest wall cavity by looking for fogging of the tube and swinging of the chest drain with respiration. Do not clamp the chest drain or apply suction. The underwater seal needs to remain below the insertion site at all times. Gross surgical emphysema with pneumomediastinum and a chest drain that continues to bubble suggests a tracheobronchial injury. Cardiac tamponade can give similar signs clinically and shock with distended veins. A combination of focused assessment with sonography in trauma (FAST) and CXR along with the mechanism of injury can help to differentiate between the two.

Complications

Complications of pneumothorax are bronchopleural fistula, empyema, scarring, pleural leaks, intercostal artery/vein injury, and pneumonitis. There is an increased risk of re-expansion pulmonary edema for pneumothoraces that have been present for >3 days.

HEMOTHORAX

Hemothorax can occur with blunt or penetrating trauma with extrathoracic injury and lead to massive blood loss and altered chest ventilation. It clinically presents as varying degrees of hypovolemic shock, increased tactile fremitus, and decreased breath sounds. A supine film CXR will often miss blood unless there is a large amount that layers posteriorly. It needs at least 200–300 mL of blood to blunt the costophrenic angles. It may see a tension hemothorax (rare). Ultrasound may be used to see a pleural effusion with accuracy. CT scan of the chest is much more accurate.

BOX 1: Indications for tube thoracostomy.

- Traumatic cause of pneumothorax (except asymptomatic, apical pneumothorax)
- Moderate-to-large pneumothorax
- Respiratory symptoms regardless of the size of pneumothorax
- Increasing size of pneumothorax after removal of the initial conservative therapy
- Recurrence of pneumothorax after removal of the initial chest tube
- Patient requires ventilator support
- Patient requires general anesthesia
- Associated hemothorax
- Bilateral pneumothorax regardless of size
- Tension pneumothorax

Management

Priorities are to restore blood volume, control airway control, and drain hemothorax using a large tube attached to a Pleur-evac. Most worrisome is continued loss of blood >200 mL/h for 3 consecutive hours. The CT scan is important, because the presence of a hemothorax often leads to tube drainage (when it is symptomatic or moderate in size). Small hemothoraces may be observed, but no study has been done to exactly describe which sizes of hemothorax need drainage. Massive

hemothoraces need operative thoracotomy or video-assisted thoracoscopic surgery (VATS).

Complications

It causes delayed hemothorax, leading to empyema and fibrothorax. Errors in tube placement lead to lung parenchymal injury or persistent air.

TRACHEOBRONCHIAL INJURIES

Clinical Features

Tracheobronchial injury most commonly presents as subcutaneous emphysema due to mediastinal air tracking into the neck. An airway injury is suspected with persistent, large air leak with respiratory collapse. Other red flag signs are stridor, hoarse voice, and difficulty swallowing. During the initial resuscitation, tracheobronchial injuries may remain unrecognized in the emergency room; although rare, they are life threatening in the first hour. Predisposing factors for tracheobronchial tree injuries are force to the chest against a closed glottis, rapid deceleration, or direct disruption from a crush injury. Blood, vomit, or foreign bodies can directly obstruct the airways and present with stridor, respiratory distress or failure, or hypoxia and cyanosis but usually without subcutaneous emphysema.

Diagnosis

Chest radiographs may demonstrate pneumothoraces and subcutaneous emphysema but will not localize tracheobronchial injuries. A high clinical suspicion is required to initiate the diagnostic process. Most of the tracheobronchial injuries (not all) can be identified by CT imaging and bronchoscopy is often helpful in these cases in diagnosing as well as identifying the location of the tracheobronchial injuries.

Management

Most tracheobronchial injuries are recognized after the stabilization of patients. Endotracheal intubation with bronchoscopy is considered when the tracheal injury is suspected. Tracheostomy or cricothyroidotomy is emergently required which allows tracheobronchial injuries to manage conservatively, but most injuries will require surgical repair.

TRAUMATIC ASPHYXIA

Clinical Features

Traumatic asphyxia is a rare phenomenon. It is seen in high-speed road traffic accidents and improperly restrained passengers or as a complication of crush injuries to the head or torso. With compressive force to the abdomen against the closed glottis, intrathoracic and mediastinal pressure tend to increase. As a result of this right atrial blood is pushed in to the innominate and jugular vein, resulting capillaries break in the cervicofacial region. As early as 2–3 hours after the injury, patients may present with facial and bulbar conjunctival petechiae, oral mucosal petechiae, facial edema, and facial cyanosis. Agitation, loss of consciousness, confusion, seizures, anoxic injury, cerebral edema, or ischemia are less common.

Management

Most cases of traumatic asphyxia carry a good prognosis and resolve spontaneously. Goals of management include adequate oxygenation and adequate cerebral perfusion to promote healing and avoid secondary neurologic injury. Mild symptoms usually reverse in 1–2 days. Patients who survive the initial hours of management prognosis remain favorable.

DIAPHRAGMATIC INJURIES

Clinical Features

Most diaphragmatic injuries occur when the abdomen is forcibly compressed and the diaphragm is stressed by high pressures. The timing of impact in the respiratory cycle plays an important role. In two thirds of cases, the left hemidiaphragm injury is common and mostly in the posterolateral area. Liver and spleen injuries accompany most diaphragmatic injuries. In rare instances, penetrating trauma can directly injure the muscle of the diaphragm. Diaphragmatic injuries may remain asymptomatic in the initial phase and they are usually missed even after examination. Bowel sounds in the chest are indicative of diaphragmatic injury. In severe defects, respiratory distress occurs as the bowel compresses the lung parenchyma which requires emergent surgical repair. Diaphragmatic injuries will present in a delayed fashion if visceral herniation does not occur initially. Vague chest pain, difficulty breathing, vomiting, or bowel obstruction are the delayed presenting features.

Diagnosis

The subtle radiographic findings in these injuries include opacifications in the lung bases, air above the diaphragm, pleural effusions, displacement of the stomach bubble into the thoracic cavity, or a nasogastric tube in the chest. Diaphragmatic injuries can be diagnosed by CT imaging which are usually missed on a radiograph. Radiologic features, an abnormal diaphragmatic line or high-riding diaphragm, and presence of intestinal loops in the chest with or without pleural effusion strongly suggest diaphragmatic injury.

Management

The main goal of ED management is to recognize the injury and support the patient's respiratory function in severe cases. Surgical repair is required in most patients and is highly successful. Pulmonary hypertension and permanent lung parenchymal damage may complicate delayed presentations of diaphragmatic injury.

ESOPHAGEAL INJURIES

Clinical Features

Esophageal injury is rare but can occur with extreme increases in intra-abdominal or gastric pressure from blunt trauma. The esophagus is one of the best-protected structures of the thorax. Blunt thoracic trauma causes esophageal injury in <0.1% of patients. Chest pain or epigastric pain with mediastinal air, fever or sepsis, or pleural effusion should prompt consideration of esophageal disruption.

Diagnosis

Both water-soluble contrast esophagogram and esophagoscopy are required to fully evaluate esophageal injuries. Chest radiographs may increase suspicion of esophageal injury if infiltrates, pleural effusion, or pneumomediastinum is present in patients with clinical symptoms. Fluid accumulation in the mediastinum will cause widening. To detect an esophageal injury, CT scan has increased sensitivity over radiographs. On a CT scan, perforation may appear as focal extraluminal air at the site of esophageal injury.

Management

The main goal of ED management is early recognition. Fluids and broad-spectrum antibiotics may be initiated as an initial therapy. Surgical closure is common in adults, but most children can be managed with supportive care and drainage of any infectious fluid collections. Antibiotics and parenteral nutrition are required to allow the injury to heal. Surgical repair should be performed in patients who fail to improve and with complications.

BLUNT CARDIAC INJURY

Blunt cardiac injury (BCI) is not a straightforward entity. Complications range from asymptomatic ecchymosis to sudden death. There is no widely accepted definition, no gold standard diagnostic test, difficult to quantify, and little consensus on how to establish the diagnosis. Research and understanding about the diseases are limited. Quantification of this disease becomes difficult due to inconsistent nomenclature also. Complications, diagnostic testing, laboratory evidence, or postmortem examination are helpful in identifying the BCI. Due to lack of uniformity and specificity, there is lack of well-validated diagnostic and treatment algorithms for BCI. Mattox et al. proposed to use the term blunt cardiac injury for all cardiac conditions resulting from blunt trauma and avoid using terms such as cardiac concussion and cardiac contusion. BCI-related specific conditions are septal rupture, free wall rupture, coronary artery thrombosis, cardiac failure, minor ECG/enzyme abnormality, or complex arrhythmia. In most cases, BCI is associated with MVC. Blunt thoracic trauma with multisystem involvement carries a high risk of BCI. One study concluded that there is 13% incidence of BCI with significant chest wall trauma (multiple rib or sternal fractures, lung contusion, scapular fracture, hemopneumothorax, major intrathoracic vascular injury, or seat belt sign). These studies provide a rationale of screening for BCI which identifies cases at high risk for the complication that will benefit from intervention.

Mechanisms and Injury Patterns

There are various mechanisms of injury identified for BCI, e.g., direct, indirect, crush injury, bidirectional or compressive, decelerative, blast, concussive, and combined. Because of its proximity to the chest wall right heart is the most common site for BCI although involvement of multiple cardiac chambers is seen in half of the cases.

Cardiac concussion (cardiac contusion): Cardiac concussion is histologically defined by myocardial hemorrhage, edema, and localized necrosis. In clinical practice, the term broadly describes injuries from chest wall tenderness to wall motion abnormalities, decreased contractility, arrhythmia, or conduction abnormalities. Most of these injuries typically subside within 24 hours without intervention and do not manifest long-term effects. Prompt further evaluation and management are required if associated clinical features such as hypotension, pulmonary edema, malignant arrhythmia, or conduction disturbances are present and represent significant contusion.

Commotio cordis: This is a condition of sudden cardiac death from BCI without any evidence of morphologic injury or preexisting disease. This condition is differentiated from contusio cordis, which does have evidence of an underlying morphologic injury and requires autopsy for differentiation. Alcohol use, drug use, and preexisting cardiovascular disease increase the risk of commotio cordis. Commotio cordis is the second most common cause of sudden cardiac death in young athletes. High-velocity impact to the chest, occurring during ventricular repolarization, is the most suitable pathophysiologic explanation for this condition. Rapid recognition of dysrhythmia and prompt, high-quality cardiopulmonary resuscitation may result in improved outcomes for these patients.

Cardiac rupture: It is possible to have cardiac wall rupture by blunt injury, in most cases fatal, and patients typically succumb rapidly to exsanguination, cardiac tamponade, or other concomitant injuries. Survival in patients with cardiac rupture with BCI is notably rare, but not nonexistent. Overall, ventricular rupture occurs more commonly than atrial rupture, but right atrial rupture is more common than left atrial rupture. The presence of a murmur, thrill, arrhythmia, or conduction disturbance suggests this injury, and the severity of the signs typically correlate with the size of the injury. Cardiogenic shock is the common presentation of severe injury.

Valvular injury: BCI-associated valvular injuries are typically acutely severe, hemodynamically consequential, and clinically manifests with cardiopulmonary sequelae, but minor valvular abnormalities detected during screening for BCI likely represent preexisting valvular disease amenable to repair if diagnosed. The morbidity and mortality of BCI-associated valvular injury depend on the location and severity of the injury of the affected valve. Aortic valve injury is considered to be most common and manifests as cardiovascular instability or cardiogenic shock. It may result from a sudden increase in intrathoracic pressure against a closed valve along with retrograde aortic pressure wave from a concomitant increase in intra-abdominal pressure. Acute mitral valve injury typically manifests as pulmonary edema and hypotension. These injuries are treated by afterload reduction and supportive care till definitive surgical repair. Tricuspid injury may present more subacutely with long-term sequelae of right ventricular dysfunction manifesting over months to years. In addition, injury to the papillary muscle or chordae tendineae injury is associated with higher morbidity and mortality.

Coronary artery injury: There is not enough evidence that suggests that coronary artery thrombosis occurs as a direct result of BCI. Most of the coronary artery injuries may progress to laceration, dissection, aneurysm formation, and/or aneurysm rupture.

Pericardial injury: The pericardium rupture of injury is not common in the setting of BCI. Pericardial injury may clinically present as pericarditis or pericardial effusion and tamponade.

Dysrhythmias: BCI most commonly manifests as sinus tachycardia, ventricular or atrial premature contractions, and atrial fibrillation. Most of the dysrhythmias may be associated with benign features, due to catecholamine release, alcohol and drug use, or electrolyte abnormalities. In many cases, they may occur as a delayed presentation of injury. In severe trauma heart block, ventricular tachycardia, or fibrillation is associated with electrolyte disturbance, acidemia, and/or hypovolemia/hypotension.

Diagnosis

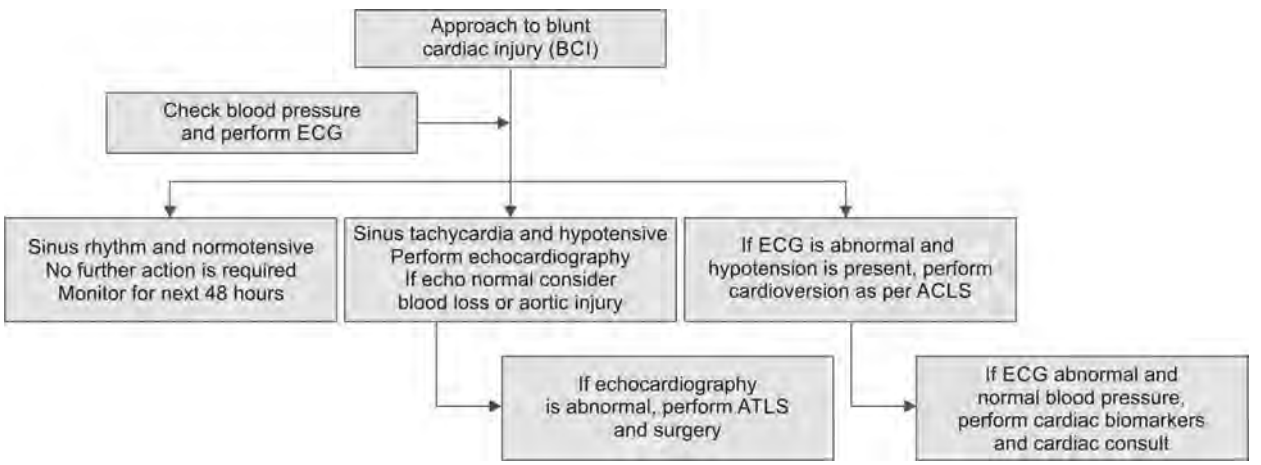
Blunt cardiac injury is a heterogeneous category of multiple specific injuries and thus a difficult condition to diagnose. The history and physical examination mostly remain nonspecific. Patients may complain of chest pain or shortness of breath; in some cases, this even includes typical angina pain, and patients may progress to myocardial infarction via an unknown mechanism. However, in polytrauma conditions, the signs and symptoms of clinically significant BCI may be masked due to other injuries. The physical examination in BCI often remains nonspecific, but findings suggestive of the high-risk mechanism of injury are ecchymosis, chest tenderness, flail chest, and crepitus. The presence of rib or sternal fractures also provides a clue for the emergency physician to proceed with the evaluation of BCI. On physical examination, findings such as friction rubs, distant heart sounds, and new murmurs are much more indicative of BCI, but difficult to appreciate ED setting, especially during polytrauma management. The high index of suspicion for BCI should be considered if patients present with dyspnea, distended jugular veins, chest wall ecchymosis, flail chest, sternal fracture, rib fracture, pneumothorax, hemothorax, great vessel injury, or hemodynamic instability which is not explained otherwise. Once the history and physical examination are completed, ECG should be performed on all patients with direct blunt chest injuries and also in patients without known blunt chest injuries. Electrocardiographic abnormalities may include sinus tachycardia, arrhythmias, and ST-segment changes. Most guidelines and supporting literature have suggested that despite a normal ECG, echocardiography should be performed as some time ECG abnormalities typically manifest within 48 hours of injury. To exclude the myocardial injury negative troponin I assay is also considered with an ECG. Creatine kinase-myocardial band (CK-MB) is neither sensitive nor specific for the detection of BCI and is no longer recommended in the diagnostic evaluation.

The combination of ECG and troponin I is adequate to exclude clinically significant injury. Echocardiography should further characterize injuries if present when these screening tests are abnormal. This test includes quantifying the degree of left ventricular dysfunction resulting from contused or concussed myocardium (appearing as an area of thickened myocardium during end-diastole) and identifying associated valvular disorders. Although the transesophageal approach is superior for the evaluation of a valvular disorder in BCI, it is more time consuming and resource intensive. With improvement in ultrasonography technology, the transesophageal approach may not need to be routinely performed. Both modalities can detect pericardial effusion caused by traumatic cardiac rupture.

Other modalities, such as CT, MRI, and magnetic resonance coronary angiography, have significant limitations in the evaluation of BCI, and may be considered only on a case-by-case basis in consultation with a trauma surgeon and/or a radiologist. In the evaluation of BCI, nuclear scintigraphy is not useful.

Treatment

All patients with abnormal ECG or positive troponin level should be admitted for observation (**Flowchart 2**). Patients with dysrhythmias and hypokinesia due to myocardial contusion should be under cardiac monitoring for at least 48 hours. Patients with features of heart failure or cardiogenic shock should be treated with inotropic agents and/or mechanical support. A standard approach should be adopted to manage the arrhythmias and for the use of antiarrhythmics. Correction of electrolyte imbalance, hypoxia, and acidosis; avoiding proarrhythmic medications; and use of defibrillation if necessary are important. Sinus tachycardia remains the most common dysrhythmia which can be managed by correcting the underlying cause, e.g., volume resuscitation, analgesia, or transfusion. Atrial fibrillation is the second most common arrhythmia, frequently caused by alcohol or drug use, fluid deficit, electrolyte abnormalities, and/or catecholamine surge. Such cases may require temporary pacemaker placement in an ED setting. Although rare, a permanent pacemaker


Approach to blunt cardiac injury (BCI)
Check blood pressure and perform ECG
Sinus rhythm and normotensive
No further action is required
Monitor for next 48 hours
Sinus tachycardia and hypotensive
Perform echocardiography
If echo normal consider blood loss or aortic injury
If ECG is abnormal and hypotension is present, perform cardioversion as per ACLS
If echocardiography is abnormal, perform ATLS and surgery
If ECG abnormal and normal blood pressure, perform cardiac biomarkers and cardiac consult

(ACLS: advanced cardiac life support; ATLS: advanced trauma life support; ECG: electrocardiogram)

FLOWCHART 2: Approach to blunt cardiac injury.

placement is required for persistent complete heart block with clinical symptoms. Patients with BCI who have ST-segment elevations on ECG may represent either traumatic myocardial infarction (from coronary rupture, dissection, or thrombosis) or myocardial contusion although there are no standard guidelines to differentiate infarction from contusion. Operative repair and immediate surgical evaluation are required for structural injuries, including myocardial rupture, pericardial rupture, hemopericardium, and traumatic valvular injuries. Depending on the specific structure injured, various temporary measures need to be performed. Mitral valve injuries with significant regurgitation may require vasodilators to reduce afterload and improve the forward stroke volume and ejection fraction. Mechanical support with an intra-aortic balloon pump may also be beneficial before valve repair or replacement in such cases. Aortic valvular injuries typically require emergent surgery not amenable to stabilizing measures. Depending on the degree of hemodynamic instability and the acuity of decompensation, pericardiocentesis or emergent thoracotomy may be indicated for hemopericardium.

INJURIES OF THE AORTA AND GREAT VESSELS

Clinical Features

High-energy mechanisms with rapid deceleration, such as motor vehicle accidents and falls, most commonly result in such injuries. These injuries are less common with penetrating trauma. Aortic injuries frequently occur at the aortic isthmus. Due to high energy mechanism and rapid declaration ascending aorta gets twisted. As a result of shearing force pseudoaneurysms or focal aortic dissection can develop which may be evident as widening of aorta and blurring of mediastinal contour.

Diagnosis

Widening of the mediastinum, loss of a defined aortic knob, presence of pleural effusion, esophageal or mainstem bronchus deviation, apical cap, or first or second rib fractures are the suggestive features on chest radiography, but CT angiography is the diagnostic modality of choice.

Management

Surgical management provides definitive treatment. But a supportive measure is important in the ED which includes pain control and beta-blocker therapy to control the heart rate and BP. The injuries are often fatal. Early recognition by an emergency physician and definitive therapy reduces mortality.

CRITICAL DECISIONS IN THORACIC TRAUMA MANAGEMENT

Any injured patient should be assessed in a systematic fashion. After blunt and penetrating trauma, thorax injuries are common in both situations; therefore, all patients who present to the ED) after trauma should be screened for thoracic injury according to the advanced trauma life support (ATLS) protocol. Because chest injury can impact each of the ABCs (airway, breathing, and circulation), a rapid evaluation of the chest is performed early in the evaluation of the injured patient to look for any life-threatening injuries. Nonlife-threatening injuries to the thorax are detected as part of the detailed secondary survey.

IMAGING TO DIAGNOSE OR EXCLUDE THORACIC INJURY

Once immediately life-threatening thoracic injuries have been excluded or managed, a secondary survey should be performed. The three most commonly used investigations to screen for thoracic injury are the portable, often supine, anteroposterior (AP) CXR; point-of-care ultrasound (POCUS), including eFAST; and CT scan with arterial-phase IV contrast. As with most decision-making in trauma, the selection of imaging investigations in the workup of thoracic trauma depends on the clinical stability of the patient. It is important to emphasize that unstable patients should not go for the CT scan.

Chest radiograph: The CXR is considered the standard initial imaging investigation for all stable or unstable trauma patients. Without moving the patient from a resuscitation trolley, a single-view AP portable CXR is often taken as fast and inexpensive with a low radiation burden and screens the entire thorax for injury. The CXR gives an overview of the lungs as well as mediastinum, aorta, diaphragm, and bony structures, including ribs, thoracic vertebrae, clavicles, sternum, and scapulae. A CT scan should be performed in stable patients with an abnormal CXR.

Point-of-care ultrasound or standard chest radiograph: In trauma, POCUS is referred to as FAST. FAST is appropriate for both stable and unstable patients. A rapid and radiation-free imaging can be obtained in the resuscitation area without transferring the patient anywhere. There are four conventional views in FAST. One of these, the subxiphoid pericardial view, plays an important role in the workup of thoracic trauma, as it assesses the heart for cardiac motion and tamponade. More recently, the eFAST has entered into clinical use with the addition of thoracic views to assess for hemothorax and pneumothorax. The subxiphoid pericardial view has a sensitivity that approaches 100% and a specificity of 97% at detecting penetrating cardiac injuries. Pneumothorax is detected if lung sliding (the normal movement of the visceral on parietal pleural during breathing) and "comet tail" artifacts (hyperechoic signals that result from normal pleural apposition) are absent, or a lung point (the junctional interface between normal and partially collapsed lungs) is observed.

When compared with the gold standard of CT scan, eFAST has a sensitivity of 86–100% and specificity of 97–100% in pneumothorax detection. This diagnostic yield makes eFAST superior to CXR in the investigation of pneumothorax because CXR has a sensitivity of 27–83% and a specificity of 99–100%. eFAST thus detects pneumothoraces that would be occult on CXR, although these injuries generally do not require chest tube placement unless the patient is symptomatic. Although for the assessment of pneumothorax, eFAST is an excellent tool, it does not provide any assessment of the bony elements of the thorax, the mediastinum (apart from the evaluation for pericardial effusion), or the diaphragm, all of which are assessed on CXR. Ultrasound is a user-dependent test and the validity of results depends on the experience of the clinician, which is not so true with CXR. Therefore, eFAST and CXR are complementary to each other rather than competing diagnostic tests.

Cross-sectional imaging: CT scan of the thorax—The CT scan of the chest is the gold standard imaging modality in thoracic trauma for stable patients, with a sensitivity of 75–85% and a specificity of 99–100%. A CT scan has few limitations in spite of its excellent diagnostic capability. It is costly, involved radiation exposure and, most importantly, necessitates the transport of the patient out of the resuscitation area at a critical time of management. Therefore, it is important to carefully select patients who will derive benefit from this diagnostic intervention.

DISPOSITION FROM THE EMERGENCY DEPARTMENT

Most thoracic injuries such as rib fractures, flail chest, and pulmonary contusions can be managed nonoperatively in the intensive care unit. Flail chest is considered when at least two consecutive ribs are fractured in two or more places and can produce significant contusion to the underlying lung parenchyma as the segment of ribs moves paradoxically against the remainder of the chest wall on inspiration and expiration. The resultant pulmonary contusion can cause respiratory decompensation. The cornerstones of flail chest management include aggressive pain control, alveolar recruitment, and careful use of IV fluids in the first few days after injury. Surgical options for flail chest (open reduction and internal fixation with rib plating) should be considered.

Blunt cardiac injury is an injury pattern that occurs due to a high-speed road traffic accident or direct blow to the chest that needs special attention and clinically manifests as either mechanical or electrical cardiac dysfunction. Mechanical BCIs, such as papillary muscle injury or septal or cardiac wall rupture, are frequently fatal and most patients die at the scene or en route to the hospital. Electrical BCI is more common, clinically present as arrhythmia, and usually self-limited. Patients with BCI should be admitted for 24 hours of continuous cardiac monitoring and obtain an ECG and three sets of troponins. Patients who have hypotension, an abnormal ECG, or uptrending troponin levels should have echocardiography done.

Endovascular therapies: The role of endovascular therapy in the management of thoracic vascular injuries is becoming popular in which the injured vascular segment is excluded from the circulation. Although most patients with vascular injury or rupture succumb on the scene or en route, patients with traumatic aortic dissections and intimal flaps are able to reach the hospital in a stable condition and are candidates for endovascular repair. The use of endovascular therapies for both penetrating and blunt trauma is becoming popular.

Operating room: Most surgeons now rely primarily on the patient's physiology, i.e., clinical evidence of shock, to guide intervention and on the indications for operative intervention. However, many surgeons still consider traditional school of thoughts for operative intervention with evidence of ongoing bleeding or chest tube output greater than 1 L, regardless of the patient's hemodynamic status although with increased acceptance of nonoperative management and a rise in the use of catheter-based interventions, early involvement of the surgical team is always most prudent.

SUMMARY

Thoracic injury is common following blunt as well as penetrating trauma, and clinically presentation ranges from a relatively benign occult pneumothorax to a fatal cardiac injury. It is important that an emergency physician be familiar with the physical examination of this condition and imaging options (CXR, eFAST, and CT scan of the chest) for further workup of thoracic trauma. The emergency medicine physician should have sound knowledge of decompressing tension pneumothoraces, quickly placing chest tubes, when indicated. Swift management of life-threatening thoracic injuries and appropriate workup of others will allow the ED physician to successfully manage patients in the ED. Every trauma patient should undergo a rapid clinical examination and several imaging modalities which include ultrasound, plain radiographs, and CT scan to screen for traumatic injuries to the thorax. It is important to be aware of the indications and pitfalls of each. Many thoracic injuries can be managed nonoperatively. Invasive bedside procedures, such as chest tube placement, are critical skills for all emergency medicine physicians who treat trauma patients. An emergency physician should be familiar with resuscitative thoracotomy, a procedure that is indicated for selected patients following penetrating and blunt trauma.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Abdominal Trauma

Sanjay Shah, Chintan Thanki

INTRODUCTION

Up to 25% of hospitalizations due to trauma involve abdominal and pelvic injuries. In patients having polytrauma, up to 20% of deaths result due to abdominal injuries. In abdominal trauma, the most commonly injured organ overall is the liver, and due to sports injuries it is the spleen. Hemorrhagic shock is the most common cause of death due to abdominal trauma whereas infection is the most common form of morbidity. The most commonly involved organs in penetrating abdominal trauma include the liver, small intestine, and colon.

ETIOLOGY

Road traffic accident is the most common mechanism for abdominal trauma. It is the cause in up to 75% of the cases, followed by blows to the abdomen in approximately 15% and falls in up to 9% of the cases of blunt abdominal trauma, and any such history should raise suspicion for the same. All cases of concomitant head or chest injuries must be ruled out for abdominal trauma. Similarly, any abdominal trauma, especially above the level of umbilicus, must always raise suspicion for associated chest trauma. A pelvis fracture should raise concern for any associated abdominal or retroperitoneal trauma. All patients with unexplained shock in absence of external bleeding must be screened for abdominal trauma.

Penetrating abdominal trauma can be caused by gunshot/firearms injury, stab wounds, and assaults in addition to the aforementioned causes of blunt abdominal trauma. Penetrating abdominal trauma may lead to ureter injuries and blunt abdominopelvic trauma may lead to urinary bladder injuries. Gunshot injuries have a lower incidence but higher overall morbidity than other penetrating abdominal injuries and up to 90% mortality. Up to 10% of children admitted for trauma have an abdominal injury, and road traffic accident is the most common cause, followed by child abuse. **Table 1** summarizes the etiology of blunt and penetrating abdominal trauma.

PATHOPHYSIOLOGY

Victims crossing the road and getting struck by vehicles are at a high risk of blunt abdominal trauma. Collision with steering wheels, bicycle handles, and occasionally airbags may lead to blunt abdominal trauma. Seatbelt-unrestrained passengers are at a higher risk. Injury due to a fall from height may lead to polytrauma where blunt or penetrating abdominal trauma may result, depending upon the surface and/or object on which the victim lands.

In gunshot penetrating abdominal trauma, the severity of the injury is proportional to the bullets' mass and square of its velocity. It can be classified as *high-velocity wound* (>1,000 m/s bullet velocity), *low-velocity wound,* and *shotgun wound*. Shotgun wounds are further classified as per the injury pattern: Type I (wounds spread >25 cm and less penetrated, likely shot from >6 m), type II (spread 10–25 cm), and type III (spread <10 cm, shot from point-blank range <3 m). In addition to the injury due to the foreign object, e.g., bullet and its transmitted heat energy, secondary injury due to fragmented bones may also be present in gunshot wounds. Moreover, bullet velocity, trajectory, and direction further determine the impact of the damage.

Diaphragmatic rupture occurs most commonly on the left side and may be caused by a blunt as well as a penetrating abdominal trauma. Although a rare condition, an undiagnosed diaphragmatic rupture would leads to strangulated abdominal contents. Rectus abdominis hematomas may develop a palpable mass below the umbilicus and mimic intra-abdominal trauma.

Retroperitoneal trauma signifies any injury to the pancreas, duodenum, kidneys, ureter, and bladder. Pancreatic injuries are associated with slightly higher morbidity and mortality when compared to other abdominal trauma. Traumatic

TABLE 1: Etiology of abdominal trauma.

Blunt abdominal trauma	***Penetrating abdominal trauma***
• Road traffic accident	• Road traffic accident
• Assault, e.g., blows to the abdomen	• Assault, e.g., gunshot/firearm, stabbing
• Fall from height	• Fall from height
• Sports injury	• Sports injury
• Industrial injury	• Industrial injury

pancreatitis may lead to significant loss of third-space fluid as hours to days are passed by before shock is apparent. No specific signs or symptoms differentiate pancreatic trauma from other abdominal traumas as such; however, the mechanism of deceleration, especially in unrestrained drivers hitting steering, often causes pancreatic trauma. Duodenal rupture also results from a high-speed decelerating mechanism. Renal injury may be associated with injury to the spine, ribs, aorta, inferior vena cava, ureter, and abdomen.

Pelvic fractures can lead to >2–3 L of blood loss which may remain difficult to halt despite aggressive resuscitation. An open book fracture with symphysis pubis joint separation > 2 cm, quadripartite butterfly fracture of all four pubic rami, and Malgaigne fracture from a vertical shear force are among the pelvic fractures associated with massive blood loss.

Coagulopathy and hyperfibrinolysis occur early in major trauma. Crush injuries are possible with lax abdominal wall, e.g., in elderly and alcoholic patients. An intestinal perforation and spillage are possible in both blunt and penetrating abdominal trauma. Missed or delayed diagnoses lead to the most serious consequences in abdominal trauma. Long-term sequelae of missed renal and genitourinary injuries are hypertension, incontinence, erectile dysfunction, chronic kidney disease, and nephrectomy.

CLINICAL PRESENTATION

The most common symptoms of abdominal trauma are based on blood loss, hypotension, and shock as well as peritoneal contamination and irritation due to ruptured gastrointestinal tract, inflammation, infection, and sepsis. The most common symptom in conscious patients would be pain in the abdominal region. Abdominopelvic injuries often present with referred shoulder tip pain which should not go unnoticeable. Splenic trauma may exhibit pain over the left shoulder whereas liver trauma exhibits pain over the right shoulder. Myocardial infarction should never be missed in shoulder pain. Some patients with abdominal trauma may have focal pain during rotation, flexion, extension, or tenderness over percussion as their only positive clinical finding. Patients presenting with difficulty in breathing following abdominal trauma should be looked for diaphragmatic rupture or injury since it can be the only presenting complaint. Renal injury may present with microscopic or macroscopic hematuria and shock. Intraperitoneal bladder rupture is associated with shock and peritonism. Extraperitoneal bladder rupture leads to microscopic hematuria and hematoma. Traumatic rupture of the membranous urethra is associated with urethral bleeding, inability to void, high-riding prostate on rectal examination, and underlying tender hematoma. Traumatic rupture of bulbous urethra causes local perineal tenderness, hematoma, and meatal bleed. Missed perineal injuries may complicate with infection and fistula.

Features of Concern (Red Flags)

Hypotension is the most important red flag for all abdominal injuries irrespective of their mechanism. It may not result until at least 25–30% of the circulatory volume has depleted. Any increase in pulse pressure should be noted and is followed by a fall in hourly urine output, further followed by anxiety and altered sensorium unless the hypotension is corrected. Dizziness and fatigue are other symptoms suggestive of blood loss and should be considered as red flags for delayed bleeding in patients who are discharged from the emergency department (ED). Fever and leukocytosis are red flags in patients with a history of blunt abdominal trauma that had presented late and there could be duodenal rupture which may progress toward sepsis. Vomiting, especially of delayed onset after discharge from the ED in apparently insignificant trauma, should also be considered as a red flag for return to the ED, since its underlying cause may vary from head injury to duodenal rupture and other intra-abdominal trauma.

EVALUATION

History

Focused history includes allergies, ongoing medications, past illnesses, pregnancy, last meal status, and the circumstances leading to the injuries. If time and situation permit, a detailed history is always useful in determining the time of injury, underlying mechanism, vehicle speed, collision type (frontal impact, lateral impact, rear impact, rollover, etc.), and details of objects/weapons involved. In case of penetrating abdominal trauma, useful information includes the type of weapon, the victim's distance and position from the weapon, the estimated number of injuries inflicted, and the estimated blood loss. Inability to void should be taken seriously since it may be as a result of shock, spinal trauma, pain, or an injured ureter, bladder or urethra. Examples of dangerous mechanisms of injury are a pedestrian struck by the vehicle, victim ejected from the vehicle, fall from height, and death of fellow passengers in a road traffic accident. These should be looked for in history if witnesses are available.

Physical Examination

After a primary survey of the airway, breathing, circulation, disability [Glasgow Coma Scale (GCS), pupils, lateralizing signs, neurological deficit], and exposure, the patient should be logrolled to look for penetrating injuries over the back and perineum, thoracolumbar spine injuries, and rectal examination for tone, prostate, blood, and other injuries. This is followed by a secondary survey whereby the patient must be examined thoroughly all over the chest, abdomen, pelvis, perineum, and each region of the body.

Any visible external injury can range from abrasions, contusions, and lacerations to puncture wounds and ecchymoses (**Fig. 1**). *Periumbilical ecchymoses (Cullen's sign) and flank ecchymoses (Grey Turner sign) are suggestive of retroperitoneal hemorrhage*. Tire marks and *"seatbelt sign"* (contusion or abrasion across the abdomen) are clues to *potential blunt abdominal trauma*. In gunshot penetrating abdominal trauma, there is an apparent entry wound and an exit wound should also be looked for. Bowel sounds should be auscultated. Ileus as a result of free intraperitoneal blood may cause loss of bowel sounds.

Tenderness, distension, dullness, rigidity, and guarding should be assessed across all quadrants. Signs of peritoneal irritation are evoked by peritoneal movement due to percussion. Palpation of a high-riding prostate suggests pelvic fracture. In penetrating abdominal injuries, sometimes there may be active bleeding from wounds or evisceration of bowel loop and omentum which requires sterile wet nonadhesive dressing.

FIG. 1: Visible external injury in abdominal trauma. ***(For color version, see plate 40)***

TABLE 2: Decision-making for investigation in the abdominal trauma patient.

Clinical status and hemodynamic	*Investigation recommendations*
Mechanism of injury nondangerous, normal vital signs, and clinical assessment reassuring	Consider foregoing transfer to the trauma center and CT scan
Mechanism of injury dangerous but vital signs stable or fluctuation in blood pressure	To define the nature and severity of the injury—CT scan useful
Unstable/prearrest—blood pressure < 100 mm Hg, weak peripheral pulses/no pulse, altered mentation	*CT imaging contraindicated*, resuscitation, early surgical consultation, preparation for operation theater, consider REBOA (resuscitative endovascular balloon occlusion of the aorta), consider transfer to the trauma center

Interpretation of Finding

The accuracy of physical examination in blunt abdominal trauma is 55–65%. Up to 45% of patients with blunt abdominal trauma may have had a normal initial physical examination. The abdominal examination will be unreliable in patients presenting with intoxication, e.g., alcohol/drugs, low GCS, spinal injury, or equivocal findings due to concomitant/distracting injuries to the head, lower ribs, spine, and/or pelvis. Pelvic bone instability maneuver can be unreliable at times and risks increment in bleeding by dislodging the clots.

INVESTIGATIONS

Not all patients presenting with abdominal pain following a blunt abdominal trauma require extensive investigations. As abdominal trauma patients present with varying degrees of signs and symptoms (stable to unstable), investigations should be decided according to their hemodynamic status (choosing abdominal CT scan for hemodynamically unstable patients would be disastrous) (**Table 2**). *However, patients with the following conditions should be further evaluated by extensive investigations:* Abdominal tenderness persists after initial analgesia; abdominal distension; external visible injury; dangerous mechanism of injury as aforementioned; additional grievous trauma to head, face, thorax, pelvis, or long bones; altered sensorium; unexplained hypotension; pregnant patients; and patients at risk of bleeding, e.g., on anticoagulants or with an active liver disease.

Basic Laboratory and Point-of-care Tests

Two large-bore intravenous (IV) cannulas are inserted and blood samples are collected to be sent for a preoperative profile that includes complete blood count (CBC), creatinine, urea, and electrolytes. Liver function test (LFT), random blood sugar (RBS), amylase/lipase, blood grouping/crossmatching, prothrombin time (PT), activated partial thromboplastin time (aPTT), human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV), and an electrocardiogram (ECG) should be documented. Urinalysis can be missed but helps in determining hematuria. Venous blood gas analysis may be useful for assessing pH and lactate levels, and thromboelastography for clotting deficiencies. In major trauma, hematocrit gives an idea of the extent and duration of hemorrhage, leukocytosis with moderate left shift occurs within several hours, and metabolic acidosis with the increased base deficit and/or lactate is suggestive of hemorrhagic shock. Elevated serum transaminases cannot differentiate between major and minor hepatic trauma and alcohol-induced liver damage.

Point-of-care Ultrasound

Point-of-care ultrasound (POCUS) is useful in terms of focused assessment by sonography in trauma (FAST) scan or an extended focused assessment by sonography in trauma (eFAST) scan that includes assessment for pneumothoraces. Ultrasound is ideal, when patients are unstable and cannot be shifted for a CT scan. The FAST scan is a bedside, rapid, noninvasive tool that does not involve radiation or contrast material and it is very effective in detecting intraperitoneal fluid as well as cardiac tamponade and pneumothorax. At the same time, it is operator dependent and cannot detect the hemorrhage "source" and diaphragmatic/retroperitoneal injuries.

X-ray

Patients should have a chest X-ray, an X-ray of the pelvis with both hips, and a thoracolumbar spine X-ray if there is tenderness or neurological deficit. X-rays can locate metallic foreign bodies in addition to the usual findings. The chest X-ray can detect free gas under the diaphragm (if done in a semierect position after ruling out spine injury) and rib fractures with any associated pneumothorax/hemothorax. X-ray of an unstable pelvic fracture may appear normal in the presence of a well-fitted pelvic binder.

Computed Tomography

An abdominopelvic CT scan with IV contrast is considered as the gold standard in diagnosing abdominal trauma since it helps in determining the anatomy and grade of injury,

FIG. 2: Contrast-enhanced computed tomography of the abdomen showing grade IV liver injury with hemoperitoneum with contrast blush.

in quantifying the free fluid, and in detecting contusion, laceration, hematoma, and inadequate perfusion (**Fig. 2**). The CT scan demonstrates active bleeding as a blush and guides the requirement of surgery or therapeutic angioembolization. A delayed scan of KUB (kidney, ureter, bladder) helps in detecting urinary extravasation. The only major disadvantages of CT are the need to transfer the patient, radiation exposure, and a possibility of contrast allergy.

Diagnostic Peritoneal Lavage

With radiological advancements (X-rays, CT, ultrasound), the role of diagnostic peritoneal lavage (DPL) has largely been dissolved. Moreover, DPL is redundant when laparotomy is already indicated. However, it may be useful when radiology is either unavailable or unreliable and the patient shows unexplained hypotension. DPL is done by infiltrating a local anesthetic agent and epinephrine followed by a closed (using a catheter over a guidewire below the umbilicus) or open (using a small laparotomy incision through the abdominal wall layers) technique and aspiration after instilling 10 mL/kg warmed normal saline. The urinary bladder should be drained beforehand. If >10 mL of frank blood is aspirated or the lavage fluid analysis shows >100,000 red blood cells (RBCs)/mm^3, then the lavage is considered positive and thus needs surgical intervention. The procedure often provides no information regarding the source or magnitude of the bleeding and retroperitoneal injuries. A solid parenchymal damage, e.g., subcapsular splenic injury, may be missed by both ultrasound and DPL in the absence of intraperitoneal free blood. Diagnostic laparoscopy is used by some clinicians in hemodynamically stable patients. Retrograde cystography is useful in bladder injuries. Suspected urinary system injuries are evaluated using a contrast-enhanced CT scan or intravenous pyelogram (IVP). Renal angiography can detect vascular trauma.

TREATMENT

Rapid Assessment

Rapid assessment of airway and breathing is the first priority. High-flow oxygen should be given and the patient kept nil by mouth. Any wounds with active hemorrhage need compression or hemostatic dressing to control the bleed. Any exposed bowel should be covered with saline-soaked nonadhesive dressing. IV crystalloids, i.e., normal saline or lactated (Ringer's or Hartmann) solutions, should be used for initial resuscitation until blood is available. Adequate pain management, antacid and antiemetic should be given. Measures should be taken to prevent hypothermia. Antifibrinolytic tranexamic acid should be given early, within 3 hours of injury if possible.

Fluid Resuscitation

The aim of fluid resuscitation is to regain hemostasis but decrease blood loss. The damage control resuscitation concept promotes minimal crystalloids and permissive hypotension to minimize bleeding followed by a balanced transfusion of frozen plasma, platelets, and packed cell volume at the earliest. This is found to control coagulopathy and improve survival.

Serial FAST scans help in estimating the severity of intraperitoneal hemorrhage. Apart from FAST scan, ultrasound is also useful to check for inferior vena cava diameter to estimate intravascular volume, guide volume resuscitation, and also predict mortality.

Adjunct

The nasogastric tube is inserted to drain gastric contents and urethral catheter to monitor urine output. In the presence of facial or basilar skull fracture, the nasogastric tube should be inserted orally. A urethral catheter is avoided in cases of blood at the meatus which is suggestive of urethral injury, scrotal hematoma, high-riding prostate, or complex pelvic injuries. A pelvic binder sling should be applied in suspected pelvic fractures. An ultrasound-guided suprapubic catheter should be placed by an experienced clinician in case of urethral injuries. Broad-spectrum antibiotic coverage, e.g., ampicillin 1 g IV, gentamicin 5 mg/kg IV, metronidazole 500 mg IV, and tetanus prophylaxis should be given as per wound contamination and patient's history of previous tetanus prophylaxis.

Hemorrhage Control and Laparotomy

Hemorrhage control in severe abdominopelvic trauma may require laparotomy as the gold standard definitive treatment, with/without pelvic fixation. Some patients may require angioembolization for hemorrhage control if the patient is stable hemodynamically. *Indications of laparotomy* (**Table 3**) include blunt or penetrating trauma associated with persistent shock as evidenced by a positive FAST/DPL, radiological evidence of free gas under the diaphragm, diaphragmatic rupture, disrupted abdominal wall with/without evisceration, peritonitis, and CT diagnosed trauma that indicates for surgery. Any penetrating injury, such as a stab wound, gunshot, and industrial puncture wound, and hemoperitoneum without a clear source remain as relative indications for exploratory laparotomy. Hemorrhage is controlled by sequentially packing the four quadrants of the abdomen. Simple bowel perforations are repaired and in complex injuries, bowel resection may be performed. After initial resuscitation, the admitting surgical team is involved as early as possible since the decision for emergency laparotomy rests on them.

Operative versus Nonoperative Management: Role of Computed Tomography

The CT scan is useful in deciding for *operative versus conservative nonoperative management* (NOM) of abdominal trauma by providing a detailed anatomy and a severity-based solid viscera injury grading. High-resolution helical CT helps in identifying vascular injuries, aneurysms, and arteriovenous fistula. Percutaneous transcatheter coiling and temporary endovascular balloon occlusion are other examples of upcoming treatment modalities. Angioembolization is useful in evidence of active contrast extravasation on CT scan and in retroperitoneal arterial bleeding. A large vessel injury should not be missed.

Both *hepatic and splenic injuries* are graded according to the American Association of Surgery for Trauma (AAST) liver and spleen injury scale (I–V), respectively. The AAST liver and spleen injury scale 1994 revision is summarized in **Table 4**. The vast majority of patients with blunt hepatic and splenic injury require conservative NOM. Liver trauma surgery objectives are hemorrhage control, bile leak control, debridement or resection of devitalized liver, and drainage. Hepatic necrosis, abscess, bile leak, and delayed hemorrhage are the most common complications of liver NOM. Overwhelming postsplenectomy infection by encapsulated organisms and splenosis are late and rare complications of splenectomy. Pneumococcal, meningococcal, annual influenza, and *Haemophilus influenzae* type B vaccinations are recommended for postsplenectomy. A complication of spleen NOM is that any possibility of operative intervention for any associated traumatic damage would be delayed or lost with time. In the absence of a strict consensus, typically such patients are advised to refrain from activities that put them at risk of splenic trauma for a time period ranging from 2 to 6 months.

Endoscopic retrograde cholangiopancreatography is the most sensitive method for diagnosing pancreatic duct injury. Distal pancreatectomy and use of external drains have demonstrated a reduction in morbidity and mortality. Complications of conservative as well as operative treatment include pancreatitis, fistula, abscess, pseudocyst, and sepsis.

Over 85% of blunt *renal injuries* require conservative management. The AAST renal injury scale is given in **Table 5**. Generally, grades I to III require conservative management, while grades IV and V may require operative management. Renal vascular injuries require revascularization as early as possible with variable guidelines. Complications after renal trauma include delayed bleeding, urine extravasation, abscess formation, and renal failure.

Pelvic trauma is often graded using the Young and Burgess classification based on the type of force: Lateral compression, anteroposterior compression, or vertical shear. Surgical management is required in complex pelvic fractures that involve the perineum, rectum, or vagina and in intraperitoneal bladder rupture. Early involvement of the obstetric team is vital for managing abdominal trauma in pregnancy, which involves fetal ultrasound, avoidance of CT scan and X-rays

TABLE 3: Indications for laparotomy.

Absolute indications (prepare for operation theater)	*Relative indications (discuss with trauma surgeon)*
Blunt: • Grossly hemodynamic unstable patient ± FAST • Generalized peritonitis • Free air under the diaphragm on chest X-ray Penetrating: • Evisceration • Abdomen, flank, back injury with hypotension • Shotgun injury (transabdominal trajectory)	Blunt: • FAST/DPL+ve in hemodynamically stable • Liver/spleen/kidney injury hemodynamically stable • Hemoperitoneum diagnosed on CT Penetrating: • Stab wound exploration

(DPL: diagnostic peritoneal lavage; FAST: focused assessment by sonography in trauma)

TABLE 4: Liver and spleen trauma grades.

Grade	*Liver description*	*Spleen description*
I: Hematoma	Subcapsular nonexpanding, <10% surface area (SA)	Subcapsular, <10% SA
I: Laceration	Capsular tear nonbleeding, <1 cm depth	Capsular tear, <1 cm parenchymal depth
II: Hematoma	Subcapsular, 10–50% SA Intraparenchymal, <10 cm diameter	Subcapsular, 10–50% SA Intraparenchymal, <5 cm diameter
II: Laceration	1–3 cm parenchymal depth, <10 cm length	1–3 cm parenchymal depth, not involving vessel
III: Hematoma	Subcapsular, >50% SA or expanding Ruptured subcapsular/parenchymal hematoma Intraparenchymal >10 cm or expanding	Subcapsular, >50% SA or expanding Ruptured subcapsular/parenchymal hematoma Intraparenchymal >5 cm or expanding
III: Laceration	>3 cm parenchymal depth	>3 cm depth or involving trabecular vessels
IV: Laceration	25–75% of hepatic lobe parenchymal disruption or 1–3 Couinaud segments within a lobe	Laceration of segmental or hilar vessels with major devascularization (>25% of the spleen)
V: Laceration	>75% of hepatic lobe parenchymal disruption or >3 Couinaud segments within a lobe	Completely shattered spleen
V: Vascular	Juxta hepatic venous injuries, i.e., retrohepatic vena cava or central major hepatic veins	Hilar vascular injury with devascularized spleen
VI	Vascular: Hepatic avulsion	–

TABLE 5: Renal trauma grades.

Grade	*Description*
I	Hematuria with normal anatomy or subcapsular nonexpanding hematoma; no laceration
II	Perirenal, nonexpanding hematoma or <1 cm renal cortex laceration with no urinary extravasation
III	>1 cm renal cortex laceration with no collecting system involvement or urinary extravasation
IV	Laceration through cortex and medulla and into the collecting system or segmental renal artery or vein injury with hematoma
V	Shattered kidney or vascular injury to renal pedicle or avulsed kidney

unless inevitable, judicious fluid resuscitation, continuous cardiotocography, and *Kleihauer–Betke tests* to identify fetomaternal hemorrhage and immunoglobulin in rhesus negative pregnant women. Pediatric abdominal trauma management priorities and strategies are similar to those of adults.

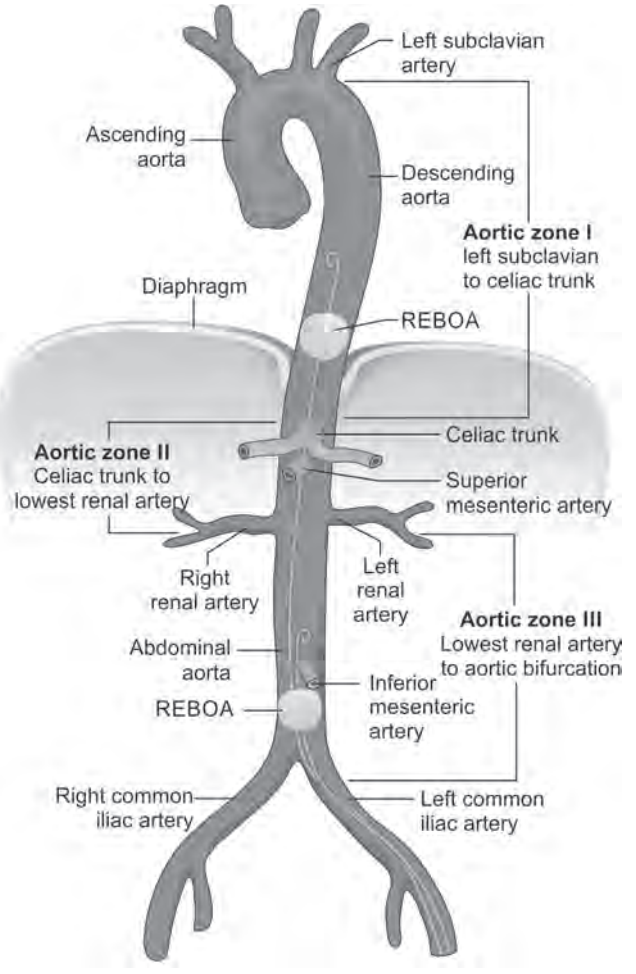
RESUSCITATIVE ENDOVASCULAR BALLOON OCCLUSION OF THE AORTA

Resuscitative endovascular balloon occlusion of the aorta (REBOA) has recently come up as a minimally invasive alternative to open aortic cross-clamping in the management of the nonresponsive category of polytrauma patients. It will help in controlling noncompressible hemorrhage arising below the diaphragm. It is being used in both blunt and penetrating abdominal trauma. The use of REBOA provides for temporary hemorrhage control and improved hemodynamics until definitive surgical/endovascular control of hemorrhage is achieved.

REBOA Technique and Indications

REBOA is being used in zones I and III of the aorta (**Fig. 3**). Zone 1 of the aorta extends from the left subclavian artery to the celiac artery. Zone 2 continues from the celiac artery to the renal artery. Zone 3 extends from the origin of the lowest renal artery to the aortic bifurcation (infrarenal aorta). Zone 1 occlusion is utilized in patients with cardiac arrest or those in hemorrhagic shock with evidence of noncompressible hemorrhage arising below the diaphragm. Zone 2 is considered to be a no-occlusion zone. Zone 3 occlusion is reserved for patients without evidence of intra-abdominal hemorrhage but with evidence of a pelvic fracture.

A clinical algorithm outlining the clinical decision-making for REBOA utilization is presented in **Flowchart 1**. For decision-making, a chest X-ray (CXR) must be obtained to rule out a major thoracic vascular injury as the cause of hemodynamic compromise. If CXR is suspicious for aortic injury consistent with mechanism (widened mediastinum, apical cap, and depressed left mainstem bronchus), then REBOA is contraindicated. The FAST exam also helps in identifying the source of hemorrhage within the abdomen, along with ruling out pericardial tamponade. Patients with hypotension [defined as systolic blood pressure (SBP) < 90 mm Hg] not responsive to initial blood product resuscitation and with a positive abdominal FAST exam would be candidates for zone 1 occlusion. Patients who are hypotensive with a negative FAST exam and a pelvic fracture would be candidates for zone 3 occlusion.



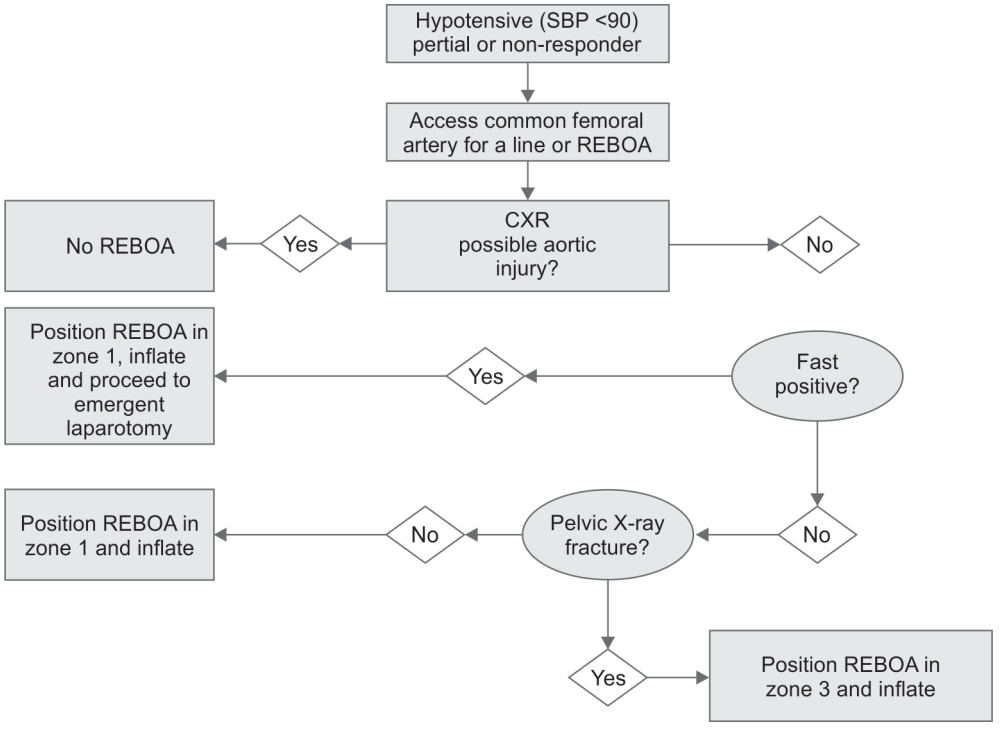
(REBOA: resuscitative endovascular balloon occlusion of the aorta)

FIG. 3: Position of balloon in REBOA.

REBOA can be divided into the following steps:

1. Arterial access with insertion of the arterial sheath (12 vs. 7 French depending on the catheter used)
2. Insertion of REBOA catheter with balloon positioning at an appropriate aortic zone
3. Balloon inflation
4. Balloon deflation
5. REBOA catheter removal
6. Arterial sheath removal

The common femoral artery (CFA) should be accessed under ultrasound guidance if available. Arterial cut-down may be required for direct visualization of the CFA in patients who are in cardiac arrest and is a more reliable method of access. Inadvertent cannulation of the superficial femoral artery has resulted in significant vascular injury and should be avoided. After the appropriately sized sheath has been placed, the aortic zone of occlusion (zone 1 or 3) must be decided based on the clinical algorithm discussed previously. Confirmation of appropriate balloon location via digital X-ray should be performed prior to balloon inflation. The catheter should be



(CXR: chest X-ray; REBOA: resuscitative endovascular balloon occlusion of the aorta; SBP: systolic blood pressure)

FLOWCHART 1: Clinical decision-making for REBOA, immediate hemorrhage control, and bridge to laparotomy.

seen on the patient's left side adjacent to the spine. Zone 1 is confirmed by visualizing the balloon above the diaphragm. Confirmation of the device in zone 3 is seen on pelvis X-ray as being in the vertical position at approximately the L2 or L3 vertebrae.

After inflation, monitoring for loss of the contralateral femoral pulse by palpation or Doppler indicates that sufficient balloon inflation has occurred. Once the device is deployed in the desired zone, it has to be secured to prevent potential complications and the time of occlusion should be noted. After balloon inflation, the patient should be sent urgently to the operating room either for exploratory laparotomy or for angioembolization. It is important to remember that REBOA is only a temporizing measure method to continue perfusion to the heart and brain en route to rapid, definitive hemorrhage control. It is emphasized that there are potential complications of REBOA related to the level and duration of balloon inflation. Overinflation of the balloon can result in either balloon or blood vessel rupture.

Once definitive hemorrhage control has been obtained, balloon deflation can occur. Incremental balloon deflation is typically required in order to avoid cardiovascular collapse. The REBOA catheter can be removed from the sheath after the balloon has been deflated. Then it is important to assess distal perfusion in bilateral lower extremities. Diminished or absent distal pulses in either lower extremity following REBOA warrant immediate investigation with angiography to identify any potential vascular complications. Neurovascular examination of the lower extremity should be done every hour for the first 24 hours after sheath removal.

The current literature regarding REBOA utilization is increasing but has been limited to large case series. The American Association for the Surgery of Trauma Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery registry has published similar findings, with a trend toward improved survival in patients undergoing REBOA compared with resuscitative thoracotomy (RT). The survival benefit is most pronounced in patients not undergoing cardiopulmonary resuscitation at the time of aortic occlusion.

The duration of occlusion remains an important factor when considering the deployment of a REBOA device. With a goal of <60 minutes of occlusion in zone 1 and ~90 minutes in zone 3, rapid access to definitive trauma/vascular surgical management is critical. The goal of REBOA is to improve survival, not prolong time to death. Partial occlusion of the aorta can be achieved by not inflating the balloon to the point of aortic occlusion.

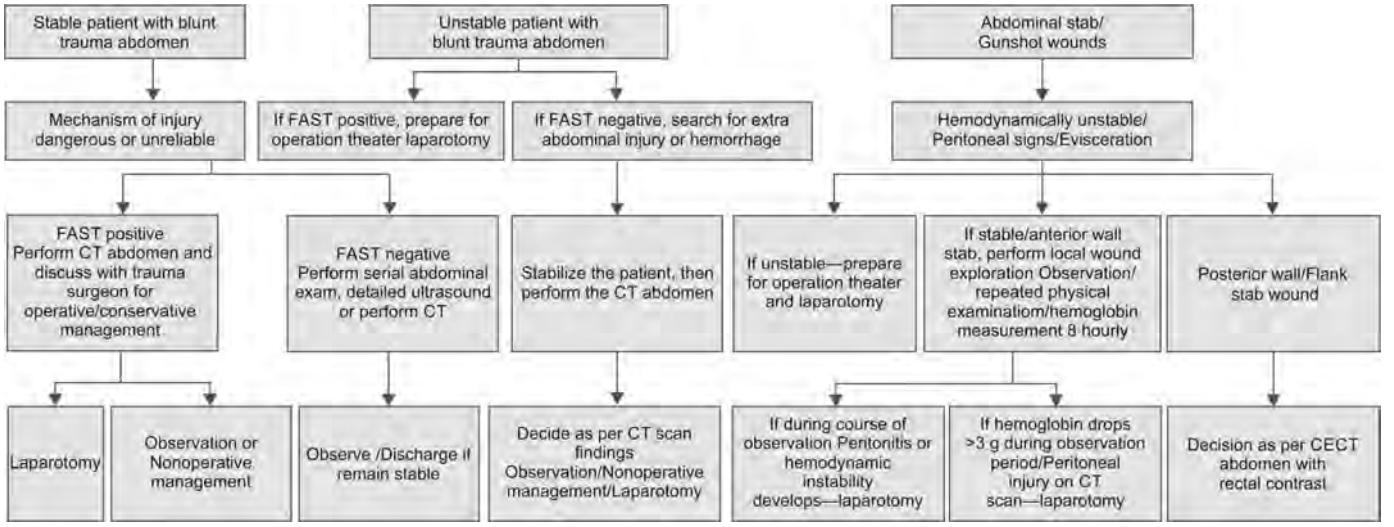
DISPOSITION

Patients with abdominal trauma require close observation and those with significant injury or hemodynamic instability require definitive surgical intervention. Patients presenting with any of the red flags such as hypotension, altered sensorium, dizziness, fatigue, fever, and vomiting should consult the ED. Complications include hemorrhage, coagulopathy, and sepsis.

SUMMARY

Abdominal trauma is not uncommon and can be blunt or penetrating. Road traffic accidents and assaults are the most common causes. Shock in trauma should raise suspicion for blunt abdominopelvic injuries since it is associated with mortality. The goal of the secondary survey is to not miss any injury, but it never foregoes the primary survey. Many a time in hemodynamically unstable patients, the primary survey may not be over in the ED but the patient goes for surgery for hemorrhage control. Hence, the primary survey

needs to complete in the intensive care unit (ICU) and so is the secondary survey. There is limited accuracy of physical examination in both blunt and penetrating abdominal trauma. Diagnostics and management go hand in hand without awaiting a detailed history or elaborate investigations. POCUS helps in identifying the presence of intraperitoneal fluid whereas CT scan is the gold standard in deciding for operative versus conservative management by quantifying the severity of injury, e.g., using the AAST organ injury scale. Severe trauma may require laparotomy, with/without pelvic fixation and angioembolization followed by intensive care and other interdisciplinary management as summarized in **Flowchart 2**.


Stable patient with blunt trauma abdomen
Unstable patient with blunt trauma abdomen
Abdominal stab/ Gunshot wounds
Mechanism of injury dangerous or unreliable
If FAST positive, prepare for operation theater laparotomy
If FAST negative, search for extra abdominal injury or hemorrhage
Hemodynamically unstable/ Peritoneal signs/Evisceration
FAST positive Perform CT abdomen and discuss with trauma surgeon for operative/conservative management
FAST negative Perform serial abdominal exam, detailed ultrasound or perform CT
Stabilize the patient, then perform the CT abdomen
If unstable—prepare for operation theater and laparotomy
If stable/anterior wall stab, perform local wound exploration Observation/ repeated physical examination/hemoglobin measurement 8 hourly
Posterior wall/Flank stab wound
Laparotomy
Observation or Nonoperative management
Observe /Discharge if remain stable
Decide as per CT scan findings Observation/Nonoperative management/Laparotomy
If during course of observation Peritonitis or hemodynamic instability develops—laparotomy
If hemoglobin drops >3 g during observation period/Peritoneal injury on CT scan—laparotomy
Decision as per CECT abdomen with rectal contrast

(CECT: contrast-enhanced computed tomography; CT: computed tomography; FAST: focused assessment by sonography in trauma)

FLOWCHART 2: Summary management of abdominal trauma.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Genitourinary Trauma

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INTRODUCTION

Genitourinary trauma, irrespective of age, has a global incidence of 10–20%, and in about 65–90% of cases, the kidney is the only organ that is injured. These injuries are about three times more common in males compared to females. Operative management (OM) remains the mainstay of management in unstable patients, sometimes after the failure of nonoperative management (NOM), and in most penetrating injuries. NOM is increasingly being utilized in stable patients at centers which have access to endovascular, endourological, and angiographic interventional facilities.

Management decisions should be based on physiological status, anatomic damage caused by the injury, and associated injuries in the patient. As general surgery and trauma surgery guidelines tend to focus on restoration of physiology whereas urology guidelines focus on organ preservation, a collaborative approach would be an ideal for optimal outcomes for the patient. The two widely used injury grading systems are: (1) The American Association for the Surgery of Trauma Organ Injury Scale (AAST-OIS) renal injury scale (**Table 1**); and (2) The World Society of Emergency Surgery (WSES) kidney trauma classification (**Table 2**). The WSES scale incorporates the AAST-OIS scale as well as the hemodynamic stability status of the patient.

MECHANISM OF INJURY

Kidney injury is commonly due to blunt trauma (90% of times) associated with rapid deceleration and rarely (1.4–3.3% of times) due to penetrating trauma usually caused by bullets or by stab. Ureter injury is rare (1%) and most occur due to penetrating injury and in about a third of cases due to blunt trauma. Ureter injury should be suspected in high-velocity

TABLE 1: American Association for the Surgery of Trauma-Organ Injury Scale (AAST-OIS) Renal Injury Scale.

Grade	*Type*	*Description*
I	Contusion	Microscopic or gross hematuria, urological studies normal
	Hematoma	Subcapsular, nonexpanding without parenchymal laceration
II	Hematoma	Nonexpanding, perirenal hematoma confined to renal retroperitoneum
	Laceration	<1.0 cm of parenchymal depth of renal cortex with no urinary extravasation
III	Laceration	>1.0 cm of parenchymal depth of renal cortex without collecting system rupture or urinary extravasation
IV	Laceration	Parenchymal laceration extending through renal cortex, medulla, and collecting system
	Vascular	Main renal artery or vein injury with contained hemorrhage
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of renal hilum that devascularizes kidney

TABLE 2: World Society of Emergency Surgery (WSES) kidney trauma classification.

	WSES grade	*AAST grade*	*Hemodynamic*
Minor	Grade I	I–II	Stable
Moderate	Grade II	III or segmental vascular injuries	Stable
Severe	Grade III	IV–V or any grade parenchymal lesion with main vessels dissection/occlusion	Stable
	Grade IV	Any	Unstable

(AAST: American Association for the Surgery of Trauma)

impact, in deceleration injury with multiple organ system involvement, and in penetrating wounds of the abdomen. The bladder is injured more commonly following blunt injury (65–86%) than following penetrating injury (14–35%). Coexisting pelvic fracture is found in the majority of patients (60–90%) with bladder injury. Urethral injuries are uncommon and occur mostly in males following direct blunt trauma. Urethral injuries in females are usually noted to occur in association with rectal and vaginal trauma.

EVALUATION AND CLINICAL FEATURES

The initial assessment should be as per the *advanced trauma life support* (ATLS) protocols. Relevant history should include the mechanism of injury, history of previous interventions in the genitourinary tract, and any congenital anomalies.

Injury to the genitourinary system should be clinically suspected if there is: (1) blood at the tip of the urethral orifice, (2) hematuria, (3) contusion over the flank, (4) fracture of lower ribs, (5) fracture of the lower thoracic or lumbar spine, (6) pelvic fracture, (7) perineal hematoma, and (8) retention of urine. It would be wise to remember that in children, the kidneys tend to get injured easier than in adults because of anatomical factors such as less perinephric fat padding, thin abdominal wall, nonossified ribs, proportionally larger size of the kidney, and fetal renal lobulations.

INVESTIGATIONS

Urine Analysis

Either microscopic or macroscopic hematuria will be present in the majority of patients (88–94%) with injury to the genitourinary system, but this does not correspond with the injury grade of injury. Macroscopic hematuria would be highly suggestive of major renal parenchymal injury; the same may also be noted in injuries to the pelviureteric junction and injuries to the renal hilum. Rarely (0.1–0.5%), microscopic hematuria and hemodynamic stability can occur in spite of major genitourinary tract injury.

Radiological Imaging: Ultrasound

The choice of imaging is dictated by the hemodynamic stability of the patient. In a hemodynamically unstable patient, the only imaging that may be feasible is the extended focused assessment with sonography in trauma (eFAST), which is useful to rapidly detect free fluid in the abdominal cavity but has poor sensitivity and specificity in detecting genitourinary injuries. Conventional ultrasound frequently underestimates renal injuries and even with a Doppler ultrasound, vascular injuries may remain undetected. Contrast-enhanced ultrasound (CEUS) shows promise in detecting extravasation and vascular damage, but it is not still widely available for use.

Radiological Imaging: Computed Tomography

In hemodynamically stable patients, intravenous (IV) contrast-enhanced computed tomography (CECT) is the standard evaluative modality for assessment of blunt as well as penetrating injuries to the genitourinary tract. This should be done with an arterial phase at 20–30 seconds, a venous phase at 70–80 seconds, and a delayed (excretory) phase at 5 minutes, to visualize the entire genitourinary system. CECT helps in identifying requirement for operative intervention such as contrast extravasation, perinephric hematoma of size 3.5 cm or more, medial tears with the urinary leak, and absence of contrast entering into the ureter. Perinephric fat stranding, perinephric hematoma, contrast extravasation into the perinephric space, and low-density fluid accumulation around the ureter are features suggestive of ureteric injury.

Intravenous Urography, Excretory Urethrography, Retrograde Urethrography

Although in many centers, IV urography has been replaced by computed tomography (CT) scanning, it can be useful for evaluating renal injuries detected intraoperatively, in an unstable patient. It is also useful in situations where CT scan facility is not available. Excretory urethrography is useful in evaluating patients with injuries to the perineum and bladder and those with isolated urethral injuries. Retrograde urethrography can be used to evaluate for urethral injuries intraoperatively or prior to urethral catheterization in suspicious cases.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is useful in the evaluation of renal injury in the pregnant woman, in the pediatric age group to minimize radiation exposure, in patients with iodinated contrast allergy when CECT image findings are indefinite, and in the follow-up of cases to avoid repeated radiation exposure.

TREATMENT OPTIONS

Renal Injuries: Nonoperative Management

General principle of non operative management are round the clock availability of close clinical assessment, facility for appropriate interventions, investigations, monitoring in appropriate level of care and blood bank. NOM should be applied in a graded manner from medical management toward further minimally invasive interventions by endoscopic or angiographic techniques, as appropriate. In general, NOM has similar complication rates to OM, but NOM results in better chances of preserving the kidneys and faster discharge from the hospital. For decision on planning NOM, a CECT is mandatory for defining injuries and hence NOM is feasible only in the hemodynamically stable patient. In the absence of a facility for CECT, in hemodynamically stable patients, other imaging modalities such as IV pyelography and ultrasound may be used to grade the injuries, but these are not as reliable as CECT due to high false-negative rates. The inability to appropriately image the patient due to hemodynamic instability itself is an indication for explorative OM. The same general principles as in adults apply in children too. While deciding on NOM, facilities and expertise available at hand should be considered and may by itself be a limiting factor in applying NOM in austere settings.

Many findings such as fragmented kidney, perinephric hematoma, associated renal pelvis transection, and complications of NOM such as urinomas are not absolute indications for operative intervention, and these may be managed by percutaneous, endoscopic, and angioembolization techniques, especially in the absence of any other indication

for surgery. Although isolated penetrating injuries to the kidney are rare in patients who are hemodynamically stable with isolated renal injury, NOM may be attempted. Hemodynamically unstable patients with renal injury should undergo OM.

Renal Injuries: Angiography and Angioembolization

Hemodynamically stable patients with contrast extravasation from the arterial system on CECT, ongoing gross hematuria with continuing fall in hemoglobin, post-traumatic arteriovenous fistula, and pseudoaneurysm formation are indications for angiography and selective angioembolization. The requirement for angioembolization does not correlate with the grade of renal injury, but success rates decrease with increasing grades of renal injury. In about 30% of patients with arterial contrast extravasation on CECT, there is no bleed detected on angiography. Stable patients undergoing angioembolization have a shorter length of intensive care unit (ICU) stay compared to stable patients undergoing nephrectomy.

Renal Injuries: Operative Management

Hemodynamically unstable patients with renal injury should undergo OM. Hemodynamically unstable patients, due to ongoing active bleed caused by avulsion of renal pedicle, expanding or pulsatile retroperitoneal or perinephric hematoma, and injury of the renal vein with non-self-limiting bleed, are indications for OM. In the hemodynamically unstable patient, an incidentally detected expanding or pulsatile retroperitoneal hematoma requires exploration, especially if no other cause of hemodynamic instability is detected during the laparotomy. Penetrating injuries to the kidney with associated retroperitoneal hematoma should be explored. Exploration in patients with associated arterial or renal parenchymal damage often results in nephrectomy. In patients with only one kidney or if both kidneys are injured, arterial repair should be attempted. Hemodynamically stable patients with a failed NOM technique are candidates for delayed OM.

When deciding on exploration and assessment for renal injury, thought should be given on the appropriateness of timing, especially in damage control scenarios. If exploration is being performed in patients where no preoperative imaging was feasible, the opposite kidney should be assessed for its presence and structural integrity by palpation. If feasible, an on-table IV pyelogram with excretory films can be carried out. Exploration of the kidney can be done by a pedicle first approach or by an anterior vertical incision on Gerota's fascia. Vascular pedicle control is essential for optimal assessment and repair of the renal parenchyma. The renal pedicle can be accessed directly by incising the posterior peritoneum lateral to the aorta on the affected side to expose and loop individual vessels, followed by medial reflection of the overlying colon to approach the kidney. Alternatively, the pedicle can be approached by medially reflecting the overlying colon on the affected side. Isolated vessels may be individually clamped or digital compressive pressure can be applied on the renal pedicle or parenchyma to control bleed. In general, renal preservation rates are much higher when pedicle control is achieved prior to addressing renal parenchymal injury. In the presence of a retroperitoneal hematoma, achieving pedicle control by central dissection and clamping is essential. Complete mobilization of the kidney is required for complete visualization and assessment.

Decision on renal preservation versus nephrectomy should be made at initial exploration, based on the hemodynamic stability of the patient, quantity of viable parenchyma, and extent of damage to the central vascular pedicle and ureter. In an unstable patient with a salvageable kidney, intraparenchymal bleeders can be sutured with absorbable sutures, and the kidney packed behind sterile pads, and definitively addressed after addressing other intra-abdominal injuries. If other injuries require a second procedure, the kidney may be reassessed and definitively addressed at that time. Repair of the renal collecting system can be without an internal stent if the approximation is complete, but if the approximation is incomplete or under tension, it will require an internal stent placement or nephrostomy to prevent urinoma formation. If parenchymal damage is over the poles of the kidney, a partial nephrectomy using a guillotine technique may be performed with suture closure of vessels and collecting system. Parenchymal defects can be addressed by capsular suturing whenever feasible.

If the kidney is deemed nonsalvageable based on the extent of destruction of parenchyma or vascular pedicle, a nephrectomy should be performed. While performing the nephrectomy, whenever feasible, the renal artery and vein as well as accessory vessels should be ligated separately to avoid arteriovenous fistula formation. The ureter as well as the vessels are ligated close to the kidney.

Urinary Tract Injury: Ureter

Ureteric contusions can be managed conservatively by close observation, especially if there is no other indication for laparotomy, by close observation. They may require stenting if there is an impairment in the drainage of urine. Partial transection of the ureter will require stenting. If stenting is not feasible, a diverting nephrostomy should be carried out.

In the hemodynamically stable patient, during operative intervention for other indications, if the ureteric injury is suspected, direct inspection by visualization of the ureters is necessary. Injury to the ureter noted during direct visualization should be repaired primarily. Partial transection of the ureter should be primarily repaired over a double "J" stent, or, if the injury is located distally, by implantation into the bladder. If there is complete transection of the ureter, it should be repaired primarily by ureteroureterostomy or by ureteral reimplantation by bladder psoas hitch or a Boari flap technique. Complete transection injuries to the distal ureter result in tenuous vascularity at the transected ends and should be managed by reimplantation into the urinary bladder as a ureteroneocystostomy. To ensure proper healing and to minimize leak and stricture formation at the repair site, all ureteric repairs should be done over a ureteral stent. In the hemodynamically unstable patient or if primary repair is not feasible, damage control can be achieved by tying up the ureter, with urinary diversion achieved via a temporary nephrostomy, followed by delayed definitive repair after stabilization.

In patients in whom partial ureter injury is recognized late, retrograde stenting should be carried out, and if this is unsuccessful, percutaneous nephrostomy followed by delayed

surgical repair should be carried out. If patients in whom complete ureter transection is recognized late, percutaneous nephrostomy followed by delayed surgical repair should be carried out.

Urinary Tract Injury: Urinary Bladder

Contusion of the urinary bladder requires no specific treatment. All penetrating injuries to the bladder, intraperitoneal rupture of the bladder, and complex extraperitoneal rupture of the bladder will require surgical exploration with a thorough assessment of the adjacent pelvic organs such as the rectum and vagina, followed by primary surgical repair. Rectal injury may require primary repair or diversion stoma, and vaginal injuries may require to be repaired primarily. Uncomplicated and isolated extraperitoneal bladder blunt or penetrating injury can be managed conservatively with clinical observation, under antibiotic coverage, with urine drainage by a transurethral or suprapubic catheter, avoiding an initial operative intervention. Patients with extraperitoneal bladder injury with persistent urinary extravasation beyond 4 weeks after the injury will require surgical repair.

Transurethral catheterization and drainage are as effective as suprapubic cystostomy and should be the preferred choice of drainage whenever feasible. Routine drainage of the bladder by suprapubic cystostomy should be avoided and only performed in situations when transurethral drainage is to be avoided such as in urethral and perineal injuries.

In the hemodynamically stable patient with intraperitoneal rupture of the bladder or who has sustained a penetrating injury to the bladder, exploration with primary surgical repair should be carried out, at the earliest. If intraperitoneal bladder rupture is the only injury with no other intra-abdominal injury, this can be carried out by laparoscopy. Patients with complex extraperitoneal bladder injury such as to the bladder neck, or with coexisting pelvic ring fracture, or injuries with coexisting vaginal or rectal injuries should undergo exploration with primarily repair. This can be carried out during the laparotomy for associated injuries or while exposing the prevesical plane for pelvic fixation.

In the hemodynamically unstable patient with associated bladder injury, temporary drainage of urine can be achieved by transurethral catheterization or by suprapubic cystostomy until the patient is optimized for surgical repair. During damage control procedures in the unstable patient with other organ injuries, temporary urinary diversion can be achieved through the bladder and exiting via the perivesical space or by means of an external ureteric stent.

Conventional repair of the urinary bladder is in double layers using absorbable sutures, while laparoscopic repair is usually in a single layer. Following surgical repair, all adult patients should have continuous drainage by a transurethral catheter until complete healing of the repair is achieved. Following surgical repair in children, suprapubic cystostomy is preferred for continuous drainage until healing is achieved. Healing occurs by 10 days in majority of patients.

Urinary Tract Injury: Urethra

Urethral injuries are relatively uncommon, occur more frequently in males, and usually result from blunt injuries. In women, injury to the urethra is uncommon and results from pelvic injuries. *Clinically, urethral injury should be suspected,* if the patient has blood present at the external urethral meatus, fullness in the suprapubic region, a palpable and distended bladder, urinary retention, evidence of perineal bruising or laceration, scrotal hematoma, high riding prostate on per rectal examination, and difficulty or inability to place a transurethral urinary catheter. Clinical assessment should include rectal and vaginal examination as there may be coexisting vaginal or rectal injuries.

Urethral injuries can be broadly divided into (1) anterior injury involving penile and bulbar regions, and (2) posterior injury involving prostatic or membranous regions. Posterior urethral injuries are further subclassified into complete and incomplete. In the complete subtype, there will be a gap between the two transected ends. The widely used classification for urethral injuries is the Goldman classification, which classifies urethral injuries into five types differentiating extent of transection, anatomic location, and involvement of bladder. In approximately 20% of cases, coexisting urethral and bladder injuries are noted. Anterior urethral injuries usually result from blunt trauma and rarely from penetrating trauma. Posterior urethral injuries usually result from pelvic trauma with pelvic fractures, and the majority tend to be complete injuries. In patients with pelvic fractures, the chance of associated injury to the urethra increases by approximately 10% for each 1 mm of pubic diastasis. Penetrating injury to the posterior urethra is rare, commonly as a result of gunshot wounds; hence, there can be associated intra-abdominal injuries.

Evaluation of urethral injuries can be done by retrograde urethrography or by flexible urethroscopy. In the hemodynamically stable patient, evaluation should ideally be done by retrograde urethrography and should precede other evaluative interventions. In the hemodynamically unstable patient with clinical evidence of urethral injury, urinary drainage should be performed by suprapubic catheterization, with delayed investigative assessment. Once the patient is stable, evaluation of the urethra should be carried out by urethrography, prior to transurethral catheterization. Although extravasation of contrast on urethrography indicates injury, the anatomic description may be difficult. If the patient is undergoing laparotomy for other injuries, direct assessment by flexible urethroscopy may be feasible in some patients. In women and in males with penile injuries, flexible urethroscopy is preferable over retrograde urethrography. Assessment of urethral injuries in the recovery period can be achieved by MRI of the pelvis, which will provide accurate anatomic details of the injury.

In patients in whom there is evident urethral injury or if there is clinical suspicion of urethral injury, urinary bladder drainage must be achieved at the earliest. In stable patients, a urethrogram should be carried out as soon as it is safe and technically feasible. If there is no contrast extravasation, transurethral catheterization may be carried out. However, if urethrography is not technically feasible safely, suprapubic drainage should be performed. An attempt at endoscopic realignment should be made in all cases, and if this is not successful, surgical repair with urethroplasty should be carried out. Penetrating injury to the urethra will require operative assessment and appropriate surgical correction.

In blunt injury to the anterior urethra, the initial management is on conservative lines, by transurethral or by suprapubic drainage, followed by a delayed accurate delineation of

injury and definitive repair. In some cases of anterior partial penetrating injuries, transurethral catheterization may be feasible. Isolated, uncomplicated penetrating injuries may be primarily repaired. In unstable patients, those requiring other urgent interventions, if anastomotic urethroplasty is not possible due to a large urethral defect, urethral marsupialization with suprapubic drainage followed by delayed reconstruction with a graft or flap after 3 months is advisable.

Blunt posterior urethral injuries and partial urethral transection injuries can be managed by suprapubic drainage or by transurethral drainage. Penetrating injuries to the posterior urethra will require operative assessment and appropriate repair. As primary repair or open realignment has a high incidence of stricture formation, a high incidence of urinary incontinence, and impotence, it is better to initially address this type of injury by suprapubic or transurethral drainage, planning definitive repair after 14 days. In stable patients with isolated complete posterior urethral injuries, urethroscopic realignment produces better results than immediate primary repair. When urethroscopic realignment is not feasible, suprapubic drainage followed by delayed urethroplasty may be planned, ideally to be carried out within 14 days. If there is a coexisting fracture of the pelvic ring, definitive repair must be delayed until after the fracture has healed. Penetrating injuries in stable patients with no serious associated injuries can undergo immediate retropubic exploration with primary repair. In unstable patients with other serious associated injuries undergoing damage control management, urinary diversion via a suprapubic catheter with planned delayed urethroplasty should be the plan. In the follow-up period, reassessment urethrography should be done once in every 2 weeks until complete healing is achieved.

Pelvic hematoma or an empty bladder due to hypovolemic shock may cause difficulty in performing suprapubic drainage, and in such situations, transurethral catheterization can be attempted by an experienced person. If this is not feasible, bladder drainage can be performed by direct exposure or under guidance using ultrasound.

Renal and Urinary Tract Injuries: Review Assessment

Mild injuries to the genitourinary tract do not require routine follow-up imaging. No follow-up imaging is required in moderate injuries with no associated urinary extravasation, except if there is deterioration in the clinical condition. In severe renal injuries, a follow-up CECT with a delayed excretory phase may be required 48 hours post admission, as urinary extravasation can be missed in a small number of patients during the initial imaging. There is risk of secondary hemorrhage caused due to rupture of pseudoaneurysm or arteriovenous fistula in about 25% of patients following moderate or severe renal trauma and usually manifests as hematuria within 2 weeks following trauma. Further evaluation by CECT or Doppler ultrasonography (USG) or CEUS will be required in those patients. In pediatric patients with moderate or severe renal injury, follow-up imaging can be adequately performed by USG or CEUS. If there is suspicion on these imaging modalities, or if they are inclusive, MRI can be utilized. Following renal injuries, return to normal activity is advised only after resolution of gross hematuria, and return to sports activities until microscopic hematuria is resolved.

SUMMARY

The management of genitourinary trauma poses peculiar challenges due to the variable anatomical, physiological, and functional characteristics of its components. Often, attention to these structures is diverted by more serious injuries to the adjacent organs and it is regained only at a later stage in the management. Most of these injuries can be managed conservatively by minimal interventions, with delayed definitive repair.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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229 CHAPTER

Extremity Trauma and Crush Injury

M Shiva Reddy, Rammohan Radhakrishnan

INTRODUCTION

Musculoskeletal injury constitutes a major part of emergency care. With increasing motor vehicle accidents, sporting activities, and aging population emergency departments receive a variety of injuries which demand early recognition, stabilization, care, and referral to the concerned departments for definitive care.

Prehospital care and triage: Successful optimization and treatment of a patient with musculoskeletal trauma require dedicated teamwork which starts from the site of the accident by the paramedical staff and their ability to assess, triage, and initiate critical interventions such as cervical collar, pelvic binder, tourniquet application, intravenous (IV) infusion to stabilize and to communicate with the hospital so that necessary preparation is done to optimally treat the patient.

Triage at the hospital: At the emergency, proper triage is done where a focused assessment of the traumatized patient is carried out using the START (simple triage and rapid treatment) system or color-coding system to get the right patient to the right place at the right time. The patient received in the emergency is undressed and initial survey, intervention, and resuscitation are carried out according to the advanced trauma life support (ATLS) protocols and assessment is made whether the patient's injuries and condition fall into life-threatening, limb-threatening, urgent semielective and elective group of injuries. Anatomical scoring systems such as abbreviated injury scale and injury severity score and physiological scoring systems such as Glasgow coma score and revised trauma score are used to assess the condition of the patient and help in triage.

Primary survey and resuscitation: Signs of shock such as agitation, confusion, cold extremities, weak distal pulses, decreased urine output, hypotension, and the deadly triad of metabolic acidosis, coagulopathy, and hypothermia should be aggressively treated with necessary transfusions [fresh frozen plasma and red blood cell (RBC) 1:2, platelets and RBC 1:5] and interventions. Pelvic fractures recognized on plain radiographs with an associated crush injury in the vicinity with the patient in shock not responding to the resuscitation should be treated immediately with the pelvic binder or external fixator and should be planned for emergency laparotomy and pelvic packing or angiography and embolization.

MANGLED EXTREMITY CARE

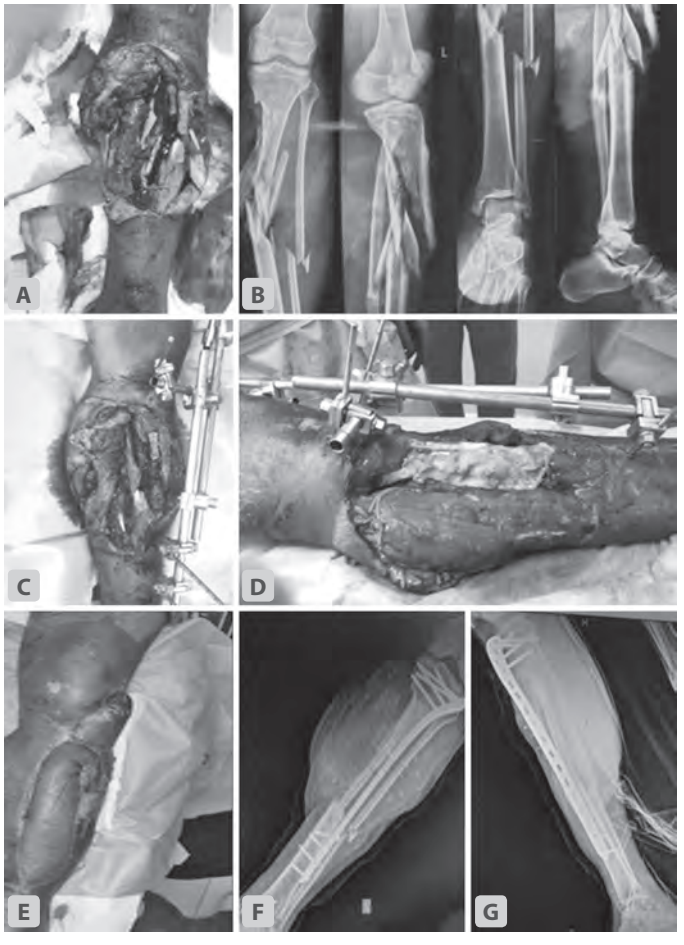
Skin and soft tissues provide the necessary milieu, cover, and protection for the bone and neurovascular structures and their management determines limb salvage versus amputation. Mangled extremity is classified using the *Tscherne classification* of closed fracture and soft tissue (**Table 1**) and *Gustilo–Anderson classification* in case of open fracture/compound injuries (**Table 2**). *All open wounds are inspected for* the degree of soft-tissue injury, presence of comminuted and segmental fractures, degree of contamination, time since injury, proximity and involvement of the joint, exposed bone and tendons, and involvement of neurovascular structures (**Figs. 1A** to **G**). All injuries, both closed and open, associated with comminuted and segmental fractures should

TABLE 1: Tscherne classification of closed fracture and soft-tissue injury.

Grade	*Presentation*
Grade 0	No or minor soft-tissue damage, indirect injury with simple fracture
Grade 1	Superficial abrasion or skin contusion, medium severity fracture pattern
Grade 2	Deep contaminated abrasion with skin or muscle contusion, severe fracture pattern by direct trauma
Grade 3	Extensive skin contusion, crush injury with severe damage to the underlying muscle, compartment syndrome, vascular injury complex fracture pattern

TABLE 2: Gustilo–Anderson classification of open bone fractures.

Grade	*Description*
Grade I	Clean skin contusion < 1 cm, usually from inside to outside > minimal muscle contusion > simple transverse or short oblique fracture
Grade II	Laceration > 1 cm long, with extensive soft-tissue damage, minimum to the moderate crushing component, simple transverse or short oblique fracture with minimal comminution
Grade III	Extensive soft-tissue damage including muscle, skin neurovascular structure, often by high-velocity/energy injury with severe cursing components
Grade IIIA	Extensive soft-tissue laceration, adequate bone coverage, segmental fracture, gunshot injuries, minimal periosteal stripping
Grade IIIB	Extensive soft-tissue injury with periosteal stripping and bone exposure requiring soft-tissue flap closure, mostly associated with massive contamination
Grade IIIC	Vascular injury requiring repair



FIGS. 1A TO G: (A and B) Severely mangled extremity with comminuted fracture; (C) Clinical picture after thorough debridement and knee spanning external fixator; (D) Bone loss spaced with antibiotic bone cement; (E) Post soft-tissue reconstruction; (F and G) X-rays showing good incorporation of the vascularized fibular graft. Compartment pressure measurement should be done in the case of comatose patients. ***(For color version, see plate 40)***

Courtesy: Dr Kesavam.

be examined periodically for pain out of proportion, pain with passive stretch, pulselessness, paresthesia, and pallor for compartment syndrome and treated with necessary fasciotomies (**Figs. 2A** to **E**).

INITIAL CARE OF THE WOUND

Initial care of wound consists of *control of hemorrhage*— by pressure bandage ligation of larger vessels (**Figs. 3A** to **F**) and *removal of gross contamination* and foreign bodies. Definitive debridement cannot be done at the trauma bay, but gross contamination and devitalized tissue can be removed by *irrigation with normal saline*. It dilutes the contamination and helps in prevention of infection and better assessment of the injury and devitalization. *Reduction of the obvious fracture deformities and dislocations*—this relieves the tension in the neurovascular structures and soft tissue around the joint and reduces the risk of infection in case of open wounds and avascular necrosis (AVN). *Approximation of wounds with large flaps with holding sutures*, *adequate dressing*, and normal saline dressing with adequate pads are important. *Stabilization with splinting*—stabilization helps in controlling the movement at the fracture site and helps in patient transport and prevents further damage to the tissue. *Initiation of broad-spectrum antibiotics*: first-generation cephalosporins for gram-positive coverage and aminoglycosides are added for gram-negative coverage; tetanus toxoid and immunoglobulins should be given as per requirment. *Adequate investigations*—bedside Doppler, ankle-brachial index, angiography rays, computed tomography (CT) with reconstruction. Communication with an orthopedician and plastic and vascular surgeons for definitive management is done.

Secondary Survey

Once the life-threatening injuries are addressed, a secondary survey from head to toe is carried out with a detailed history of the nature of the injury, speed of the collision, last meal, allergies, bleeding diathesis, and medications for medical comorbidities. Patients are shifted to the operation theater or intensive care according to the hospital protocols and patients' condition for the respective departments to continue the further evaluation and treatment.

EXTREMITY TRAUMA

Proper recognition of morphology of fracture and its classification helps in recognition of the forces involved, extent of the soft-tissue injury, planning the treatment, communication, and prognosis of the offered treatment.

Shoulder Girdle and Humerus

The shoulder joint consists of sternoclavicular acromioclavicular glenohumeral joints and scapulothoracic articulation. Shoulder injuries result due to direct fall, traction injuries, high-velocity road trauma resulting in fracture-dislocations, brachial plexus injuries, and scapulothoracic dissociation. Patients presenting with shoulder girdle injuries require prompt neurovascular examination and trauma series X-rays [anteroposterior (AP), scapular Y view, and axial view].

FIGS. 2A TO E: (A and B) Right proximal tibial fracture with impending compartment syndrome; (C to E) Application of spanning external fixator, two incision lower limb compartment release. ***(For color version, see plate 41)***

Courtesy: Dr Kesavam.

Sternoclavicular Dislocations

Anterior (common) and posterior (rare) dislocations require prompt attention and treatment because of the close proximity of vital neurovascular structures. Patients can present with dysphagia and difficulty in breathing. Serendipity view and CT scan help in assessment. Posterior dislocation needs early recognition and reduction with the help of orthopedic and thoracic surgeons. Postreduction the joint is stable and can be managed with arm sling for 3–4 weeks followed by range of motion (ROM).

Clavicle Fractures

10% of all fractures result from falls and sporting injuries. These are classified into medial third 5%, middle third 80%, and lateral third 15% depending on the location. Most of the clavicle fractures can be treated with arm sling. Segmental, displaced fracture with tenting skin, floating shoulder, and open injuries with exposed bone warrant surgical fixation.

Acromioclavicular Injuries

Acromioclavicular joint injuries result from falls directly over the shoulder. Injuries range from simple sprains to frank dislocations resulting from coracoclavicular and acromioclavicular ligament injuries. Trauma series X-ray shows vertical displacement of >100% and posterior and subcoracoid displacement needs ligament reconstructive surgery.

Shoulder Fracture-dislocations

Anterior dislocations result from abducted and externally rotated force with capsulolabral detachment (**Figs. 4A** to **D**). Bankart's lesion in young adult occurs due to fall with an outstretched hand and in older patient resulting in fracture-dislocation. Along with trauma series X-rays, the west point view shows anterior glenoid fractures and the Stryker notch view shows the extent of the Hill–Sachs lesion. CT scans are taken in selected patients with complex fractures and to evaluate the glenoid and humeral head. These dislocations should be reduced at the earliest with various techniques which involve traction and counter traction leverage and shoulder manipulation. Physicians should be well versed with more than one technique. 5-10% of fracture-dislocation cannot be reduced in the emergency room (ER) and will require general anesthesia. Reduced shoulders are immobilized in an arm sling for 1–2 weeks followed by physiotherapy. Complications include fractures, axillary nerve injury, rotator cuff tears, AVN, and recurrence. Patients with

FIGS. 3A TO F: (A) Left arm-twisting injury while trying to bend the iron rod in the machine. Note the broken arm encircled around the iron rod. (B) After a thorough wash. (C) Dressed and splinted in extension. (D to F) X-rays are taken at the bedside after proper splinting. ***(For color version, see plate 42)***

Courtesy: Dr Kesavan and Dr Selvaseetharaman.

Bankart lesion and Hill–Sachs lesion present with recurrence and need early arthroscopic repair.

Posterior dislocations are uncommon, easily missed, and commonly occur in patients with seizures. Trauma series X-ray reveals light bulb sign with loss of overlap of normal glenoid and humerus in the AP view. In the absence of fracture and locking, closed reduction can be attempted in emergency under sedation with traction disimpaction. Postreduction is immobilized with arm sling and advised orthopedic follow-up. Complications: Fractures and missed posterior dislocations can present with pain and restricted external rotation which need open procedures. Inferior dislocations are very rare and present with a forward flexed arm. Multiple attempts may be needed if there is buttonholing of the capsule.

FIGS. 4A TO D: (A) X-ray showing humeral head fracture with anterior dislocation; (B and C) Images showing displaced fracture with reduced dislocation; (D) After definitive fixation.

Courtesy: Dr Kesavan.

Scapulothoracic Dissociation

This is very rare resulting from high-energy traction injury and occurs in multiple injured patients. A high index of suspicion is needed in the presence of hematoma in the axillary region and increased distance between the medial borders of the scapula on the chest X-ray. These injuries are associated with neurovascular injuries and dislocations around the shoulder girdle. Magnetic resonance imaging (MRI) confirms vascular and neurologic injuries.

Proximal Humerus Fractures

Proximal humerus fractures are more common in older adults with osteoporosis and result in fall on outstretched hands. Fractures are classified based on the number of fracture fragments and displacement. Most of the fractures are minimally displaced and can be managed conservatively with an arm sling. Three-part and four-part fractures are treated with open reduction internal fixation (ORIF). Displaced comminuted fracture-dislocations can result in AVN and are treated with hemiarthroplasty or reverse shoulder replacement.

Humerus Fractures

They have bimodal distribution; in the young, these fractures are commonly associated with motor vehicle accidents in the elderly, these are because of trivial falls associated with osteoporosis and pathological fractures (unicameral cysts, primary and metastatic malignancies). Orthogonal X-rays and soft-tissue and neurovascular assessment should be done and documented. Midshaft and long spiral fractures are associated with radial nerve palsy with wrist drop and weakness in finger extension and disturbed sensation. Most of the fractures can be treated with U-slab of plaster of Paris (POP) followed by functional brace. <1 cm shortening and 20–30° of angulation are accepted. Bilateral fractures, floating segmental fractures, and open injuries with neurovascular injuries are treated with ORIF. Complications are delayed union, nonunion, radial nerve palsy, and wrist drop.

Elbow and Forearm

Elbow and forearm trauma result from motor vehicle accidents, fall onto an outstretched hand (FOOSH), and side-swipe injuries and constitute 0.5% of all fractures. Orthogonal X-rays with traction help to delineate the fractures and plan management. Special attention is paid to the soft tissue and neurovascular examination. Distal humerus fractures can be divided into supracondylar, single-column, bi-column, and coronal shear fractures. Supracondylar fractures are more common in the pediatric population comprising 5–10-year age group and can be divided into extension type (98%) and flexion type (2%). Distal pulse along with neurology has to be checked at regular intervals. Anterior humeral line and Bauman's angle are used to evaluate fracture angulation and displacement in the X-rays. Minimally displaced fractures can be reduced and splinted with POP application with flexion not exceeding 70–90°. With absent distal pulse reduction and manipulation of the displaced and malrotated fractures under sedation can be attempted in the emergency with prompt orthopedic and vascular intervention at the earliest. Single-column and bi-column fractures of the distal humerus are more common in the 50–60-year age group and are usually T- and Y-shaped condylar fractures. These fractures are commonly intra-articular and need a CT scan with reconstruction, orthopedic evaluation, and congruous intra-articular reduction and fixation. Coronal shear fractures involve capitellum and trochlea with extension into lateral and medial epicondylar regions. Traction X-rays and CT scan help in planning the surgical fixation of the articular fragments. Olecranon fractures resulted from falls and motor vehicle accidents because of triceps pull. These are splinted and treated with tension band wiring or plating.

Elbow Dislocations

Elbow is the second most commonly dislocated joint in the body resulting in disturbance in the three-point relationship between epicondyles of humerus and olecranon. Posterior dislocation is more common than anterior and divergent dislocations. Associated fractures of both the coronoid and the proximal bones with special attention to the soft tissues and neurovascular structures should be done swiftly and reduction should be attempted under sedation. Postreduction elbow is placed in the sling and X-rays are mandatory to evaluate the reduction, presence of associated fractures, and status of the distal neurovascular structures. Stiffness and heterotrophic ossification are the complications associated with injuries around the elbow joint.

Forearm and Wrist

Forearm injuries are a common presentation in the emergency in both pediatric and adult populations (**Figs. 5A** to **G**).

FIGS. 5A TO G: (A to C) Anteroposterior X-ray showing loss of proximal arc congruity with spilled teacup sign denoting lunate dislocation on lateral and CT scan images; (D and E) X-rays showing K-wire fixation across the reduced lunate; (F and G) Follow-up X-rays.

Courtesy: Dr Ajith Yadav.

Proximal radioulnar, distal radioulnar joints (DRUJ), and interosseous membrane (IOM) provide stability and needed freedom for the bowed radius to rotate on a straight fixed ulna. Among fractures of the forearm, the following fractures require special attention to diagnose the associated fracture-dislocations and associated nerve injuries.

Monteggia fractures: These are proximal ulna fractures with radial dislocation (posterior in adults and anterior in children) at the proximal radiocapitellar joint. Posterior interosseous nerve injury is the most common nerve injury associated with Monteggia fracture,. X-rays showing both elbow and wrist joints are mandatory to diagnose the associated fracture-dislocations. These fractures require operative management and should be splinted and referred for orthopedic consultation.

Galeazzi fractures involve fracture of the middle to distal third radius fracture and with distal radioulnar joint (DRUJ) disruption. X-rays are examined for the shortened radius on AP and dorsal or volar angulated ulna in lateral X-rays. These are the fracture which require surgical management to restore the biomechanics of the forearm.

Essex–Lopresti lesion: It is longitudinal disruption of the interosseous membrane with radial head fracture-dislocations and disruption of the DRUJ. Radial head fracture with widened DRUJ space with positive ulnar variance should raise the suspicion of additional interosseous membrane injury. They need orthopedic consultation for further management.

Wrist involving carpal bones and distal radius is common in *FOOSH injuries.* Distal radius fractures are more common in the older age groups because of osteoporosis and in young because of high-energy trauma and sporting. All the wrist injuries are examined for the possibility of DRUJ, carpal bone fractures (scaphoid), lunate and perilunate dislocations, entrapment syndromes such as carpal tunnel syndrome, and other neurovascular injuries. AP, lateral, and oblique X-ray views are necessary to study the displacement, angulation, articular congruency, and involvement of the carpal bones. Suspected fracture scaphoid, lunate and perilunate dislocations, comminuted distal both bone fractures require CT with reconstruction for the assessment and planning for the surgery. Extraarticular distal radius fracture with minimal angulation can be manipulated and splinted in emergency with the POP slab and with pain control measures. All the splinted forearm and wrist injuries need regular consultations to exclude complications such as compartment syndrome, displacement of the reduced fractures, and nerve injuries.

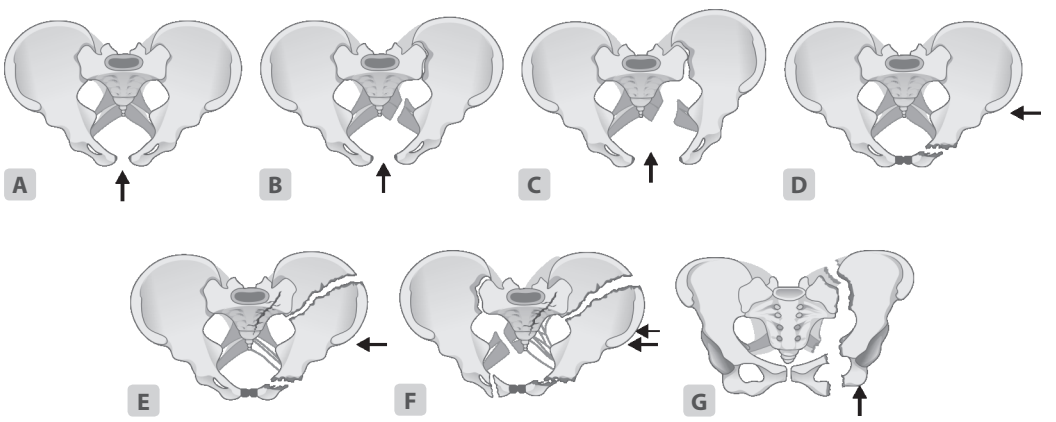
Pelvis

Planning and treatment of the pelvic trauma patient start even before the patient arrives in an emergency. An emergency team with proper arrangements should be in place. Pelvis trauma is very challenging to treat as an immense amount of trauma is needed to cause it and it carries high rates of morbidity and mortality. The pelvis is stabilized anteriorly by symphysis and posteriorly with strong ligaments such as sacrospinous, sacroiliac, sacrotuberous, and iliolumbar connecting the different parts of the pelvis and inferior osseous spine. *Pelvic trauma is classified using the Young and Burgess mechanism* of the injury (**Figs. 6A** to **G**). This is commonly used to predict distant associated injuries, resuscitation needs, and mortality rates.

Tile classification: This is based on biomechanical stability used for surgical planning. Emergency teams should be able to resuscitate, diagnose, and treat the associated injuries. Priority is given to get the hemodynamics corrected and exclude causes of bleeding from the thorax, abdomen, pelvis, and extremities. Simple AP view of the pelvis and inlet and outlet view radiographs give ample information to ascertain the degree of the injury and its effect on the stability of the pelvis. CT scan of the pelvis with reconstruction is needed for detailed study and planning of the surgery.

Stable fractures: These fractures involve only one part of the ring (pubic rami fractures), are minimally displaced (<2.5 cm of diastasis), and are avulsion fractures (ischial tuberosity) and transverse sacral fractures.

Unstable fractures: These involve the pelvic ring in two places with the involvement of the posterior ring. These result from a combination of AP, lateral, vertical, and rotational forces during the impact. Diastasis of >2.5 cm and widening of sacroiliac joint, vertical fractures of the sacrum with asymmetrical sacral foramina, and avulsion fracture of the 5th lumbar transverse process with vertical displacement suggest highly unstable injury. *Open book fractures* are stabilized with large towel sheets around the pelvis at the

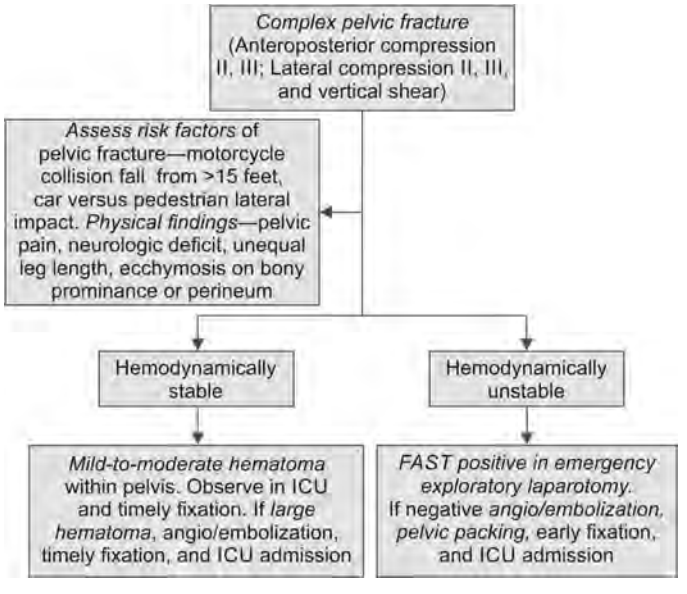


FIGS. 6A TO G: (A) Anteroposterior compression type I; (B) Anteroposterior compression type II; (C) Anteroposterior compression type III; (D) Lateral compression type I; (E) Lateral compression type II; (F) Lateral compression type III; (G) Vertical shear.

level of the greater trochanter to reduce the pelvic volume with caution in lateral compression injuries. *Open pelvic fractures and their associated injuries* are carefully examined. *Tell-tale signs* over the abdomen, flanks, and perineum are inspected for contusions to exclude degloving injuries *(Morel Lavallee syndrome).* The penis should be examined for blood at the meatus. Rectal and vaginal examination is done to rule out communicating fractures. Bilateral hips and lower extremities are checked for fractures and associated soft-tissue injuries with a detailed neurovascular examination. Hemorrhage is a devastating complication of multiple injured patients. Common pelvic sources include venous plexus, cancellous bony surfaces, arterial bleeding (internal iliac vessels), and abdominal injuries. Clinical assessment, labs, judicial usage of the available facilities, diagnostic peritoneal lavage (DPL), focused assessment with sonography in trauma (FAST), CT angiography with embolization or timely laparotomy, and pelvic packing can have detrimental effects in multiple injured patients, especially in nonresponders. Management guidelines for pelvic trauma are summarized in **Flowchart 1**.

Femur and Hip

Femur and hip fractures result from dashboard injuries in high-velocity collisions and from trivial falls in the elderly in association with osteoporosis and metastatic lesions. Acetabulum with proximal femur fractures with dislocations, ipsilateral neck of femur, and shaft of femur fractures need special attention to the neurovascular injuries, loose bodies in case of dislocations and time since injury in case of fracture neck of the femur as these influence the total outcome. All the devices such as traction and braces over the patient should be removed as these are contraindicated in pelvic fractures,


Complex pelvic fracture (Anteroposterior compression II, III; Lateral compression II, III, and vertical shear)
Assess risk factors of pelvic fracture—motorcycle collision fall from >15 feet, car versus pedestrian lateral impact. Physical findings—pelvic pain, neurologic deficit, unequal leg length, ecchymosis on bony prominance or perineum
Hemodynamically stable
Hemodynamically unstable
Mild-to-moderate hematoma within pelvis. Observe in ICU and timely fixation. If large hematoma, angio/embolization, timely fixation, and ICU admission
FAST positive in emergency exploratory laparotomy. If negative angio/embolization, pelvic packing, early fixation, and ICU admission

(FAST: focused assessment with sonography in trauma; ICU: intensive care unit)

FLOWCHART 1: Management guidelines for pelvic trauma (large pelvic hematoma means extend outside the pelvis, resuscitation should be continued in the angiography room, temporary bilateral internal iliac artery embolization is preferred).

fracture-dislocations with ligamentous injuries, and fractures involving open injuries with gross contamination. Physical examination reveals leg length discrepancies, deformities in case of fracture-dislocations. And shortened and externally rotated attitude in case of intertrochanteric and subtrochanteric fractures. Patients can present with hypotension with raised lactate levels, degloving injuries, compartment syndrome, and neurovascular injuries. Trivial falls with refusal to bear weight should raise the doubt of rami fractures or impacted neck fractures and stress fractures are to be screened with CT and MRI. Fracture neck of femur and fracture-dislocations should be reduced at the earliest in an emergency or in operation theater by an orthopedic surgeon as these are associated nerve traction injuries and AVN of a dislocated hip.

Complications such as pulmonary embolism with involvement of more than two long bones, compartment syndrome, heterotrophic ossification, and sciatic nerve injuries (fracture-dislocations) need to be checked and keep the patient informed.

Knee and Leg

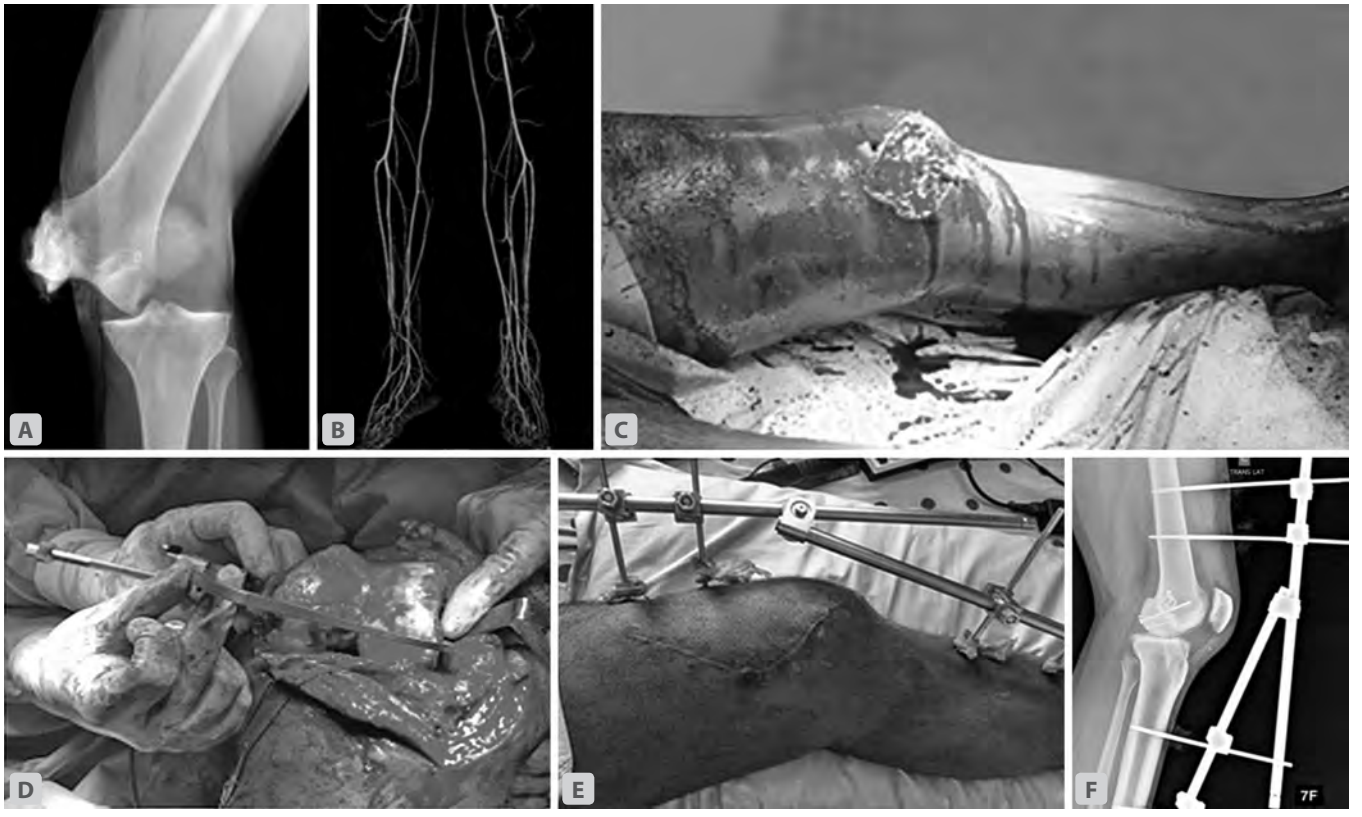
Knee injuries occur in both trivial falls (old age and morbidly obese) and high-energy collisions. They present with pain, instability from ligamentous injury, open injuries with varying degrees of contamination, and involvement of the joint. Understanding the mechanism of injury, examination, and proper diagnostics can minimize the short falls. X-rays of AP and lateral views should be screened for fractures, avulsion injuries [anterior cruciate ligament (ACL) avulsion, Segond fracture], Hoffa's fracture, proximal tibial condyle, fibular head fractures, and osteochondral fragments. *Knee dislocations*. Instability with contusions around the femoral and popliteal areas should raise the suspicion of spontaneously reduced dislocation of the knee (**Figs. 7A** to **F**). Frank dislocations are reduced at the earliest and patients are screened with ankle-brachial index, angiography, and planned for revascularization and fasciotomy procedures.

Open Fractures and Floating Knees

Comminuted open fractures should have X-rays with one joint above and one below with traction to realign the comminuted fracture pattern and help in planning. Floating knees and comminuted fractures associated with ligamentous injuries and other organ injuries are immediately braced and orthopedic, vascular, and plastic surgeons should be informed while the patient is resuscitated with proper wound care, antibiotics and optimized for surgery. Stable fractures and knees with ligamentous injury are stabilized with brace and crepe bandage and referred for orthopedic consultation for complete detailed examination and evaluation with MRI.

Ankle and Foot Injuries

Ankle injuries are regular presentations in the emergency. They range from ankle sprains to frank fracture-dislocations. The majority of the sprains result from supination and external rotation, injuring lateral anterior talofibular and calcaneofibular ligaments tear. Medial-sided injuries are rare because of the stronger deltoid ligament. Syndesmotic sprains



FIGS. 7A TO F: (A) X-ray showing medial knee dislocation. Also note the button over the lateral femoral condyle. (B) Normal lower limb arteriogram. (C and D) Intraoperative picture showing the open wound. The wound extended for fracture fixation and ligament reconstruction. Also, knee spanning external fixation is placed to secure the reduction. (E) Healed wound with ex fix in situ. (F) Post ligamentous reconstruction X-ray lateral view showing ex fix in place. ***(For color version, see plate 43)***

Courtesy: Dr Ajith Yadav.

result from injury to anterior tibiofibular, posterior tibiofibular, and inferior transverse ligaments. Physical examination of the syndesmosis reveals pain and tenderness on the squeeze test and crossed leg test with the widening of the medial space on X-rays. All ankle and foot injuries should have AP, lateral, and oblique views of the foot and also AP and lateral views of the ankle. These are screened for medial clear space, medal tibiofibular overlap, associated avulsion fractures of the 5th metatarsal base, talar avulsion fractures, and peroneal tendon avulsions. Most of the ankle sprains are treated *with RICE (rest ice compression and elevation regime)* with a stirrup brace or below-knee POP for 3–6 weeks. Clear instructions to the patient and their attendees should be given to approach an emergency in case of increased swelling, discoloration of the fingers, and pain which is increasing out of proportion.

Ankle Fractures

These are classified according to the *Denis and Weber classification* as they can predict syndesmotic injuries. Fractures involving the fibula at or above the ankle mortise are unstable and require operative management. *Pilon fractures (fracture distal tibia)* are intra-articular extending into the metaphysis and are associated with high-energy trauma with extensive soft-tissue involvement with associated fracture in the pelvis and lumbar spine. These injuries require CT scans with reconstructions and admission for early total care or damage control depending on soft-tissue status, involvement of other fractures, and physiology of the patient. All injuries around the ankle and foot are examined for swelling, soft-tissue status, and involvement of the neurovascular structures and are documented and photographed.

Foot injuries range from simple metatarsal fractures to fracture calcaneum, fracture-dislocation of the talus, and tarsometatarsal junction (*Lisfranc fracture*). Axial load and fall from height are the reasons for injuries. Associated injuries in the knee, hip, and spine are screened and treated. Focused history, understanding the mechanism of injury, detailed examination, adequate investigations, and timely consultation and referral to concerned specialists will help the emergency physician to avoid complications.

SUMMARY

With increasing motor vehicle accidents, sporting activities, and aging population musculoskeletal injury constitutes a major part of emergency departments which demand early recognition, stabilization, care, and referral to the concerned departments for definitive care. Successful optimization and treatment of the patient with musculoskeletal trauma require dedicated teamwork which starts from the site of the accident and by the team of specialists in the hospital.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Vascular Injury

Rohan Shah

INTRODUCTION

"Vascular injury" refers to injury to a blood vessel—an artery or a vein. Trauma to the vascular system can be devastating. These injuries are categorized by the type of trauma that caused them—blunt or penetrating injury. A blunt injury can occur when a blood vessel is crushed or stretched. A penetrating injury can occur when a blood vessel is punctured, torn, or severed. Either type of vascular trauma can cause the blood vessel to clot (thrombosis) and interrupt blood flow to an organ or extremity or cause bleeding which can lead to life-threatening hemorrhage. These injuries can occur in the civilian or military setting. Fortunately, in the civilian setting, it is an uncommon injury that presents to the trauma bay but penetrating vascular injuries are becoming increasingly common in the developed countries. Estimates are that penetrating injuries to the extremities account for 5–15% of traumas. However, overall vascular injuries account for 1% of all traumatic injuries to extremities. Penetrating vascular injury can be classified as extremity, junctional, or noncompressible. Patients with major vascular injuries require multiple team disciplinary physicians. Patients with these injuries may present with obvious clinical deterioration or may progress to a life-threatening condition from a stable clinical condition. Diagnosis can be obvious but at other times subtle and difficult to diagnose. The advancement of endovascular therapies and the advent of computed tomography (CT) with angiography has made progress in the management of such injuries.

ETIOLOGY AND INCIDENCES

Peripheral vascular injuries subdivide by the mechanism of injury and anatomical location.

- *Penetrating wounds*: Stabbing by knives/glass, gunshot, intravenous (IV) drug abuse. Firearm injury constitutes around 50% of penetrating injuries while 30–40% injuries are caused from sharp instruments such as knives or glass.
- *Blunt trauma (adjacent to the major artery)*: Joint displacement, bone fracture. The most common cause of blunt injury is motor vehicle accidents.
- *Invasive procedures*: Arteriography, cardiac catheterization

Arterial injuries are most common, and isolated venous injuries are least common. A venous injury is more likely to occur in combination with an arterial injury. Traumatic vascular injuries are most common in the extremities, which account for 75% of vascular injuries. Of these injuries, lower extremity injuries are slightly more common than upper extremity injuries. In the elderly patient, the preexistence of atherosclerotic disease, particularly peripheral arterial disease, is important in the assessment of the magnitude of injury and consideration for repair.

PATHOPHYSIOLOGY

The mechanism of injury is important in initial assessment. It is helpful to know the type of weapon, angle of entry, and depth of penetration in penetrating injuries but this information is often unknown. To understand the physiology involved in penetrating vascular injuries, it is important to discuss kinetic energy. As kinetic energy is directly proportional to the mass of the object and exponentially proportional to the velocity of the object, vascular injuries by high-velocity weapons are more severe. Similarly, an object that has a greater surface area has the ability to cause more severe vascular injuries but neither the velocity nor object characteristics can independently predict the amount of damage caused; it is more often a combination of both. Vascular anatomy of the great vessels and the particular branch points of the more distal vasculature are important in identifying and potentially preventing morbidity and mortality in the setting of injury. Mechanisms of penetrating vascular injury are: (1) Puncture, (2) laceration, (3) complete transection, (4) partial transection, (5) aneurysm, (6) arteriovenous fistula, and (7) dissection. When the arterial vessel is transected, vascular spasm coupled with low systemic blood pressure appears to promote clotting at the site of injury and to preserve vital organ perfusion better than is the case with ongoing uncontrolled hemorrhage. Ischemia to distal tissues → anaerobic metabolism consumes all substrate → irreversible cell disruption and death → edema → progression of damage.

CLINICAL PRESENTATION

Clinical presentation of penetrating vascular injury is classified into hard and soft signs of injury. This will allow the physician

to decide the best management plan. Signs that are classified as hard signs represent immediate intervention while signs that are classified as soft signs represent diagnostic testing to better elicit the type of injury.

Hard signs:
- External arterial bleeding
- Rapidly expanding hematoma
- Palpable thrill, audible bruit
- Obvious arterial occlusion—pulseless, pallor, paresthesia, pain, paralysis

Soft signs:
- History of arterial bleeding at the scene
- Diminished unilateral distal pulse
- Neurologic deficient
- Proximity of penetrating wound to the major artery
- Small nonpulsatile hematoma
- Abnormal flow–velocity waveform on Doppler ultrasound
- Abnormal ankle-brachial pressure index (<0.9)

DIAGNOSIS

Palpable distal pulse, even if diminished, suggests that the proximal arterial injury is limited. The reasons for diagnostic studies are to:
- Prevent unnecessary operation
- Document the presence of the surgical lesion
- Localize the surgical lesion to plan an operative approach

Arteriography: This is performed by the radiologist using intra-arterial digital subtraction angiography or CT angiography. It is also performed by the surgeon either in the emergency room (ER) or in the operating room.

Duplex scan: It uses real-time B-mode (brightness image) and pulsed-wave Doppler image (flow determination). The physical exam can be augmented by the use of a Doppler ultrasound probe, pulse oximeter, or measurement of the patient's bedside ankle-brachial index. Physical and ultrasonographic exams can be limited in the trauma bay; pulse waves may transmit through fresh thrombus, and vasospasm or vasoconstriction can make healthy vessels difficult to palpate. An ankle-brachial index >0.9 effectively rules out a significant arterial injury causing ischemia and can eliminate the need for further investigation. Oximeter readings of normal pulsatility and saturation can similarly rule out arterial injury in patients with various orthopedic injuries. Ultrasound is efficacious at diagnosing arteriovenous fistulas or pseudoaneurysms and for follow-up of interventions but is limited in the acute phase. CT angiography is a rapid diagnostic tool that can guide endovascular or open surgical intervention in the absence of significant renal dysfunction. The specificity and sensitivity of CT approach catheter-based angiography; however, smaller intimal tears and defects may be missed. Digital subtraction angiography remains the best choice for visualizing smaller vessels and is preferred for hand or foot trauma with evidence of ischemia.

MANAGEMENT

Treatment of peripheral vascular injury is evolving because of endovascular therapies. Guidelines advocate for embolization of injuries to lower extremity branch vessels, including pseudoaneurysms or arteriovenous fistulas, in hemodynamically normal patients without hard signs of vascular injury. The vast majority of stab or gunshot wounds will cause limited soft-tissue damage, muscle ischemia, and/or simple fractures that demand no or very limited wound debridement and bone fixation. The vascular injury can be treated early on without considering the other tissue damage. High-energy penetrating soft-tissue injuries, mostly seen in the military setting, cause frequently major soft-tissue damage with sometimes small and large entry and exit holes, extensive wound contamination, and soft-tissue ischemia as well as compound fractures. These injuries need, in general, early restitution of blood flow of the large damage vessels, e.g., by shunts, while time is consumed by initial wound debridement and necessary fracture stabilization.

The decision for endovascular or open intervention can be difficult and is guided by the patient's clinical status and the anatomy of the injury. When patients are unstable, an open surgery takes precedence; however, in the reasonably stable patient, data are scarce to guide decision-making. As technology changes rapidly, the traditional thinking of mandatory surgical exploration is challenged. Blunt traumatic vascular injuries are largely amenable to endovascular therapy, and some previously high-mortality, penetrating injuries such as those to the visceral vessels can now sometimes be successfully treated with covered stenting. Medical management and observation have been shown to be effective for a range of arterial and venous injuries, particularly subcentimeter intimal flaps or intramural hematomas. Thoracic aortic as well as axillo-subclavian injuries are associated with favorable endovascular outcomes and have the most robust data supporting their use. Patients presenting with penetrating injuries to the chest or severe pelvic injuries may have initial resuscitation augmented by an aortic occlusion balloon.

Initial intervention: Management of penetrating vascular injury in the ER can be classified in hemorrhage control and damage control resuscitation. Adequate vascular access should be obtained immediately.

Hemorrhage control: Direct pressure, tourniquet, or topical hemostatic agent are different modalities. Direct pressure will be the most important step for hemorrhage control. Small vascular clamps are also useful. The use of resuscitative endovascular balloon occlusion of the aorta as an adjunct effectively controls hemorrhage in patients with noncompressible hemorrhage.

Damage control resuscitation: Hemorrhage is controlled without coagulopathies. Permissive hypotension, prevention of coagulation, and balanced component therapy are three principles of damage control resuscitation. Systolic blood pressure (SBP) of 90 mm Hg is acceptable in permissive hypotension strategy with the use of minimal, if any, crystalloid and resuscitation with blood products. Severe traumas will receive a massive transfusion protocol with the use of blood, fresh frozen plasma, and platelets in a 1:1:1 ratio. Simple measures, such as rewarming, prevention of tissue hypoperfusion, and hemorrhage control, can go a long way in reducing the development of the lethal triad of hypothermia, acidosis, and coagulopathy. Administration of tranexamic acid within 3 hours of major trauma has shown reduced mortality.

Definitive management: Definitive treatment is usually surgical or endovascular. Different modalities according to the extent of injuries are available, i.e., bypass graft, ligation,

resection with end-to-end anastomosis, patch angioplasty, lateral arteriorrhaphy or venorrhaphy. Patients with external bleeding or a rapidly expanding hematoma should undergo immediate operation. Exploration of a vascular injury is best performed under general anesthesia in the operating room or, if possible, in a hybrid suite. If signs of acute extremity ischemia are present and there are no other sites of hemorrhage, intravenous heparin should be administered.

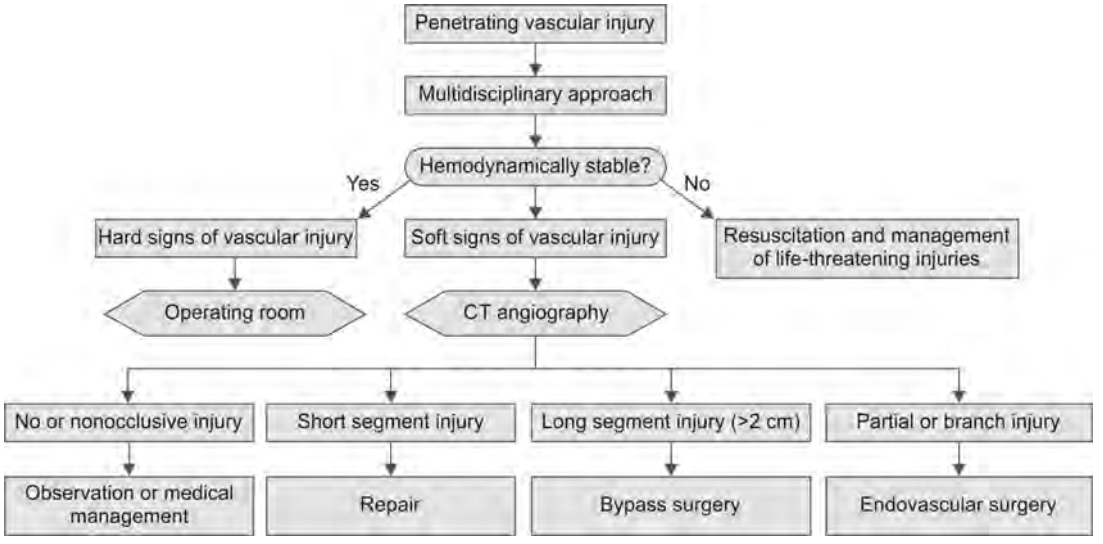
COMPLICATIONS

Isolated vascular injury may come with an amputation rate as low as 3%, but penetrating trauma, increased transport times (longer warm ischemia time), and coagulopathy may push the amputation rate up to 33% and higher. Injury to femoral vessels has the highest mortality in comparison to brachial, popliteal vessels because the proximal femoral vessel has the highest flow, no collaterals, may not easily be assessable for bleeding with tourniquet, and may come as multiple vascular injury. Most of the complications for penetrating vascular injuries are delayed and occur after initial evaluation and repair. The ER physician should also consider large vessels injury and nerve injury when evaluating severe trauma.

- Delayed thrombosis (e.g., postoperative anastomoses or shunt placement)
- Intermittent claudication
- Chronic pain (nerve compression/ischemia)
- Edema (venous compression/elevated compartment pressure)
- Aneurysm/Pseudoaneurysm formation

SUMMARY

Penetrating vascular injuries are serious and common presenting complaints in the emergency department (ED). They are associated with significant morbidity and mortality if not addressed early and cared for in the appropriate manner. The management of these patients has improved dramatically by implementing evidence-based clinical practice guidelines. Clinical practice guidelines have proven effective in decreasing mortality from injuries sustained in wartime. The approach to vascular injury in the ED is summarized in **Flowchart 1**.



FLOWCHART 1: Approach to vascular injury in the emergency department

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231 CHAPTER

Management of Orthopedic Injuries

Sandeep Jain

INTRODUCTION

Orthopedic injuries are one of the most common diseases encountered in the emergency department (ED). These are seen in the population of all ages, though modes are different. They can range from subtle soft-tissue injuries to devastating life-threatening injuries. It is important not only to save life and the limb but also to return the patient to a preinjury functional status. Minor fractures or subluxations are one of the commonly missed injuries during trauma management in the ED.

ETIOLOGY OF ORTHOPEDIC INJURIES

Injuries are caused due to transfer of external physical force to the patient's body. Common modes include road traffic injuries, railway accidents, falls, assaults, and sports-related injuries. As injuries can present in various forms, it is important to understand common terms used to describe orthopedic injuries:

- *Fracture*: Disruption in the continuity of a bone, which could be involving one cortex (unicortical) or both the cortices (bicortical).
- *Dislocation*: Disruption of a joint leading to complete loss of contact between articular surfaces.
- S*ubluxation*: Disruption of a joint leading to partial loss of contact between articular surfaces.
- *Sprain*: Stretch or a tear in the ligament of the joint caused due to excessive force.
- *Strain*: Stretch or a tear in the muscle fibers or a tendon resulting from excessive tension or repetitive use.

CLASSIFICATION OF ORTHOPEDIC INJURY

Based on Associated Soft-tissue Injury

Closed fracture: Break in continuity of bone without any breach in the overlying skin.

Open fracture: Bony disruption with a break in overlying skin. These are commonly classified by the Gustilo–Anderson classification (**Table 1**).

Based on Physiology

Common fractures: Fractures caused to healthy bones due to the application of excessive force—direct, bending, axial loading, or twisting force.

Pathologic fractures: Fractures in a diseased bone with the application of minor force, e.g., metastasis, osteoporosis.

Stress fracture: The repetitive force applied to the same area leading to fatigue and weakening of the bone.

Based on Anatomical Site

Epiphyseal fractures: Those involving the epiphyseal plate in children during growing years which can lead to deformities.

Metaphyseal fractures: Those involving areas between epiphysis and diaphysis.

Diaphyseal fractures: Those fractures that involve the shaft.

FRACTURE HEALING

Fracture healing is a complex process involving three phases:

1. *Inflammatory phase (up to 5 days)*: This phase is immediately after fracture, where the blood vessels supply bone break, leading to hematoma formation. This clot formation provides the initial matrix. There is accumulation

TABLE 1: Gustilo–Anderson classification.

Types	*Description*
Type I	Wound 1 cm, minimal contamination or muscle damage
Type II	Wound 1–10 cm, moderate soft-tissue injury
Type IIIa	Wound > 10 cm, gross contamination with extensive soft-tissue damage but adequate soft tissue for coverage
Type IIIb	Significant soft-tissue loss needing flap for coverage
Type IIIc	Associated vascular injury needing repair regardless of the degree of soft-tissue injury

of neutrophils, macrophages, and lymphocytes which removes damaged tissue. Additionally, proinflammatory mediators such as interleukins and cytokines are secreted.
2. *Reparative phase (5–28 days)*: In this phase, release of the vascular endothelial growth factor (VEGF) promotes angiogenesis within the clot. Mesenchymal stem cells recruited to the site differentiate into fibroblasts, chondroblasts, and osteoblasts which help in laying down of fibrocartilaginous matrix—soft callus which holds the two bone ends together. Subsequently, this soft callus undergoes calcification and woven bone is laid down ultimately leading to the formation of hard callus of immature bone.
3. *Remodeling or maturation phase (months to years)*: The hard callus undergoes remodeling due to a continuous process of bone formation by osteoblasts and bone resorption by osteoclasts leading to the replacement of callus into the trabecular bone.

CLINICAL PRESENTATION

Common presentations include pain, swelling, deformity, and loss of function. Most of the times, diagnosis is easy but sometimes it may be missed. The patient may present with minimal or no swelling with mild pain on putting stress over the bone. A good history-taking with a focus on the mechanism of injury helps to diagnose most fractures.

History: The patient usually gives a history of trauma leading to pain and swelling. Knowing the precise mechanism of injury helps in predicting the site of injury, for example, fall on outstretched hand leading to Colles fracture, dashboard injury leading to posterior dislocation of the hip, holding a child from hand causing pulled elbow, fall from height with feet first leading to calcaneal fracture and vertebral fractures, respiratory distress or dysphagia following blow to chest suggestive of sternoclavicular dislocation. Sometimes, the history of direct trauma may not be forthcoming, especially in diseased bones, e.g., stress fracture of the metatarsal bone, fracture neck of the femur in an osteoporotic patient causing sudden loss of movement of the hip. In the ED, a good history-taking for orthopedic injuries is as important as other medical or surgical cases. Special consideration should be given to age, hand dominance, past medical history, current medications, state of the affected bone, and occupational history.

Physical examination: A good physical examination is the cornerstone for the diagnosis of musculoskeletal injuries as it helps to direct further imaging. Adequate analgesia helps in gaining the cooperation of the patient for appropriate examination.

Inspection: Inspect for limb position, swelling or deformity, and overlying skin. An abducted and externally rotated lower limb is suggestive of fracture femur or pelvic fracture; loss of contour of shoulder indicates shoulder dislocation. Skin bruising or laceration may indicate an underlying fracture or a sprain. A pale limb compared to others may indicate neurovascular compromise. If a limb has been splinted before arrival to the ED, it should be opened to assess the condition of the overlying skin. In the presence of a stretched or tented skin, the fracture should be reduced urgently to avoid conversion to open fracture.

Palpation: Deformity or localized tenderness over a bone or a joint suggests fracture or subluxation/dislocation. Palpable crepitus is highly suggestive of an underlying fracture. Pain on weight-bearing could be a sign of occult fracture. Palpation should start in the normal area away from the suspected site of injury. The aim is to localize the point of maximal tenderness. It should be done well beyond the area of tenderness due to the possibility of referred pain. For example, pain in the shoulder could be due to sternoclavicular subluxation, fracture of the clavicle, humerus head fracture, scapula fracture, or rib fracture. It is important to palpate for distal pulsation, sensation, and movement to assess neurovascular status. In delayed presentation, compartments should be palpated to look for compartment syndrome.

Movement: It assesses both active and passive movements. If the patient is able to actively move across the complete range of motion, it effectively rules out any significant injury.

Red Flag Signs

- Cold, pale, immobile limb with absent distal pulsations
- Severe deformity
- Expanding hematoma
- Open fractures
- Fractures associated with hemodynamic instability
- Severe pain not explained by the apparent injury suggests compartment syndrome.

INVESTIGATIONS

Radiographs are commonly ordered for confirmation of diagnosis and treatment planning. X-rays should be ordered based on focused history and physical examination. A good radiograph examines the area of interest in two planes perpendicular to each other. It should include one joint above and below the fracture site. In children, images of the opposite side should be taken for comparison to differentiate fracture from the epiphyseal growth plate. It is important for the emergency physician to understand various changes in alignment of bones to be able to read the radiographs.

The fracture line can be described based on its direction relative to the long axis of the bone (**Fig. 1**):

- *Transverse*: Fracture line runs perpendicular to the bone.
- *Oblique*: Fracture line runs at an angle of 45–60°. It is due to compression and bending forces.
- *Spiral*: Fracture line spirals around the shaft. Usually, torsional forces are involved.
- *Comminuted*: Fracture has more than two fragments.
- *Intra-articular*: Fracture line extends into the articular surface of the bone.
- *Segmental*: Two or more fracture lines running through the bone, together isolating a segment of the bone.
- *Greenstick*: It is an incomplete fracture seen commonly in children. Bone is broken on one side and bent on the other side.

Displacement: It defines the alignment of fracture segments. It is described in terms of the position of the distal fracture segment relative to the proximal fragment. For example, in anterior shoulder dislocation, the head of the humerus lies anterior to the glenoid. Some types of displacement are as follows (**Fig. 2**):

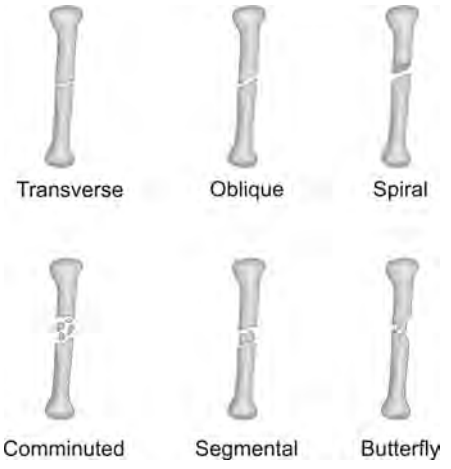


FIG. 1: Types of the fracture line.

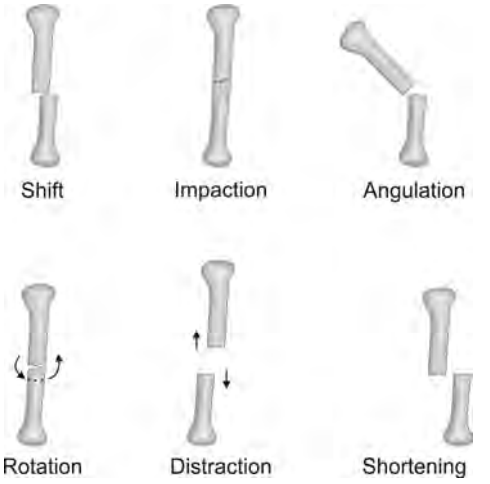


FIG. 2: Types of fracture displacement.

- *Shift*: It is caused by loss of alignment of two fractured segments.
- *Impaction*: Fracture segments are compressed together. These are usually stable fractures and are seen more commonly in cancellous bones.
- *Angulation*: Two fracture segments lie at an angle to each other.
- *Distraction*: It is caused due to excessive traction during reduction leading to the distance between two segments.
- *Rotation*: It causes rotation of the distal fragment along the longitudinal axis of the bone.
- *Shortening*: It happens when the two fractured segments overlap each other leading to reduction in the length of bone.

Some clinical decision rules such as *Ottawa Ankle Rules and Ottawa Knee Rules* are used to reduce exposure to radiographs, but they should be used in conjunction with the history and clinical examination. Ultrasonography is also being used now in ED for confirmation of fractures at the bedside. CT scans delineate fractures and dislocations better than conventional X-rays and provide three-dimensional information. MRI defines soft-tissue injuries better and is easily available.

INITIAL MANAGEMENT

Initial management of any orthopedic emergency is aimed at control of pain and reduction of swelling.

In a prehospital setting or with minor injuries, the RICE method has been proven to provide relief:

- *R*est: Reduction of movement reduces pain and prevents further bleeding.
- *I*ce: Cold compress causes local vasoconstriction and thus reduces swelling.
- *C*ompression: Wrapping the part in elastic compression bandages helps to reduce swelling.
- *E*levation: Raising the affected part at or above the heart level improves venous return and reduces swelling.

Splinting: It stabilizes the fracture segment and prevents further soft-tissue injury. This can be achieved with any locally available hard material such as wood, cardboard, or metal rod. There are commercially available splints such as malleable wire, foam-covered malleable aluminum, and foam-covered cardboard splints which can be easily used for extremity fractures. Various splints are as follows:

FIG. 3: Arm sling.

Figure-of-eight bandage: Historically, this was used for clavicle fractures but has been proven equal to arm sling in efficacy.

Arm sling: It is the most versatile and easy-to-apply splint for upper limb fractures. It supports the shoulder, arm, and forearm (**Fig. 3**).

Shoulder immobilizer: It is a Velcro appliance which keeps the arm in adduction and forearm close to chest and shoulder in internal rotation. It is used for shoulder injuries (**Fig. 4**).

Knee immobilizer: This device extends from the thigh to just above the ankle. It keeps the knee in extension and is used for fracture of the patella, tibial plateau fracture, and meniscal or ligamentous injuries of the knee (**Fig. 5**).

Pain Control

Analgesics: Nonsteroidal anti-inflammatory drugs (NSAIDs) or narcotic analgesia should be used early for pain control. It can be given intravenously or intramuscularly.

FIG. 4: Shoulder immobilizer.

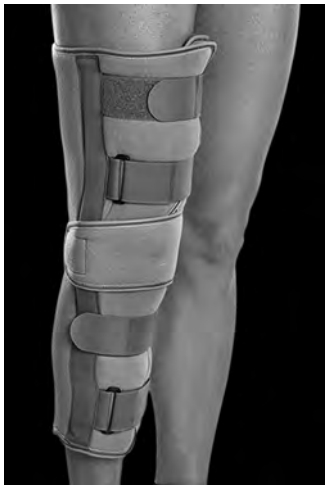


FIG. 5: Knee immobilizer.

Peripheral nerve blocks: Digital nerve blocks and wrist or ankle blocks are used for hand and feet injuries. Femoral or axillary nerve blocks can be used for proximal injuries.

Procedural sedation: Use of sedatives such as propofol, midazolam, or ketamine is needed for painless manipulation of fracture in the ED.

Fracture hematoma blocks: This is used for the reduction of fractures of distal radius or ulna. 10–20 mL of 2% Xylocaine is infiltrated into the hematoma which allows easy and painless reduction.

Fracture Reduction and Immobilization

In ED fracture, immobilization can be done with plaster of Paris or fiberglass bandage which is lightweight and sets early. Splints differ from casts as they are not circumferential and thus allow for subsequent tissue swelling without compromising intracompartmental pressure. Splints allow greater mobility but lesser stability than casts. After adequate analgesia or procedural sedation, an assistant applies longitudinal traction along the axis of the long bone. Any deformity is corrected with manual manipulation and splint applied. Assessment of neurovascular status before and after reduction and splint application should be done in every case.

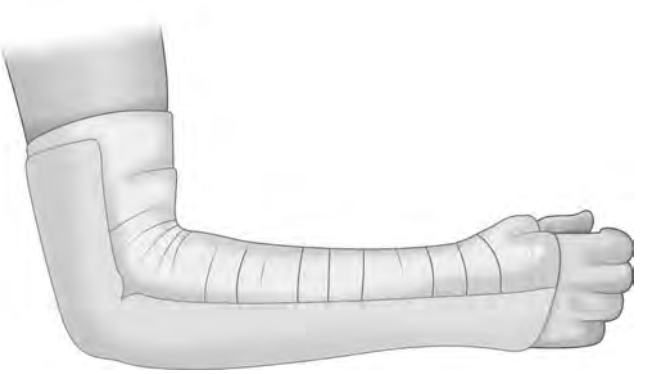


FIG. 6: Long arm gutter splint.

Splinting Technique

The length of the splint should be sufficient to cover one joint above and below. The extremity should be placed in position of function. It should have at least 8–10 layers in the upper limb and 10–12 layers in the lower limb. Measurements are preferably taken before application on the uninjured side. The fractured limb is placed in a stockinette from the proximal to the distal end. A layer of soft cotton is then applied over the limb with extra padding over bony prominences to prevent pressure sores. The splint is soaked in lukewarm water till bubbling stops. Excess water is removed by creasing it in between the index and middle fingers. The splint is then applied and a roller bandage is applied over the splint. It is left to dry till the plaster sets. Some commonly used splints in the ED are as follows:

Long arm gutter splint: It is used for forearm, elbow, and distal humerus fractures. It starts from the head of metacarpals on the ulnar side and extends to the upper arm on its lateral surface (**Fig. 6**).

Thumb spica: It runs from the proximal forearm on the dorsal aspect and involves the thumb (**Fig. 7**).

Long back slab: Starting from the upper thigh on its posterior aspect proximally to the metatarsophalangeal joint distally, it is used for fractures of knee and leg. Plaster is set in a direction where the anterior superior iliac spine, patella, and second toe are in one line with the knee flexed to about 20° (**Fig. 8**).

Thomas splint: This is a traction splint used for fractures of the femur. It is used in conjunction with skin traction. Before applying the splint, the procedure is explained to the patient and provided good analgesia. An appropriate size is selected by measuring the medial length of the uninjured lower extremity and adding 15–20 cm. The circumference of the proximal normal thigh is measured at the groin and 5 cm is added to it. The correct-sided splint has a shortened medial bar and a longer lateral bar with an elevation at its upper end. After selecting the appropriate splint, it is secured with slings along with its length stopping just short of the heel. Skin traction is then applied to the leg leaving room for movement of the foot. Longitudinal traction is then applied to the limb and Thomas splint is slid up till the perineum. The string of skin traction foam is fastened to the distal end (**Fig. 9**).

FIG. 7: Thumb spica.

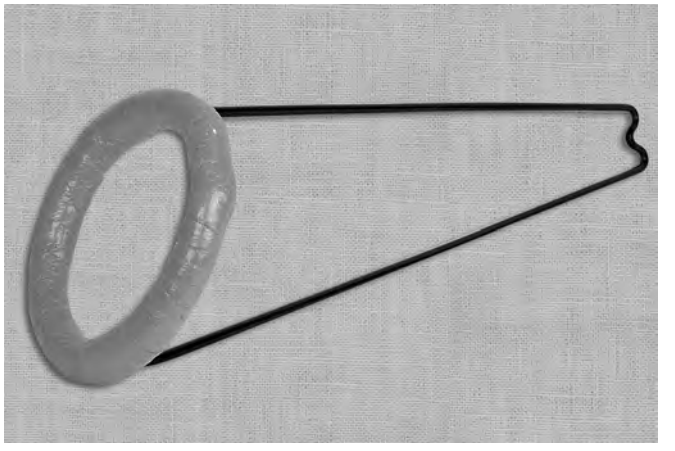


FIG. 9: Thomas splint.

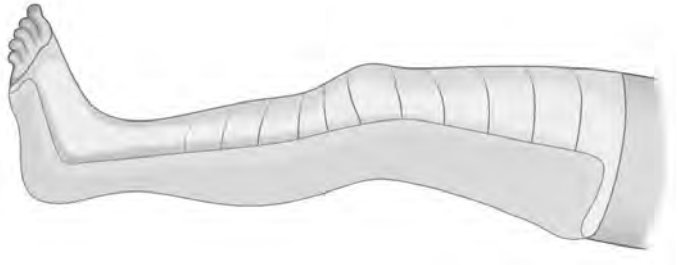
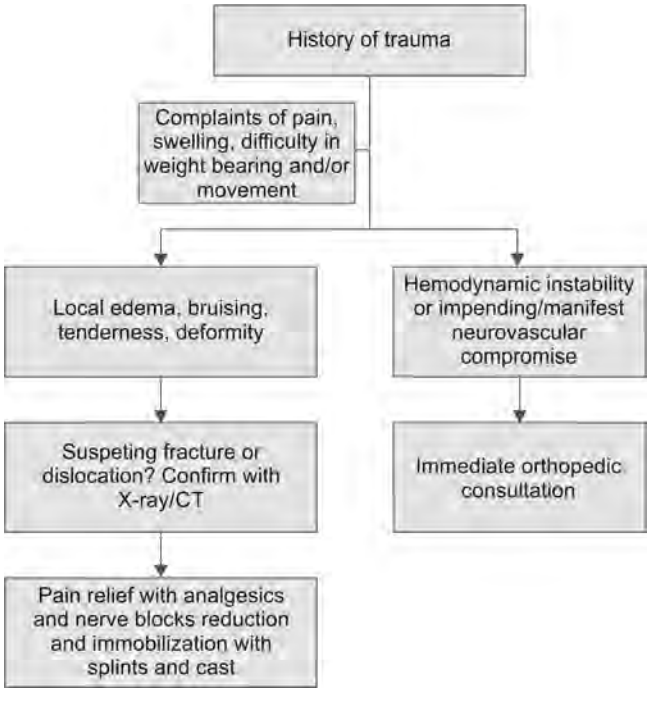


FIG. 8: Long back slab.


History of trauma
Complaints of pain, swelling, difficulty in weight bearing and/or movement
Local edema, bruising, tenderness, deformity
Hemodynamic instability or impending/manifest neurovascular compromise
Suspeting fracture or dislocation? Confirm with X-ray/CT
Immediate orthopedic consultation
Pain relief with analgesics and nerve blocks reduction and immobilization with splints and cast

FLOWCHART 1: Approach to orthopedic injury in the emergency department.

Open Fractures

Open fractures are known to be distracting injuries. All patients should be managed with the advanced trauma life support (ATLS) principle of airway, breathing, circulation, disability, exposure (ABCDE). After initial stabilization, only fracture is addressed. The most important step in management is to irrigate the wound thoroughly with saline followed by splinting. Wide-spectrum antibiotics should be administered early. The need for tetanus immunization is to be assessed in every case. There should be no attempt to digitally explore any wound in the ED. In bleeding wounds, saline-soaked gauze can be packed in the depth of the wound and direct pressure applied over it with compression dressing. The use of tourniquet is justified in the presence of uncontrolled bleeding.

Sprains

Ligament injuries are classified into first-, second-, and third-degree sprains.

First-degree sprains involve tear of only a few fibers with tenderness and minimal swelling, no functional disability, or abnormal joint movement. Rest with/without immobilization is the treatment.

Second-degree sprains involve partial tear with pain, tenderness, and functional disability with normal joint motion. This needs immobilization.

Third-degree sprain has a complete tear and also shows abnormal joint motion in addition to pain, swelling, tenderness, and functional disability. Best functional outcomes are seen with surgical repair.

SUMMARY

Orthopedic injuries are common presentations in the ED. Pain, swelling, and limitation of movement of the affected part suggest the diagnosis. Initial management includes pain relief and immobilization. Identification of red flag signs warrants immediate orthopedic consult. Diagnosis is confirmed with X-rays/CT scan or MRI. The aim of the treatment is not only to save the life and the limb but also to help the patient return back to the preinjury functional level (**Flowchart 1**).

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

ONLINE REFERENCES

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CHAPTER

Common Orthopedic Procedures

Mihir Dholakia

INTRODUCTION

Many patients who sustain blunt trauma also incur injuries to the musculoskeletal system. These injuries often appear to be dramatic but only infrequently cause immediate threat to life or limb. However, musculoskeletal injuries have the potential to distract team members from more urgent resuscitation priorities. Major musculoskeletal injuries indicate that the body sustained significant forces. For example, a patient with long-bone fractures above and below the diaphragm is at an increased risk for associated internal injuries. Unstable pelvic fractures and open femur fractures can be accompanied by brisk bleeding. Severe crush injuries can cause renal failure. Orthopedic procedures are an integral part of "D"—disability in advanced trauma life support (ATLS) and also in "C"—circulation methods such as splinting, reduction of dislocation, and immobilization in spine boards; cervical collar' application and analgesia blocks are all a part of the procedural protocol in the emergency department.

IMMOBILIZATION OF CERVICAL SPINE AND APPLICATION OF CERVICAL COLLAR

Rigid cervical collars alone do not provide adequate immobilization; they simply aid in supporting the neck and promote a lack of movement. They limit flexion by about 90%. This is used in providing immobilization along with spinal immobilization. The unique purpose of the cervical collar is to protect the cervical spine from compression. The effective cervical collar sits on the chest, posterior thoracic spine and clavicle, and trapezius muscles, where the tissue movement is at a minimum.

A rigid cervical collar:

- Should not be used alone to immobilize
- Must be properly sized for each patient
- Must not inhibit a patient's ability to open the mouth
- Should not obstruct or hinder ventilation in any way.

In some patients, pulling the skull back to the level of the backboard can produce severe hyperextension and padding is needed between the back of the head and the backboard to prevent such hyperextension (**Fig. 1A**). A child's larger sized head relative to the body size, combined with the reduced development of the posterior thoracic muscles, produces hyperflexion of the head when a child is placed on a backboard. Padding beneath the shoulders and torso will (**Figs. 1B** and **C**) prevent this hyperflexion.

Application of a cervical collar: In a two-person technique, one maintains inline immobilization of head and cervical spine and the collar is slid underneath the neck and the strap turned over to the front up to the chin. Secured with straps, the size is approximately from the angle of jaw up to the superior

FIGS. 1A TO C: (A) Placing the folded towel or padding under the head in adult aligns the airway structure. (B) When the child is supine without padding the shoulder, the neck can flex and airway obstruction can occur. (C) By placing the folded towel or padding, all airway structures are properly aligned.

border of trapezius in finger-breadths. Small, medium, large, and extra-large collars should be available. The techniques for cervical collar application are shown in **Figures 2A** to **F**.

HELMET REMOVAL

The two-person technique is used for immobilization of the cervical spine. The next step is the expansion of the helmet and opening of the visor shield. Pull the helmet backward while tilting it forward to clean the nasal bridge and apply gentle extension to clear the occipital protuberance. The method of helmet removal is shown in **Figures 3A** and **B**.

IMMOBILIZATION OF TRAUMA PATIENT AND LOG ROLL

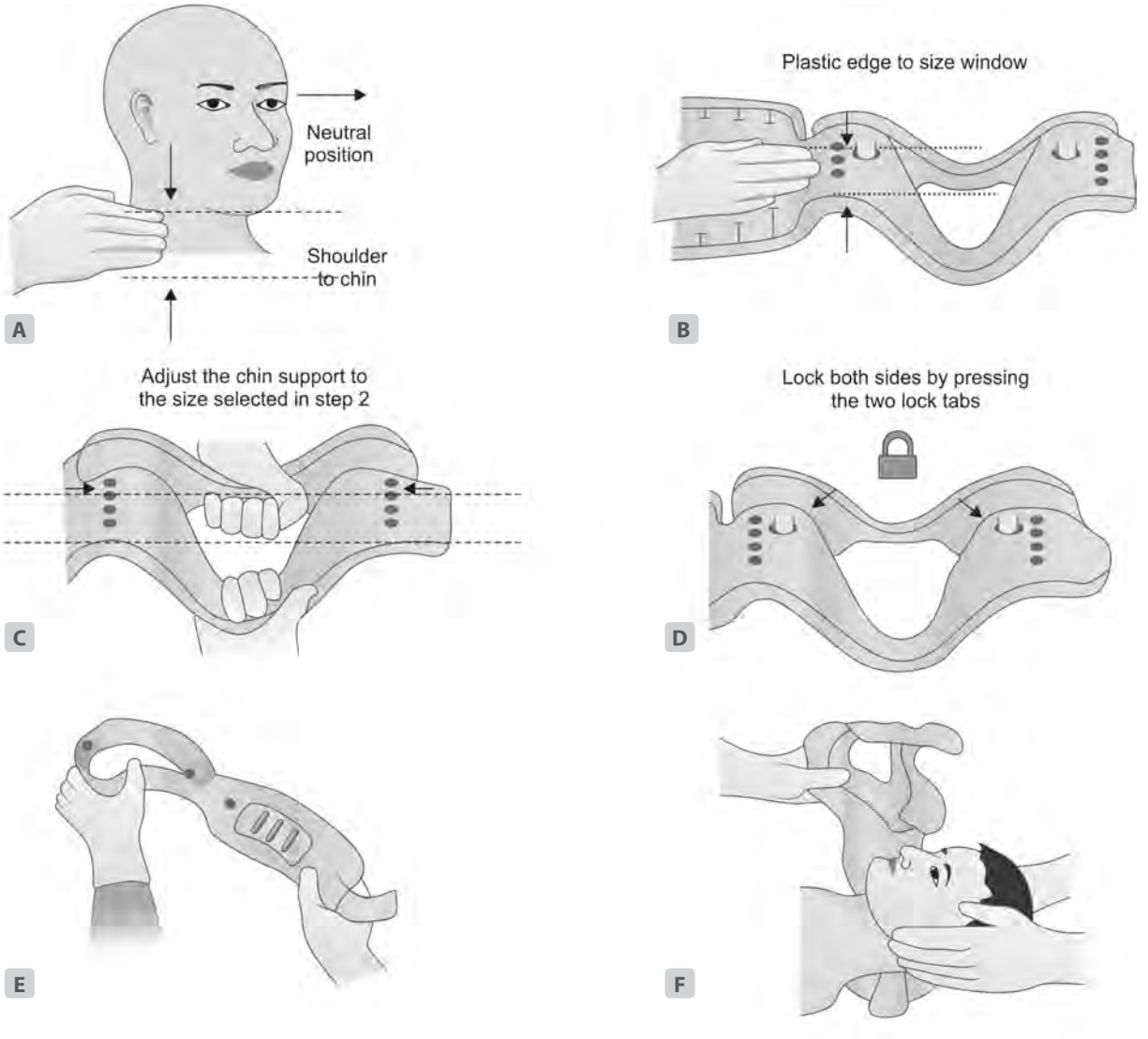
The principle is to fully immobilize a supine patient to a long backboard while maintaining the head and neck in a neutral position and minimizing the risk of additional injuries. The patient's head and neck are moved into a neutral inline position when a cervical collar is applied. The spine board is slid beneath the back by an acceptable method. Maintaining manual stabilization, the upper torso is secured to the backboard. Padding is inserted under the patient's head as needed to maintain a neutral inline position. The final step in immobilizing the patient to the board is secure the lower extremities.

Log roll: This is a four-person technique. One person maintains inline immobilization of the cervical spine—a taller person near the shoulder and a shorter person near the leg. One holds the shoulder and pelvis and the other crosses the arm over the pelvis and knees and then simultaneously at a count from the head end, turn the patient like a log. The fourth person examines the back for any steps or injury marks and clears any debris over the couch. The method for spine board immobilization and log roll is shown in **Figures 4A** and **B**.

FRACTURE MANAGEMENT: TRACTION

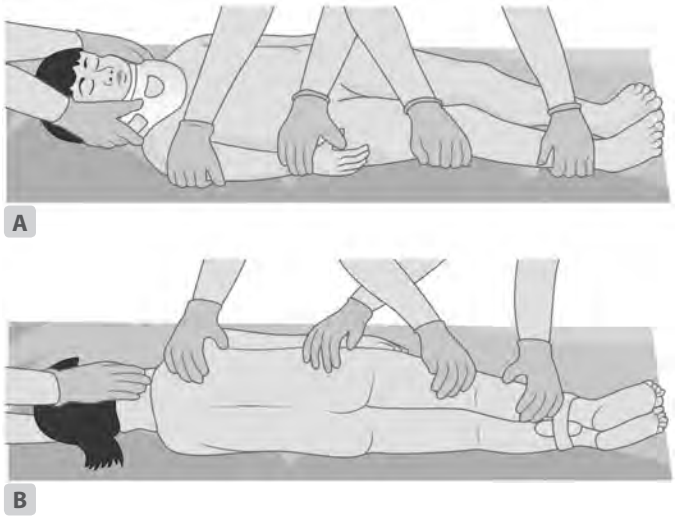
Skin Traction

Skin traction is used for elderly neck femur fractures and distal femur fractures as a temporary method of immobilization till



FIGS. 2A TO F: Techniques for cervical collar application.

FIGS. 3A AND B: Gently slip the helmet about halfway and then stop and remove the helmet and stabilize the cervical spine. Apply a cervical collar and secure the patient to a long backboard. Pad is needed to prevent neck flexion or extension.



FIGS. 4A AND B: Log-roll technique.

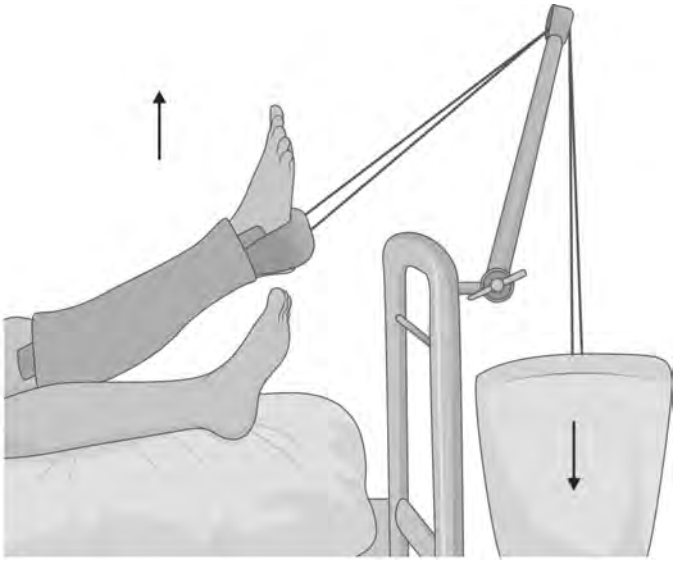


FIG. 5: Skin traction.

a definitive method such as fixation is done (**Fig. 5**). Adhesive or nonadhesive skin traction is used for reduction in pain with weights up to 2–3 kg of mild traction. Always check the distal neurovascular status after application of traction. *Disadvantages* include that it cannot give more traction, can lead to maceration of the skin, not a very effective method of traction, and can lead to neuropraxia with tight bandages.

Skeletal Traction

Skeletal traction is used for effective traction for a longer period of time, through a Steinmann pin or Dirham (threaded) pin (**Fig. 6**). With this method, more weights (up to 7–10 kg) can be attached if the bone quality is good. In osteoporotic patients, the Dirham pin is used to engage the thread in bone. *Main disadvantages* are that this is an invasive method through the bone, can lead to bone infection and superficial skin infection, and can get loose in very weak bones. *Types of skeletal traction* are described depending on the area it is applied, e.g., skull traction, distal humerus traction, proximal hip screw traction, distal femur traction, proximal tibia traction, distal tibial skeletal traction, and calcaneal pin traction.

Materials and equipment required for skeletal traction are sterile tray and drape (including T-handle/hammer), sterile gloves of proper size, 1% or 2% plain lignocaine, power drill, povidone–iodine solution, traction stirrup for leg, strings to hang weights, and blunt plugs to cover the sharp ends of the pin.

Principles of skeletal traction: Skeletal traction is used prior to definitive surgical treatment to improve pain and prevent shortening from soft-tissue contraction. It is inserted from the side that has neurovascular structures at most risk (e.g., in distal tibia—medial to lateral; proximal tibia—lateral to medial; calcaneal—medial to lateral). Apply local anesthetic up to the periosteum to prevent pain while insertion. Always check the pulse and distal neural status after pin insertion and application of traction.

Distal Tibial Pin

Place the patient in the supine position and place a bolster under the knee for flexion at 60–90°. Palpate the adductor

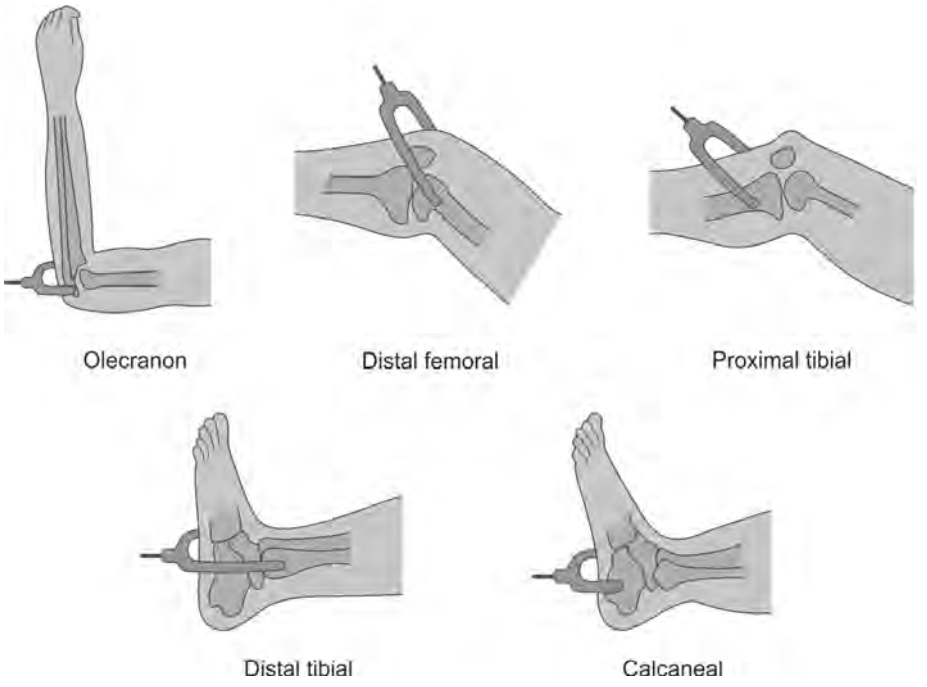


FIG. 6: Site of skeletal traction.

FIG. 7: Skull traction.

tubercle onto the anterior one third of the femur. Infiltrate the skin with anesthetics up to the periosteum. The pin is inserted bi-cortically from the medial to the lateral side.

Proximal Tibial Pin

Place the patient in the supine position. Rotate the knee into neutral or slight internal rotation. Infiltrate the skin and periosteum with an anesthetic agent, 1.5 cm below and posterior to the tibial tuberosity which is the site of insertion, from lateral-to-medial to avoid injury to the common peroneal nerve.

Skull Traction

It is used to apply a traction force to the skull to enable the reduction of dislocated facets. It is used in cervical spine injury (**Fig. 7**) and as a preoperative method for surgical stabilization of the cervical spine. *Cervical traction*: Cervical tongs are indicated in serious cervical injuries, conservative management of cervical fracture, and dislocation. Common complications are bleeding, sore on the skull, sepsis, and worsening neurological status. Cervical tongs may be contraindicated in children, local sepsis, and skull fracture.

FRACTURE MANAGEMENT: SPLINTING AND CASTING

Acute trauma to bone leads to fracture. Acute pain and deformity prompt the patient to visit the emergency department. Pain management, reduction of the fracture, and immobilization are the key elements in the management. In the majority of cases, a plain X-ray is sufficient but sometimes computed tomography (CT)/magnetic resonance imaging (MRI) is required. Reduction of fracture and splinting are recommended to reduce pain and blood loss and to prevent injury to the surrounding structure. Reduction of fracture is helpful in re-establishing anatomic alignment and promote fracture healing. Local hematoma works as a medium for callus formation, which then bridges together the two ends of the fractured bone. Common fractures and their splinting procedures are given in **Table 1**. Padding in a cast or splint is a balance between protecting the soft tissues and maintaining immobilization. Underpadding will result in skin breakdown or frank ulceration. Overpadding may lead to a loosen cast or splint and poor support.

Key features: Proximal and distal extents should have a cuff of soft roll of three to four layers with a minimum of two layers of padding spanning the two extremes. Bony prominences require attention and adequate padding to avoid crumping of padding and compromising soft tissues and neurovascular structures. Do not bend the joint once the material has been applied. Never use water above room temperature when working with fiberglass splints or casts, as heating may cause thermal injury. Delay means unusable and half-hardened plaster. Plaster slabs should be 8 layers thick for the upper extremity and 10 layers thick for the lower extremity. If an assistant is helping, hold the injured extremity underneath the stockinette and padding and never use fingers to stabilize the limb; always use the palm.

TABLE 1: Common orthopedic injury and splinting procedure in the emergency department.

Injury	*Orthopedic procedure/spilt*
Distal phalanx fracture of the hand	Finger protector splint
Boxer's fracture	Ulnar gutter splint
Metacarpal fracture	Radial or ulnar gutter splint
Scaphoid fracture	Thumb spica splint
Carpal fracture	Dorsal splint of the forearm
Radius and ulna fracture	Sugar tong splint
Elbow dislocation	Posterior long arm (elbow) splint
Supracondylar fracture of the humerus	Posterior long arm (elbow) splint
Proximal humerus fracture	Coaptation splint, sling, and swathe
Shoulder dislocation	Shoulder immobilizer or sling and swathe
Metatarsal fracture	Posterior short leg (posterior ankle) splint
Ankle sprain	Posterior short leg (posterior ankle) splint
Ankle dislocation	Trilaminar ankle splint
Distal tibia/fibula fracture	Trilaminar ankle splint
Knee dislocation	Knee immobilizer or a knee splint
Patellar dislocation	Knee immobilizer or a knee splint

Emergency physician should be aware of the complications of the splinting and casting as described below:

- *Pressure sores*: Avoid by providing sufficient padding over bony prominences and areas of stress.
- *Inadequate immobilization*: Overpadding allows for more mobility.
- *Joint stiffness of adjacent joints*: Avoid by immobilizing only the necessary joints and splinting the affected joint in a functional position.
- *Compartment syndrome*: Avoid by not wrapping the extremity too tightly with the elastic bandage as well as performing a postsplinting functional and neurovascular assessment.

TYPES OF SPLINTS

Crammer Wire/Malleable Splints

Crammer wire is made up of malleable aluminum wires attached to a strong but flexible aluminum rod. The splint can bend easily at any angle (**Fig. 8**). The main purpose is to keep the upper or lower limb in the desired position and preoperative management of the patient for immobilization. Available in various sizes ranging from the width of 2″, 4″, 5″, and 6″ and length of 12″, 18″, and 24″, malleable splints are temporary methods for upper and lower limb immobilization. They are reusable, waterproof, and lightweight. They are made up of malleable aluminum with foam and padding, fastens in place with tape or strap, and can be cut by household scissors (**Fig. 9**).

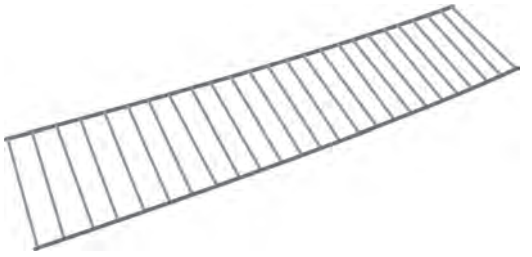


FIG. 8: Crammer wire.

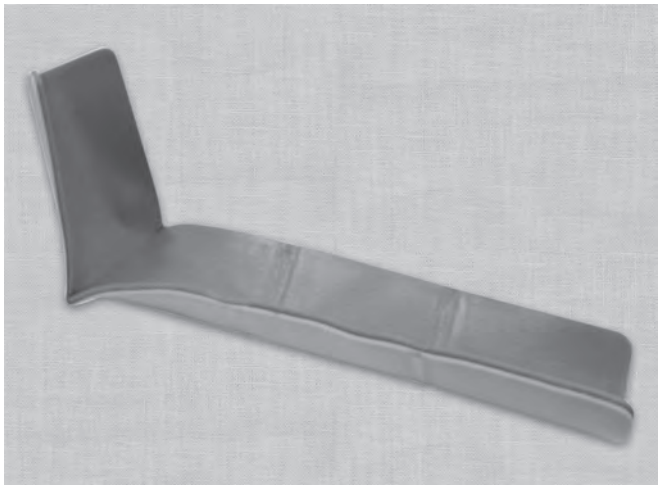


FIG. 9: Malleable splint.

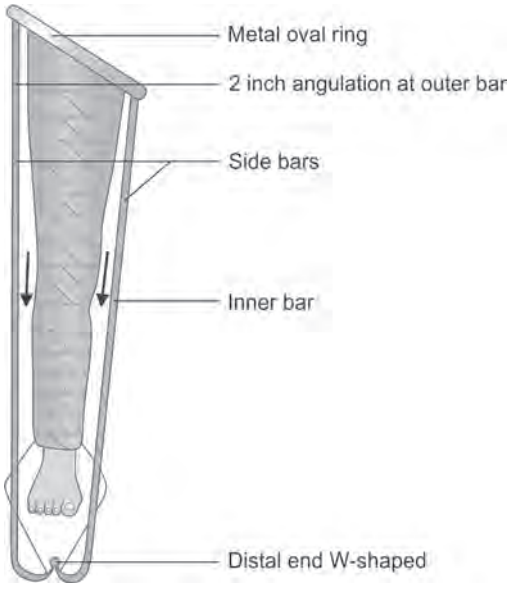


FIG. 10: Thomas splint.

Thomas Splint

It was devised by Hugh Owen Thomas. It was initially used for tuberculosis of knee, but now commonly used for immobilization of hip and thigh injuries (**Fig. 10**). A modified Thomas splint adapted the original splint to include a traction screw and footplate and limb support. It is used for subtrochanteric fractures and shaft femur fractures. It is easy to use and apply whilst maintaining maximum patient comfort.

It reduces morbidity in 80% of cases. There is a ring at the proximal end of the groin (45° placed angle), which goes about 6 inches beyond the footplate. It can be used with traction and is different for left and right sides. Look for neurovascular deficit once traction is given after the application of splint. It is helpful in transporting the patient.

Inflatable Splints

These are a good first-aid and temporary measure for immobilization of fractures which surround the extremity including the digits. Few disadvantages are involved such as risk of occlusion of blood vessels which becomes greater in the extremity in which blood supply is already compromised. Unwanted high pressure may lead to necrosis of digits. It is a plastic piece of first aid equipment that is premade in the shape of a limb (**Fig. 11**).

Coaptation Splint

Used over the shoulder, this is a splint to immobilize the shoulder and humerus (**Figs. 12A** and **B**). This splint is most commonly used for mid-shaft humerus fractures, which have a tendency to fall into varus angulation. By incorporating a valgus bump at the level of the medial elbow, angulation can be avoided.

Essential materials: Materials used are 6″ stockinette, three rolls of 6″ soft roll, three rolls of 6″ plaster; three 6″ compressive bandages, and 2″ tape, It is a large sling. *Steps*: Measure the length of the plaster slab from the axilla of the affected arm, distal around elbow flexed to 90°, then up the lateral arm, and then over the top of the shoulder to the level of the middle one third clavicle. Create a cast eight layers thick. Place soft padding layer over the skin side and over the backside of the cast. Cut one stockinette down the middle, approximately 24″, long enough to pull the remaining stockinette up to the axilla. Wet the slab and place it on the padding of the extremity. Wrap the remaining slab down around the elbow flexed to 90°. Starting at the elbow, wrap the splint using a 6″ compressive bandage, moving proximally. Secure the compressive bandage with 2″ tape. Once dried, place the arm in a large sling to keep the elbow flexed to 90°. The stockinette may be left tied about the neck or cut off for patient comfort.

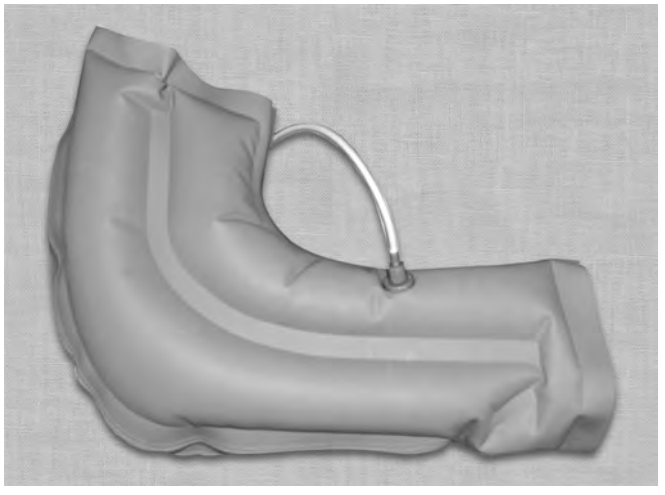


FIG. 11: Inflatable splint.

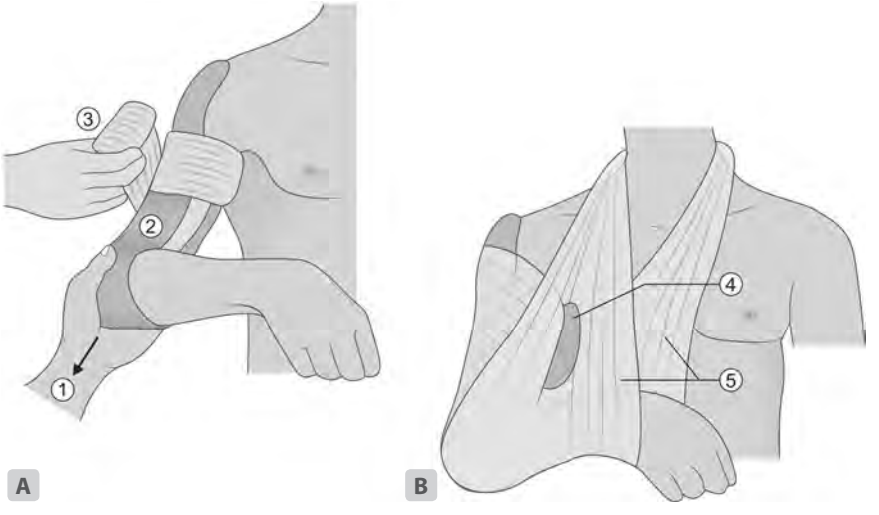
UPPER EXTREMITIES IMMOBILIZATION

Long-arm Splint and Long-arm Cast

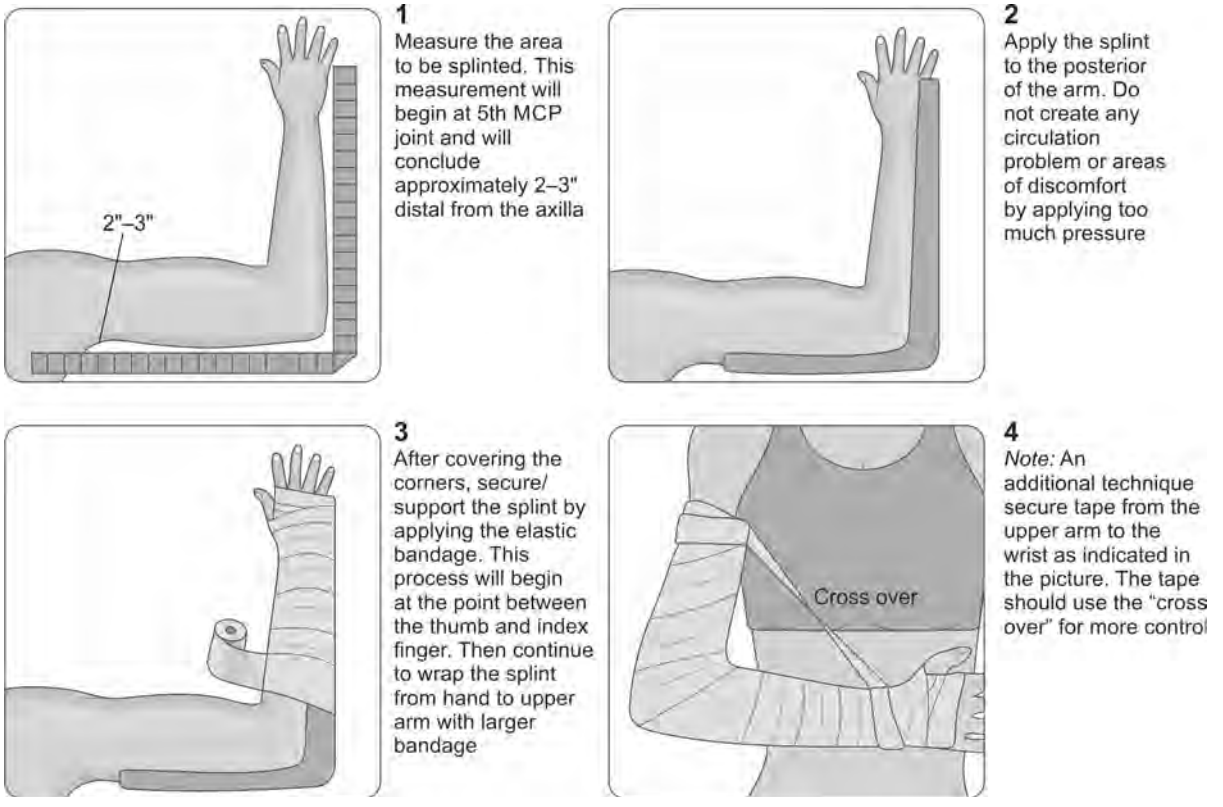
These are used to immobilize distal humerus and elbow and upper forearm (**Fig. 13**).

Materials: Materials used are three rolls of 4″ soft roll, three rolls of 4″ plaster, one roll of 4″ and 6″ compressive bandage, 2″ tape, and a sling.

Steps: Measure plaster slab from the wrist to the axilla with the elbow at the desired degree of flexion. Apply soft roll from wrist proximally to axilla. Place three to four layers of extra padding over the posterior elbow. Wet plaster and put it over the medial or posterior aspect of the elbow from the wrist to the mid-forearm to just above the mid-humerus (at the deltoid insertion). *Long-arm cast:* It has similar steps to long-arm splint except that it has to stay clear of the thenar eminence and metacarpophalangeal (MCP) joints to allow full hand range of motion (ROM). Extend the cast from the wrist to three finger-breadths distal to the axilla using 4″ fiberglass.



FIGS. 12A AND B: Coaptation splint.


1
Measure the area to be splinted. This measurement will begin at 5th MCP joint and will conclude approximately 2–3" distal from the axilla
2"–3"
2
Apply the splint to the posterior of the arm. Do not create any circulation problem or areas of discomfort by applying too much pressure
3
After covering the corners, secure/ support the splint by applying the elastic bandage. This process will begin at the point between the thumb and index finger. Then continue to wrap the splint from hand to upper arm with larger bandage
4
Note: An additional technique secure tape from the upper arm to the wrist as indicated in the picture. The tape should use the "cross over" for more control
Cross over

(MCP: metacarpophalangeal)

FIG. 13: Long-arm splint.

Advance 50% with each wrap. Ensure no further flexion of the elbow during casting due to the risk of compression of neurovascular structures by excess material. Cut thumbhole in distal stockinette and pull back over thumb and hand to create padded cuff at the mid-palmer crease. Fold proximal stockinette over to create padded cuff over the proximal upper arm. Use fiberglass to apply the final cast layer. Stay 1 cm from the edge of the cuff to protect soft tissues. For any edema or compartment syndrome, the cast should be bivalve using a cast saw.

Sugar Tong Splints

Along-forearm splints is used to immobilize the elbow and wrist. The slab is cut for thenar eminence and stops at the mid-palmar crease. It is used for immobilizing Colles fracture. The reduction of a wrist is held by a long, curved mold applied to the splint, maintaining radial height and restoring volar tilt.

Ulnar Gutter Splint

A forearm splint is used to immobilize the wrist and fourth/fifth digits.

Materials: Materials used are one 3″ soft roll, one 4″ soft roll, two rolls of 4″ plaster, one roll of compressive bandage, and 2″ tape. *Method*: Measure the length of plaster from the distal tips of fourth/fifth fingers along the medial aspect of the forearm to two finger-breadths distal of the level of antecubital fossa. Wet the plaster and lay along the length of the forearm, placing a 2″ distal slab over the volar and dorsal fourth/fifth digits. Stay medial, to keep from impinging on the third digit. Flex fourth/fifth digits to 90° at the MCP joint, adjusting plaster so that it does not wrinkle on the volar aspect. The volar slab will now be longer than the flexed digit and can be trimmed back with shears. Wrap the splint from the distal to the proximal with 3″ compressive dressing (**Fig. 14**).

Short-arm Cast

It is a durable immobilization of the forearm and wrist (**Fig. 15**). The materials needed are forearm length 4″ stockinette, one soft roll of 3″, and one roll of 3″ fiberglass. *Method*: Roll 4″ stockinette onto the affected arm from the level of the proximal interphalangeal (PIP) joints to several inches above the elbow. Roll on the soft roll from the mid-palmer space crease to two finger-breadths distal to the antecubital fossa. Wet 3″ fiberglass and wrap once around the wrist and move distally, up to the mid-palmer crease. When passing through the first webspace, use shear to cut transversely through 90% of material to avoid impingement in webspace. Stay clear of the thenar eminence and MCP joints to allow full hand ROM.

Thumb Spica Cast

It immobilizes the first MCP and wrist joints (**Fig. 16**). The materials used are a forearm length of 6″ of one stockinette, 4″ of one stockinette, one roll of 3″ soft roll, two rolls of 2″ fiberglass, and one roll of 3″ fiberglass. *Method*: Roll a 4″ stockinette onto the affected arm from the level of PIP joints to several inches above the elbow. Cut a longitudinal slit halfway along 1″ stockinette and pull it over the thumb so that the slit is oriented toward the first web space, causing the material to

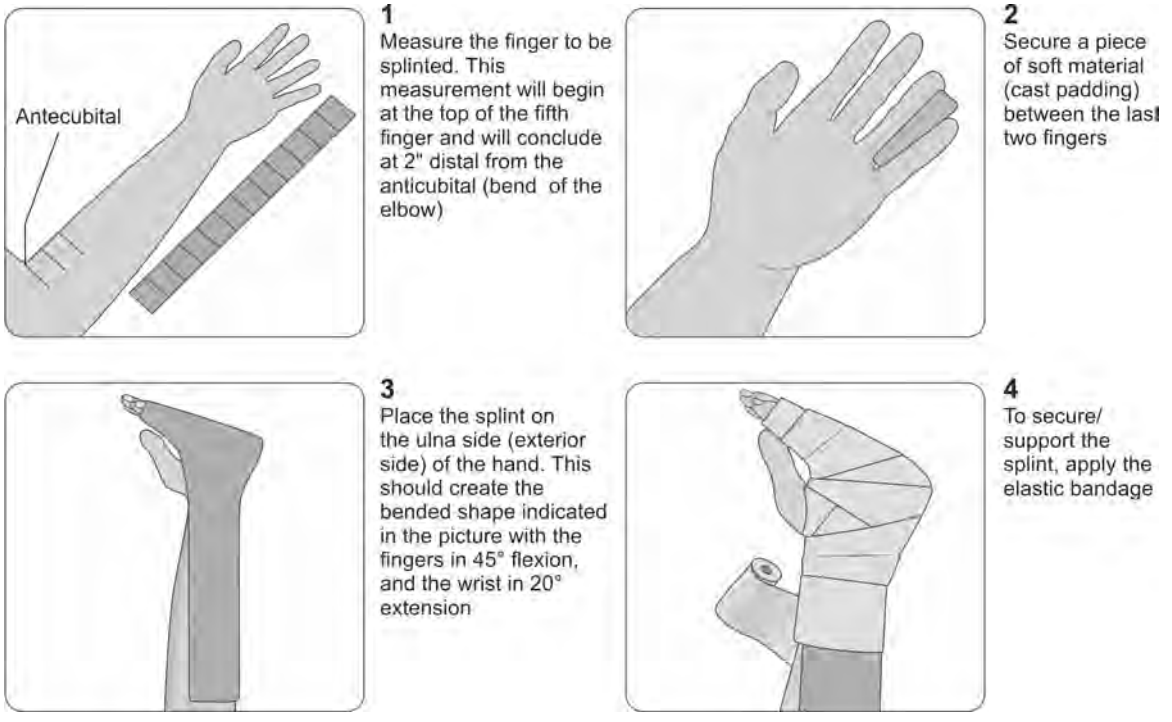

Antecubital
1
Measure the finger to be splinted. This measurement will begin at the top of the fifth finger and will conclude at 2" distal from the anticubital (bend of the elbow)
2
Secure a piece of soft material (cast padding) between the last two fingers
3
Place the splint on the ulna side (exterior side) of the hand. This should create the bended shape indicated in the picture with the fingers in 45° flexion, and the wrist in 20° extension
4
To secure/ support the splint, apply the elastic bandage

FIG. 14: Ulnar gutter splint.

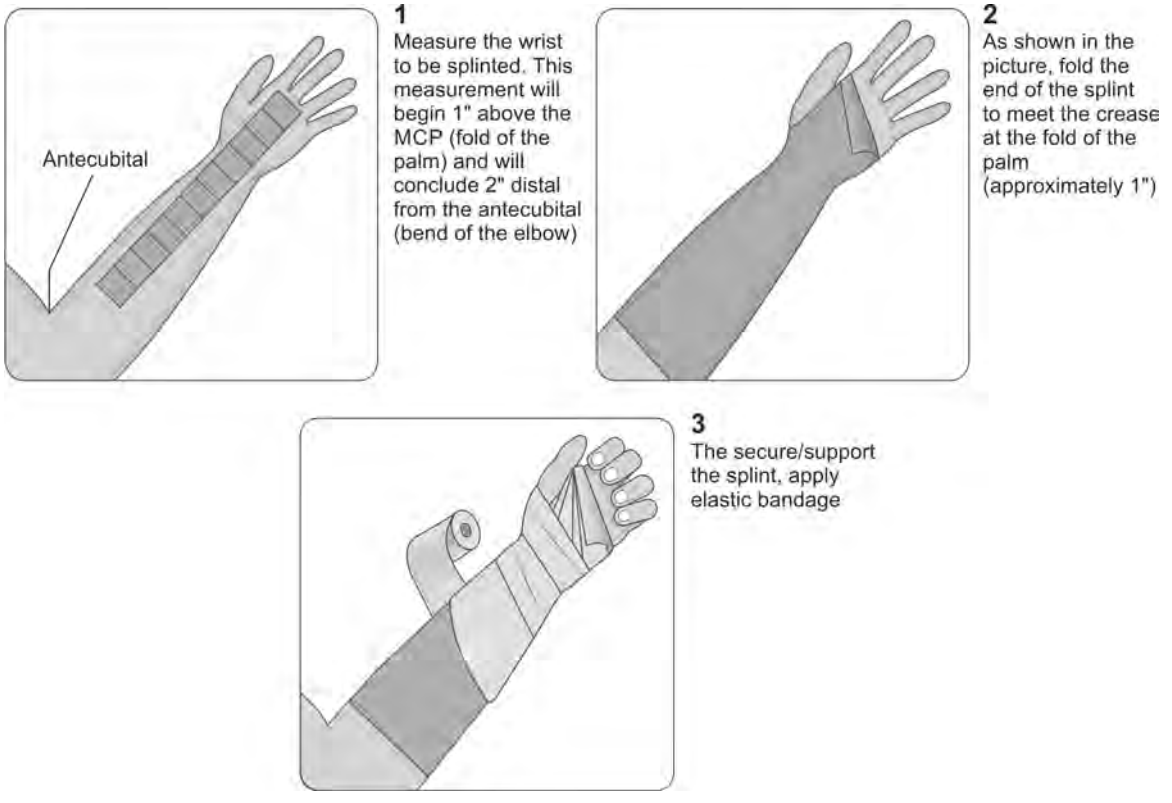

Antecubital
1
Measure the wrist to be splinted. This measurement will begin 1" above the MCP (fold of the palm) and will conclude 2" distal from the antecubital (bend of the elbow)
2
As shown in the picture, fold the end of the splint to meet the crease at the fold of the palm (approximately 1")
3
The secure/support the splint, apply elastic bandage

FIG. 15: Short-arm splint.

flare over the lateral base of the thumb. Then roll on, on the soft roll from the mid-palmer crease to two finger-breadths distal to antecubital fossa. Extend up the thumb to the level of the nail plate. Wrap around the wrist and move distally up to the mid-palmer crease. When passing through the webspace, ensure that impingement is avoided in webspace. To achieve the desired positioning, give the patient a wrapped roll of fiberglass or plaster bandage to gently squeeze, putting the thumb in "soda can position" (abduction, extension, and pronation).

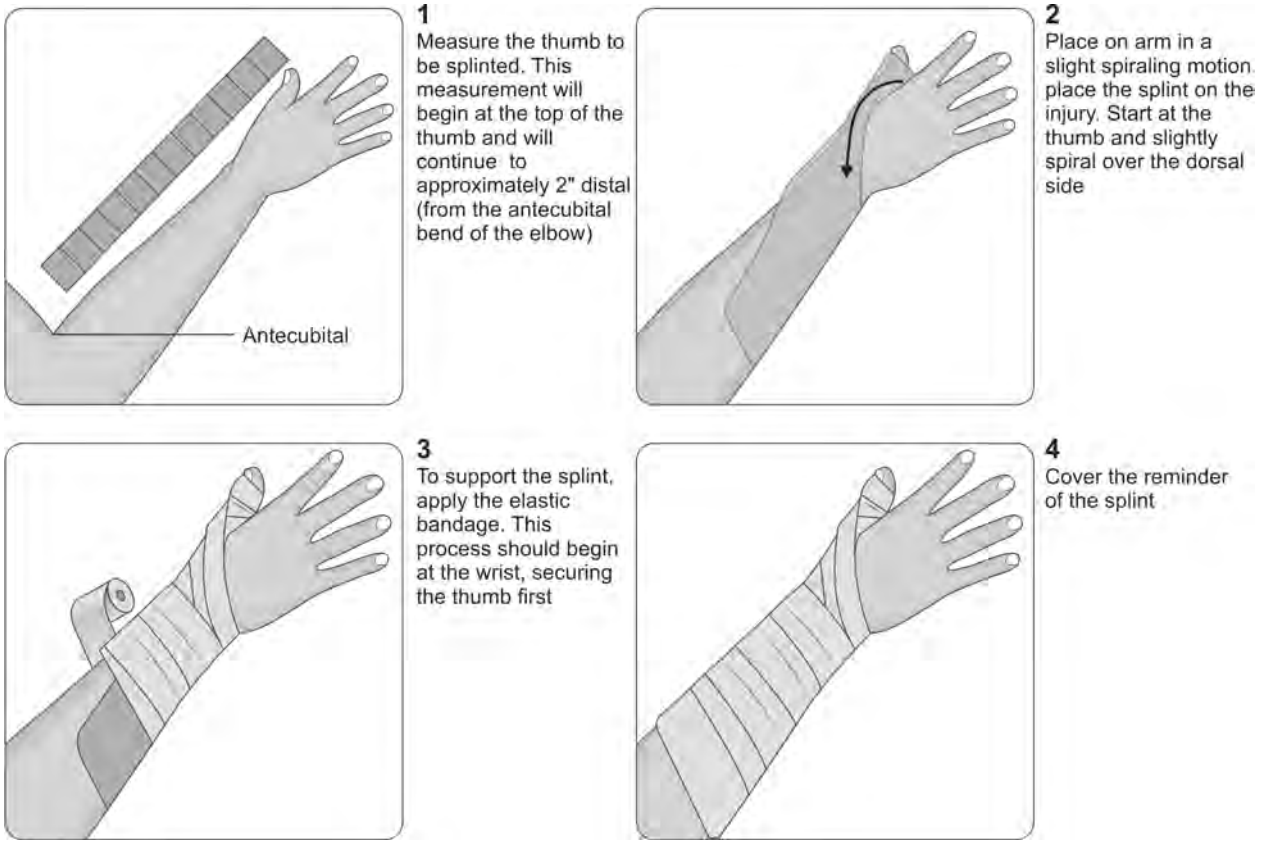

1
Measure the thumb to be splinted. This measurement will begin at the top of the thumb and will continue to approximately 2" distal (from the antecubital bend of the elbow)
Antecubital
2
Place on arm in a slight spiraling motion place the splint on the injury. Start at the thumb and slightly spiral over the dorsal side
3
To support the splint, apply the elastic bandage. This process should begin at the wrist, securing the thumb first
4
Cover the reminder of the splint

FIG. 16: Thumb spica splint.

Metacarpal Mitt Splint

It is a functional hand splint for metacarpal fractures. Measure plaster slab from the base of the thumb, running over the dorsum of the hand, around the ulnar aspect, and back along the volar surface to the base of the thumb.

LOWER EXTREMITIES IMMOBILIZATION

Long-leg Splinting

It is a long, well-padded splint for immobilization of both the knee and the ankle (**Fig. 17**). Measure a 6″ long plaster slab from two to three finger-breadths distal to buttock crease, along the posterior leg with the knee flexed 10–15° to toes. Measure two long 4″ plaster slabs from the proximal thigh to the plaster heel. Have an assistant hold foot elevated with the ankle in the neutral position and knee flexed to 10–15°. Create a plantar footpad extending from the toes to the above ankle using five layers of 6″ soft roll. Extend the splint as approximal as possible without impingement on the inner groin or buttock to maximize immobilization.

Long-leg Cast

Its principles are similar to those of long-leg splint. It is used for temporary immobilization. Extend the cast as proximal as possible without impinging on the inner groin or buttock to maximize immobilization. The knee should be flexed 10–15° to allow the leg to swing through and to take tension off gastrocnemius for fracture reduction.

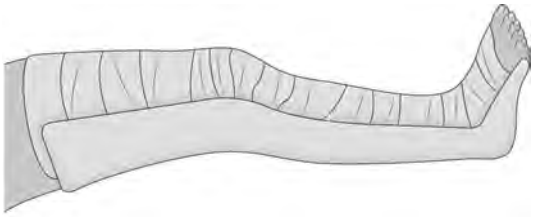


FIG. 17: Long-leg splinting.

Robert Jones Bulky Dressing

It implies relative knee immobilization using a soft roll. It can be used for any joint though. Wrap knee with soft roll beginning over the proximal tibia and extending to the distal femur. Continue wrapping back and forth over the knee until dressing is five to six layers thick. The dressing may be over wrapped with a compression bandage secured with tape or used in conjunction with a knee immobilizer.

Short-leg Cast

Its principles are similar to a short-leg splint (**Fig. 18**). Wrap foot and ankle, starting distal to the metatarsophalangeal (MTP) joint, and extend proximally using a soft roll to the level of the tibial tubercle. In addition to reduction mold, a triangular anterior tibial mold and midfoot arch mold should be considered for a well-fitting cast.

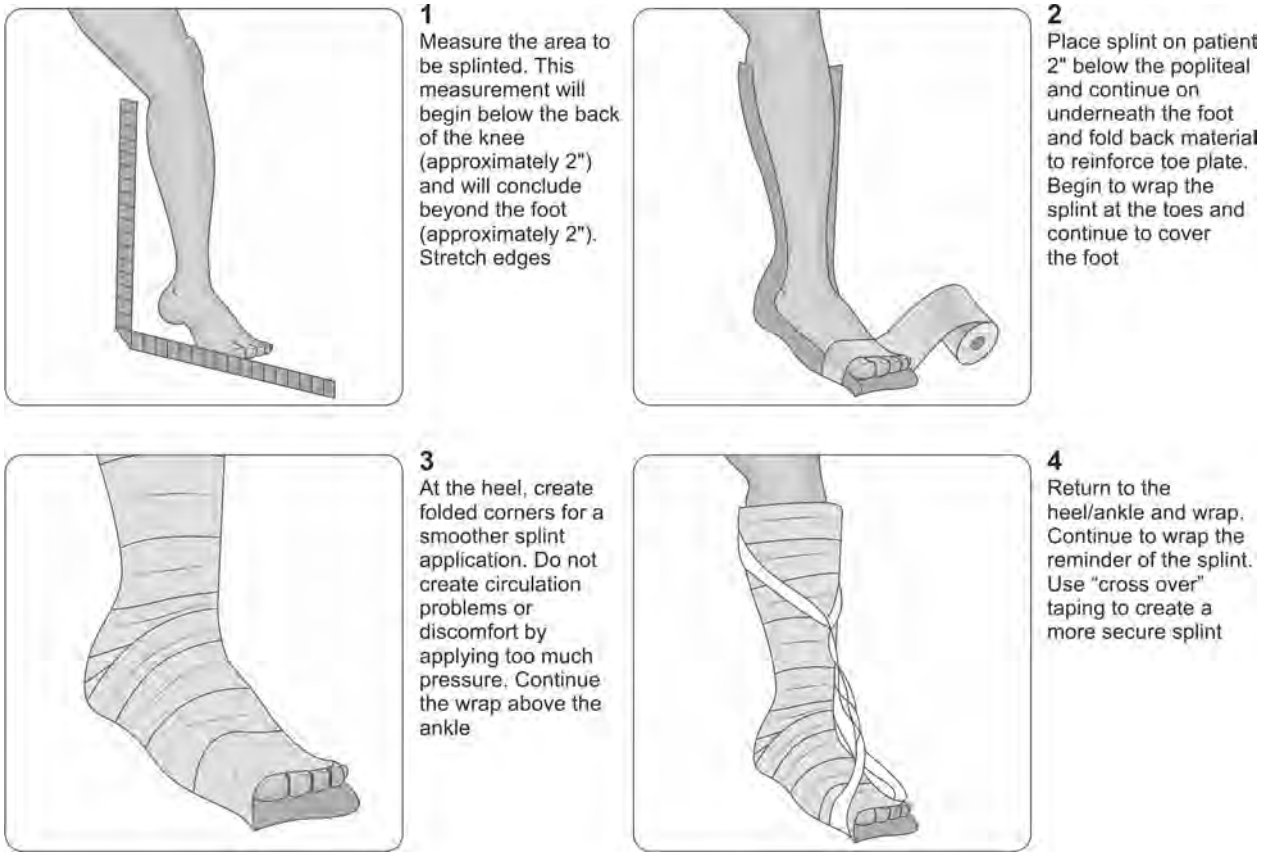

1
Measure the area to be splinted. This measurement will begin below the back of the knee (approximately 2") and will conclude beyond the foot (approximately 2"). Stretch edges
2
Place splint on patient 2" below the popliteal and continue on underneath the foot and fold back material to reinforce toe plate. Begin to wrap the splint at the toes and continue to cover the foot
3
At the heel, create folded corners for a smoother splint application. Do not create circulation problems or discomfort by applying too much pressure. Continue the wrap above the ankle
4
Return to the heel/ankle and wrap. Continue to wrap the reminder of the splint. Use "cross over" taping to create a more secure splint

FIG. 18: Short-leg splint (posterior ankle splint).

JOINTS DISLOCATION: REDUCTION TECHNIQUES

Shoulder Dislocation

Anterior dislocation: It is the most common form of shoulder dislocation. It is possible to reduce the dislocation with the help of analgesics, intra-articular block or sedation. Lay the patient supine with the affected arm adducted to the side with the elbow extended. Stand on the affected side and grip hand, pilling axial traction and making small, short vertical oscillations, as though shaking his/her hand. Gradually, abduct the arm with continued oscillations at 90°, externally rotate the shoulder, and continue abduction and oscillations. The reduction should occur by 120° of abduction. *Traction-countertraction*: Place a sheet around the patient's torso, into the affected axilla. Lay the patient supine and give a sheet to the assistant or tie it to the far bed rail. Abduct the affected arm 45° and pull axial and inferior traction. Continue attempts of gentle external rotations, and lateral traction with maintained axial traction can aid the humeral head in clearing the glenoid (**Fig. 19**).

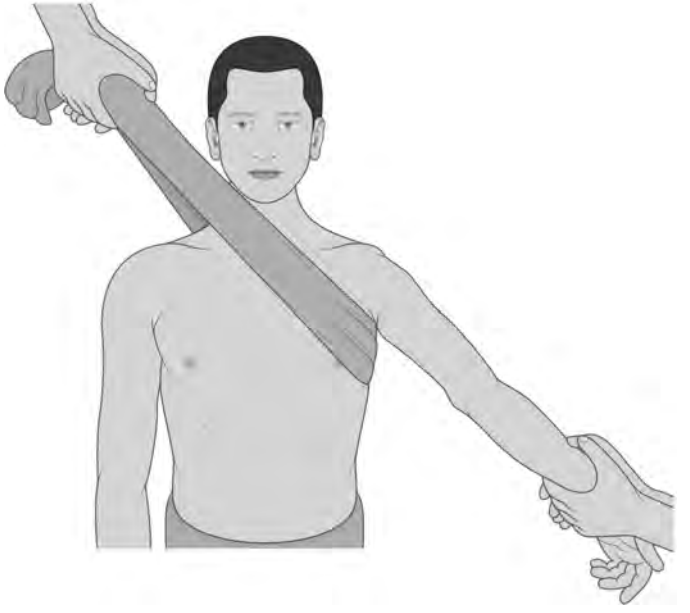


FIG. 19: Traction-countertraction method.

Stimson's-gradual relocation using hang: Use broad pieces of stockinette or tape to secure weight, being careful of possible skin damage Do not consider in patients with fragile skin. Allow gentle traction for 15–20 minutes. It may increase weight up to 10 lbs (**Fig. 20**).

Posterior dislocation: It is much less common. Classic mechanisms include seizure and electric shock. It is difficult without proper sedation. Forward and flex the affected arm to 90°. Abduct across the midline and internally rotate. The assistant on the contralateral side of the body can pull axial traction while the humeral head is milked anteriorly. External rotation can sometimes help with final reduction.

Inferior dislocation: Also called *luxatio erecta humeri*, it presents as arm fixed in abduction. *Traction-countertraction*: Pull axial and superior traction and gradually decrease abduction to

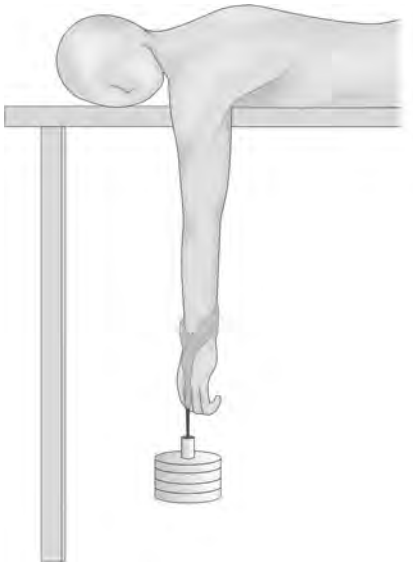


FIG. 20: Patient lies prone with the weight attached to the wrist.

reduce the humeral head. *Two-step technique*: The basic is to convert an inferior dislocation into an anterior dislocation. This procedure is initiated by standing at patient's head, push downward directed force on lateral mid-shaft humerus, while pulling upwards on the medial elbow.

Elbow Dislocation

Most dislocations are posterolateral and can be either simple or complex (with associated fractures). To reduce the dislocation, the patient can be positioned either prone or supine on the bed (**Fig. 21**).

Metacarpophalangeal Dislocation

Similar to interphalangeal joint dislocations, most MCP dislocations are dorsal. The reduction should avoid axial traction or hyperextension and can be achieved with joint flexion. Wrist flexion also helps by relieving tension on flexor tendons.

Interphalangeal Dislocation

Proximal interphalangeal dorsal dislocations: Simple—middle phalanx in contact with the condyle of the proximal phalanx. *Complex*—shortening with bayoneting of the middle phalanx over the proximal phalanx. The reduction should not involve axial traction, especially in complex dislocations, or the volar plate may become interposed in joint. Reduce with hyperextension of the middle phalanx with palmar-directed force. Once dislocation is reduced, buddy tape is applied to bordering digit. Associated intra-articular middle phalanx fracture requires a dorsal extension blocking splint. *PIP volar dislocations*: Reduce with dorsal-directed force and axial traction. Immobilize in extension due to central slip injury. *Rotatory PIP dislocations*: To relax lateral bands, flex MCP and PIP to 90° and pull axial traction. This may require an open reduction. *Dorsal distal interphalangeal dislocations*: These are similar to PIP dorsal dislocations. There is a risk of volar plate interposition with axial traction. Attempt reduction with hyperextension and palmar-directed force.

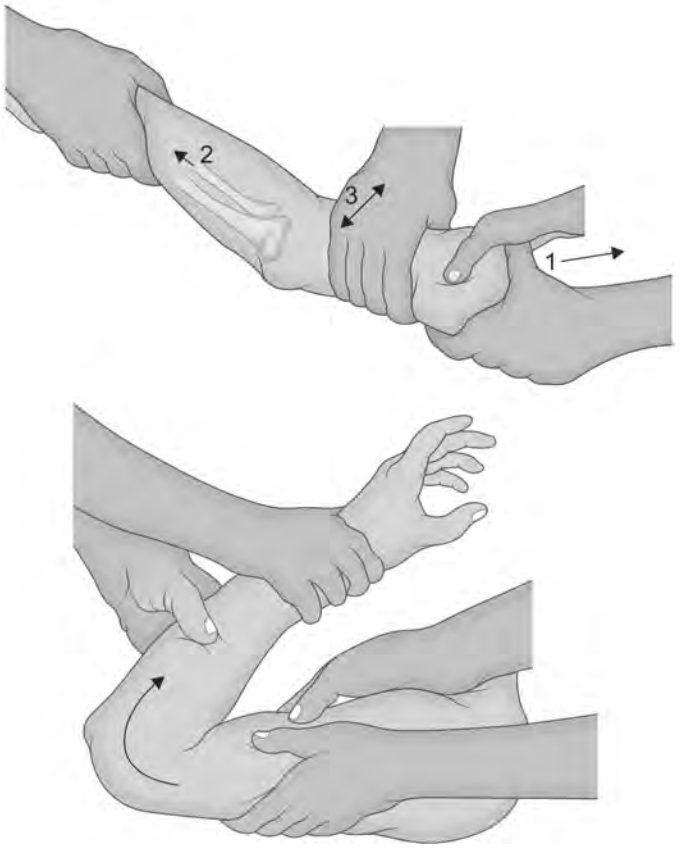


FIG. 21: Reduction of elbow dislocation.

Hip Dislocation

It requires adequate sedation to allow for reduction without further injury to the articular surface. Hip dislocations can be either anterior or posterior, with the posterior being the most common. Reduction maneuvers, regardless of dislocation, involve axial traction in line of deformity. A maximum of two attempts should be done. An assistant can help by placing his/her hands on the pelvis and providing countertraction. *Allis maneuver:* It involves axial traction with gradual hip flexion combined with alternating internal and external rotation. Always look for ipsilateral knee injuries for intra-articular fracture (**Fig. 22**).

Knee Dislocation

Anterior dislocation is most common and posterior. Neurovascular injuries are common, and an evaluation of distal pulses on presentation may decide the line of management. Obtain an ankle-brachial index even in cases where pulses are present before and after reduction. Any medial/lateral translation or rotation of the tibia should be corrected as axial traction is applied. Splint knee at 20–30° after reduction and obtain X-ray.

Ankle Fracture-dislocation

Ankle fracture-dislocation is a result of rotational injuries. The classification of injury is helpful in management and to do a neurovascular examination. Any concern for soft tissues requires urgent reduction prior to imaging. Fractures often result in lateral displacement of the talus under the

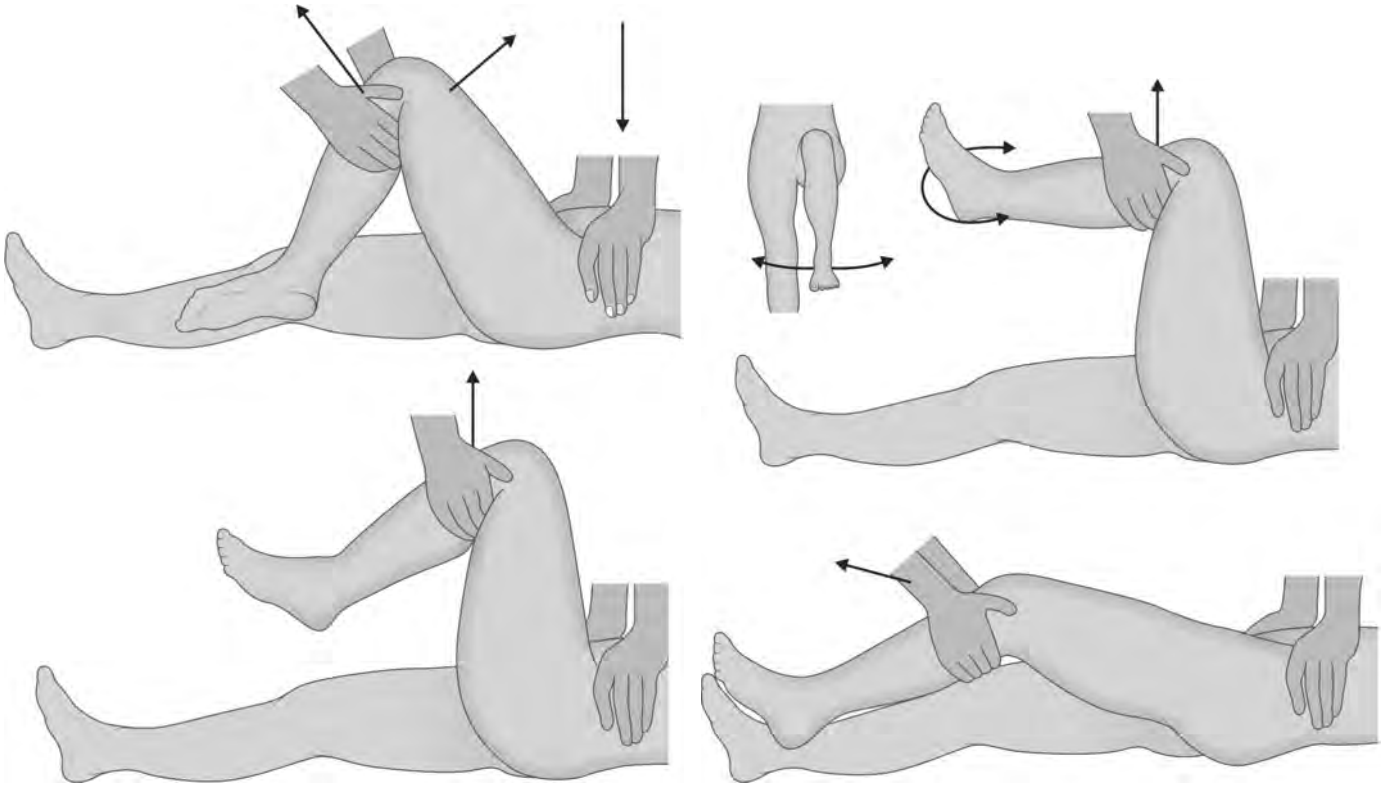


FIG. 22: Allis maneuver.

tibial plafond due to external rotation through the ankle at the time of injury. Dislocations associated with fractures of the tibial posterior malleolus can be very unstable with posterior displacement of the talus. Reduction requires plantar flexion of the foot, axial traction, and anterior translation of the hindfoot. Unstable ankle fracture-dislocations can be best treated by reduction, immediately followed by X-ray to confirm reduction prior to splinting.

Subtalar Dislocation

The talus often remains in place, with medial or lateral displacement of the calcaneus and dislocation of both the talonavicular and the talocalcaneal joints. Early reduction of closed dislocations is important to relieve pressure on the skin and soft tissues. It may require adequate sedation with knee flexion and ankle plantar flexion. Medial dislocations are fixed in supination. Lateral dislocations are fixed in pronation. Obtain CT scan in all cases of high-energy trauma.

LOCAL ANESTHESIA AND BLOCKS

Fast-acting local anesthesia in the emergency department is most commonly lidocaine, either 1% or 2% solutions, no >4 mL/kg. The maximum effect of lidocaine is reached in 5 minutes and will last for 30–60 minutes. Infiltrate lidocaine around the entire periphery of the wound to work in a systematic fashion. It can be used intradermally/intramuscularly about the periphery of lacerations or infected sites.

Hematoma Block

It is used for extra-articular fractures. Analgesia can be provided by infiltrating lidocaine directly into the fracture hematoma, allowing the local anesthesia to diffuse about the injury. Fractures presenting more than 1 day after injury are less amenable to the block due to clotting of hematoma. Review the X-ray and palpate the fracture site and consider local neurovascular structures to determine a path for injection. Sterile preparation is initiated and a use 22G needle to inject the fracture site. Prior to infiltrating, attempt to aspirate hematoma. A small amount of blood aspirate is essential for infiltration by a local anesthetic. If the bone is encountered, infiltrate small amounts of lidocaine below the periosteum. Progress the needle along with bone until it falls into fracture defect and hematoma.

Intra-articular Blocks

Infiltration into a joint is an effective method to provide analgesia for a reduction of dislocation or intra-articular fracture.

Median Nerve Block

First identify the palmaris longus and flexor carpi radialis brevis and longus tendons by having the patient oppose the thumb and fifth digit and flexion of wrist. The injection site will be between these two tendons at the level of the proximal palmar crease. If the patient lacks the palmaris longus tendon, the site will be ulnar to the flexor carpi radialis tendon. Insert a 24G needle at the insertion site and advance approximately 1 cm at which depth the needle will pop through the flexor retinaculum.

Radial Nerve Block

The superficial sensory branch of the radial nerve divides at the level of the radial styloid to provide sensation over the dorsum of the hand. To give a subcutaneous injection of

2 cc of 1% lidocaine over the lateral aspect of radial styloid, lateral to the palpable radial artery, redirect the needle toward the Lister's tubercle to continue infiltrating lidocaine subcutaneously, creating a large wheal that extends to the middle of the dorsum of the wrist.

Ulnar Nerve Block

The injection site is at the distal ulna, proximal to the wrist and dorsal to the flexor carpi ulnaris tendon.

Digital Block

Each digit is innervated by a pair of dorsal digital nerves. By infiltrating local anesthetic proximal to the digit, these four nerves may be blocked. *Subcutaneous technique*: Using a 26G needle, create a subcutaneous wheal of 1% lidocaine just proximal to webspace or radial side of the digit. Advance needle volery and infiltrate to block the volar digital nerve. Aspirate to ensure that the needle is not in the digital vessel. Ensure that infiltration does not contain epinephrine to cause vascular spasm and necrosis. *Transmetacarpal technique*: This targets the common volar digital nerve between the metacarpal heads prior to its division. Insert the needle through the volar skin at the distal palmar crease on the radial side of the metacarpal neck of the digit. Circumferential ring blocks should not be used as an increase in pressure can result in necrosis.

ARTHROCENTESIS

Indications of arthrocentesis:

- Evaluate monoarticular arthritis.
- Evaluate traumatic arthritis.
- Identify the cause of an effusion.
- Rule out joint infection.
- Diagnose inflammatory versus noninflammatory disorders.
- Identify intra-articular pathology (fracture or intra-articular disruption).
- Identify crystal-induced arthritis.
- Use as a pain control measure (by aspiration of fluid).
- Inject therapeutic agents.

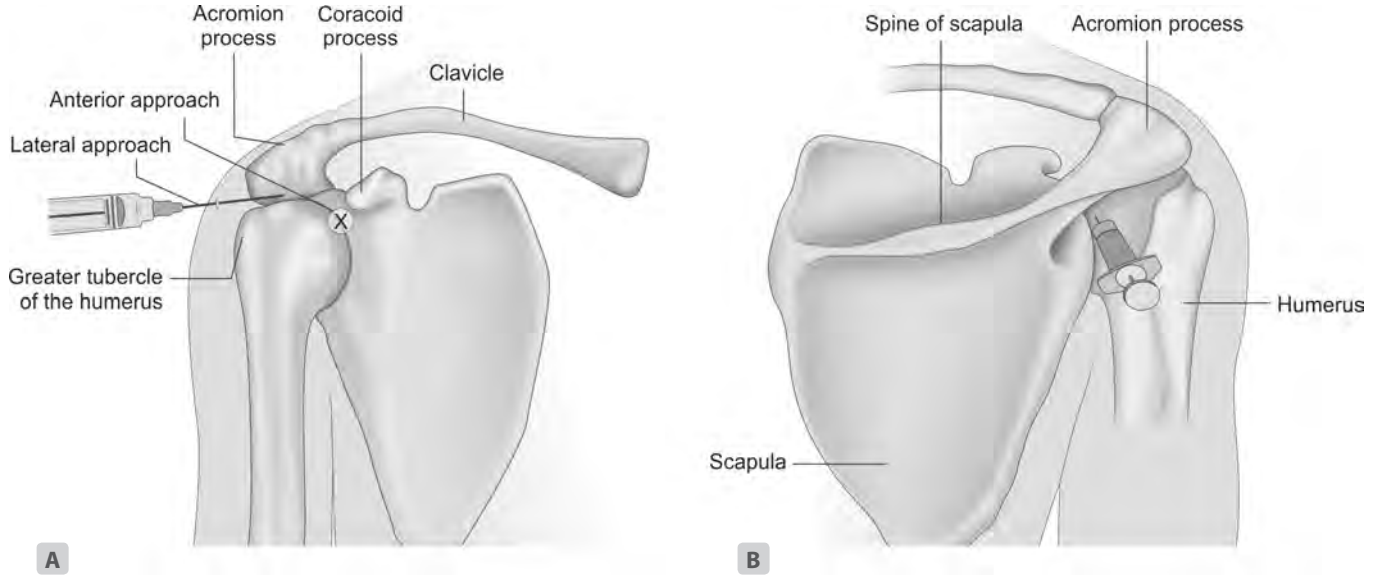
Intra-articular Injection and Aspiration

Each intra-articular injection should be performed in a sterile fashion to minimize the risk of introducing infectious pathogens. Prepare the site with povidone iodine, chlorhexidine, or iso-propyl alcohol as per the institutional protocol. After each procedure, dress with clean gauze. Aspirations should be performed using an 18G/20G needle to allow aspiration of thick substances. Patients with larger body habitus may require the use of a longer spinal needle in order to get intra-articular access.

Shoulder—Anterior approach: Palpate the coracoid process on the anterior aspect of shoulder. Place a needle 1 cm lateral to the coracoid process and just medial to the head of humerus. Advance the needle posteriorly and angled slightly superolaterally. *In the posterior approach*, palpate the posterolateral corner of the acromion; two finger-breadths inferior and one fingerbreadth medial. The needle should be oriented obliquely from this point toward the coracoid process, which can be palpated with the anterior aspect of the shoulder (**Figs. 23A** and **B**).

Elbow—Lateral approach: On the lateral aspect of elbow, palpate the soft spot in the center of a triangle by three bony landmarks; (1) lateral epicondyle of the distal humerus, (2) radial head, and (3) olecranon. Enter the elbow joint from this point by staying parallel to the articular surface of the radial head. *Posterior approach*: With the elbow flexed to 90°, palpate the soft sport approximately 5 cm proximal to the olecranon process on the posterior aspect of the elbow (**Fig. 24**).

Wrist—Dorsal approach: It utilizes the interval between the third and the fourth extensor compartments of the wrist. Palpate Lister tubercle on the dorsum of the wrist. Insert the needle distal to the tubercle, at the level of the joint, between the extensor pollicis longus and the extensor digitorum



FIGS. 23A AND B: (A) Shoulder joint arthrocentesis (a) lateral approach (b) anterior approach; (B) Shoulder joint arthrocentesis posterior approach.

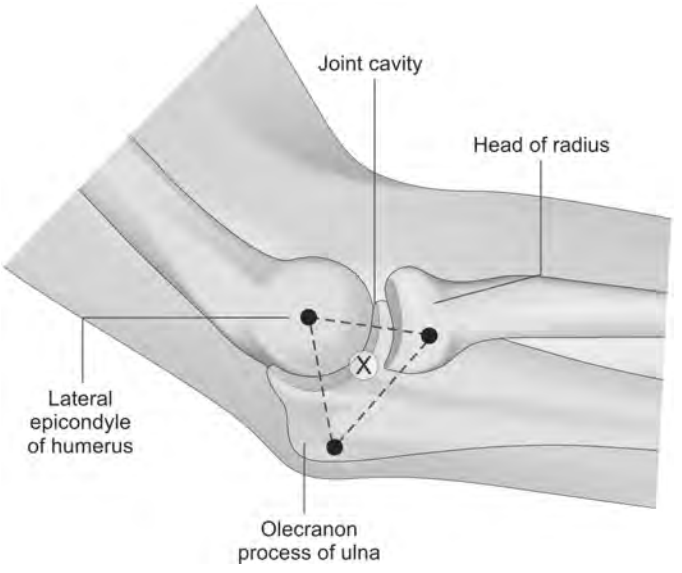


FIG. 24: Site of elbow arthrocentesis.

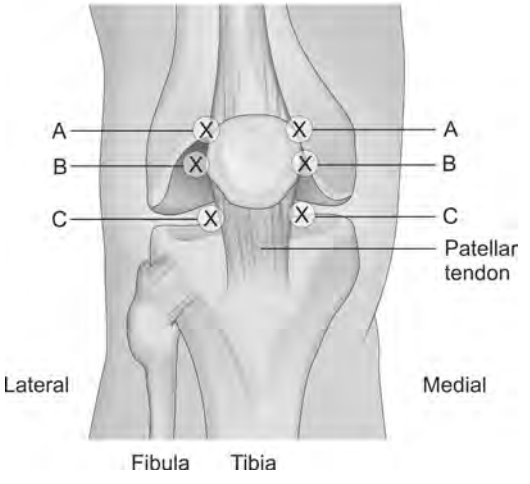


FIG. 25: Site for knee arthrocentesis.

communis tendons. Angle the needle distally to account for the volar tilt of the articular surface. *Medial approach*: Palpate the soft spot between the extensor carpi ulnaris and the flexor carpi ulnaris of the medial aspect of the wrist. Pass the needle between the tendons distal to the ulnar styloid.

Ankle: An anteromedial approach to the ankle is a must. The patient should be positioned supine and the anterior ankle prepped in a sterile fashion. Identify the tibialis anterior tendon at the level of the joint and introduce a 20G needle medial to the tendon. Angle the needle caudal to account for the slope of the dome of the talus.

Knee—Anterolateral approach: Same site as the lateral portal for knee arthroscopy. With the knee flexed to 90°, palpate the lateral joint line and borders of the patellar tendon. Palpate the soft spot lateral to the patellar tendon and above the joint line. Pass the needle superomedially, into femoral the notch. *Superolateral approach*: Mark the superolateral corner of the knee with the patient supine and knee fully extended. With one hand sublux the patella laterally as the needle is passed deep into it, toward the femoral notch (**Fig. 25**).

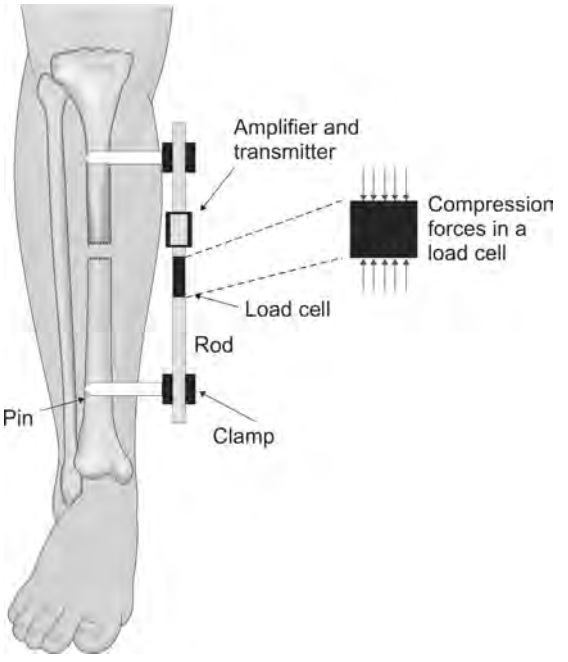


FIG. 26: External fixator.

EXTERNAL FIXATOR, PELVIC BINDER, EXTERNAL PELVIC FIXATOR

External Fixators

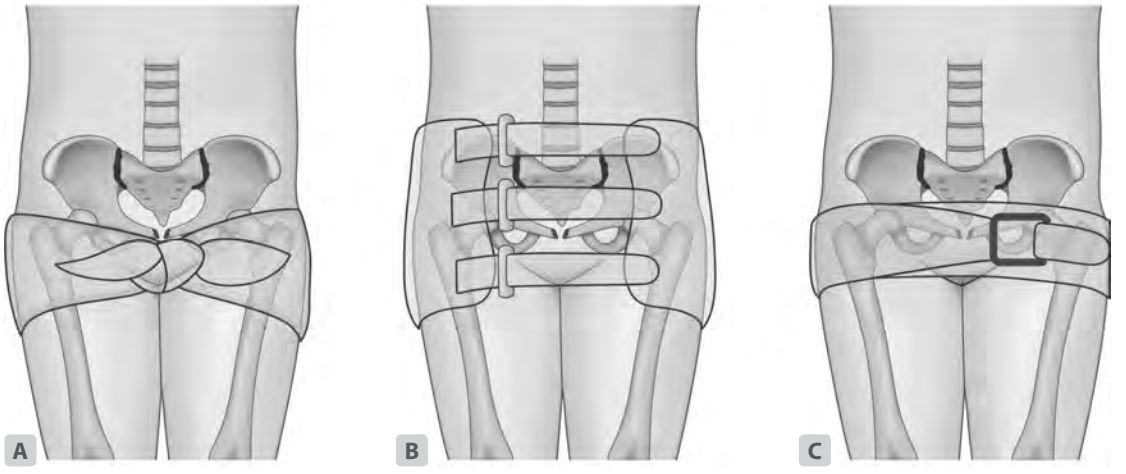
External fixators are used to maintain the length, alignment, and rotation of the fracture. This can be used as temporary or permanent. There are various types of external fixators, e.g., uniplanar, multiplanar, unilateral, bilateral, and circular. With absolute proper fracture stability, the external fixator promotes the bone healing process (**Fig. 26**).

Pelvic Binder

It is a device to compress the pelvis in those with a pelvic fracture in an effort to stop bleeding. It is specifically recommended for open-book pelvic fractures. A bedsheet or anything which is noncompressible and nonelastic may be used as well. The device should be placed over the upper femur, specifically over the greater trochanters. It is used only for short term. Skin ulceration may develop with long-term use. Open pelvic fractures, perineal lacerations, intra-abdominal injuries requiring surgery, morbid obesity, burns, and severe pelvic soft-tissue injury are the relative contraindications for pelvic binder placement (**Figs. 27A** to **C**).

External Pelvic Fixator

It is used as a damage-control orthopedics modality for fracture stabilization to prevent bleeding from the surfaces of pelvic bones. The fixator provide pelvic stabilization, by reducing the pelvic volume and bleeding from the stumps of fracture; it determines the arrest of the hemorrhage. There is containment of retroperitoneal hematoma. It reduces bleeding from the fracture fragments and the motility of the fracture, promoting the clotting of blood. Necessary equipment are sterile tray with drapes, Schanz pins, local anesthetic (2% lignocaine),



FIGS. 27A TO C: Pelvic binder.

T-handle, povidone-iodine cleansing solution, drill bit (3.2 mm) and handheld power drill, external fixator rods-external fixator clamps, spanners to tighten the clamps, and dressing material to cleanse and dress the pin sites.

SUMMARY

Orthopedic injuries following trauma are common presentations in the emergency department. Various procedures related to orthopedic injuries are performed to stabilize the patient. There are various orthopedic procedures which an emergency physician should know: Splinting, casting, reduction of dislocation, arthrocentesis, application of pelvic binder. The emergency physician should be aware of the indications, contraindications, and complications of the common orthopedic procedures.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Geriatric Trauma

Devendra Richhariya

INTRODUCTION

Emergency physicians face a unique set of challenges while managing elderly patients with trauma. Older patients are more vulnerable to trauma due to the combination of comorbid health conditions, prescribed medications, and frailty which increases the chances of subsequent complications, including infections, pneumonia, venous thromboembolism, and multisystem organ failure. Patients > 65 years old with trauma show an increase in mortality rate as compared to younger patients with similar injury severity score (ISS). It has been observed that elderly patients are undertriaged in most of the time and trauma care gets delayed. Any patient older than 70 years of age with trauma should be treated in the trauma unit as mortality increases 7% for every year beyond age 65 years. Apart from challenges during management, a physician has to face more significant obstacles to recovery than younger patients but most elderly trauma patients return to independent or preinjury functional status despite overall higher mortality, longer hospitalization, increased resource use, and higher rates of discharge to rehabilitation. The most important aspect in improving outcomes in elders with trauma is understanding the fact similar trauma principles apply to the elderly, with more aggressive evaluation and resuscitation. This chapter provides insight into the challenge of treating geriatric patients with trauma, covering differences in anatomy and physiology, triage, and resuscitations as well as addressing some special situations, including elder abuse, hypothermia, and suicide.

GERIATRIC ANATOMY AND PHYSIOLOGY

Frailty, Aging versus Underlying Disease

Mortality after trauma increases with age, but chronologic age is less important in trauma than frailty. Frailty is defined as impairment of the function of multiple systems that increases the susceptibility to physical and physiologic stressors. Quantification of frailty is difficult because of the long and time-consuming tools, which difficult to apply in the emergency setting. The patient's baseline functional status and evidence of sarcopenia may be considered as surrogate markers of frailty. Frail patients with multiple comorbidities have poor functional status and have worse outcomes after trauma.

Head and Neck

The leading cause of traumatic death in the elderly is due to traumatic brain injury. The brain shrinks with an increase in age and is more susceptible to tearing and bleeding from the shearing forces in trauma as decreasing brain volume causes stretching of the bridging veins. With increase in age, cerebrovascular autoregulation and free radical clearance are also impaired which further worsens brain injury in elderly patients and also delays recovery. Elderly patients if taking oral anticoagulants (OACs) are at a higher risk for significant intracranial bleeding in case of even minor head trauma. Thus, the clinician should have a lower threshold for computed tomography (CT) scan imaging in patients >65 years old with even minor head injury.

Cardiac

Elderly patients with congestive heart failure (CHF), and those on warfarin or β-blockers, have diminished cardiac reserve and are at a higher risk of poor outcomes after trauma. Structural and functional cardiac changes during aging lead to decreased reserve and a further significant reduction in cardiac function during the stress of trauma. There are no clear studies to guide management in the emergency department (ED) but during the evaluation of a geriatric trauma, careful cardiac examination and medication history should be performed by the clinician. Inotropic and chronotropic medications should be considered in poor cardiac output and hypotension and balloon pump in severe refractory cases.

Pulmonary

The physiology and mechanics of breathing also alter with age. Impairment of respiratory muscle mechanics occurs due to an increase in chest wall rigidity and worsening kyphosis, and when associated with a weak diaphragm may lead to a decreased fraction of expiratory volume in 1 second (FEV1) and decreased vital capacity and result in an overall decline in respiratory reserve. Chronic obstructive pulmonary disease in the elderly also has diminished lung function due to underlying, pulmonary fibrosis, or scarring and elderly patients can have significant hypoxia at lower levels of physiologic stress. Elderly patients with trauma become

more susceptible to the stresses of acute blood loss and fluid resuscitation.

Abdomen

Liver and kidney disease: Ischemic, reperfusion injuries, and risk of hemorrhage are very high with the underlying renal, hepatic disease with cirrhosis. Susceptibility to post-trauma complications also increases in elderly patients with trauma. Elderly populations are more prone to contrast-induced nephropathy (CIN) due to increased incidence of kidney disease, which may make them. Elderly on oral hypoglycemic medications can increase the risk of CIN and need to communicate with the radiologist in view of limited scans with contrast to avoid iatrogenic harm. Elderly patients typically have less muscle mass, and a high normal value may reflect acute kidney injury or chronic kidney disease; thus, a normal creatinine level should be interpreted with caution.

Musculoskeletal

Fragile bones and skin: Elderly patients are more susceptible to fractures even in the absence of underlying osteoporosis due to expected physiologic changes to both muscle and bone. Older patients have a loss of muscle mass leading to sarcopenia and a subsequently decreased structural support; weaker bones and aging bones are more easily fractured with minor trauma, for example, in falls from standing. Sarcopenia is one of the defining characteristics of frailty syndrome. With increase in frailty, functional decline occurs, leading to decreased mobility and deconditioning, increasing the risk of falls and injury. The elderly are at an increased risk of musculoskeletal injury; thus, emergency physicians should have a low threshold of obtaining plain film radiographs. Advanced imaging such as CT or magnetic resonance imaging (MRI) of the hip should be recommended even with normal radiographs who are unable to walk after trauma.

HISTORY: MECHANISM OF INJURY

Falls

The rate of falls is increasing in the elderly and is a leading cause of trauma-related mortality. Elderly patients with falls generally need hospitalization and even intensive care, if complications occur, and subsequently require discharge to a rehabilitation facility. The elderly are more likely to die from secondary complications as a result of trauma and less likely to die as a direct result of the trauma. Traumatic brain injury (TBI) is the most common direct cause of death from a fall.

Risk Factors

The most important risk factors for falls and related sequelae of the falls are frailty and comorbidities. The pattern of injury is directly related to the mechanism. The exact cause of falls may be difficult to determine in an emergency setting as falls are often multifactorial. In the geriatric population, several risk factors of falls have been identified and many of these patients may have occult infections (**Table 1**). Gait abnormalities and slow reaction times due to underlying arthritis, poor vision, sarcopenia, and chronic medication may contribute to fall in the elderly.

TABLE 1: Risk factors responsible for geriatric trauma.

Acute illness	New medications, syncope, dysrhythmias, CVA, TIA, acute MI, seizure acute renal failure, infection, hypoglycemia, AAA, dehydration, acute fractures
Chronic medical conditions	Osteoporosis, osteoarthritis, CVA, ischemic heart disease, anemia, DM, HTN gait or balance impairment, visual impairment, depression, polypharmacy, Parkinson disease, dementia
Environmental factors	Rugs, lighting, stairs, bathtubs/showers, footwear, walking aids, uneven ground, weather, pets
Others	Older age, female alcohol or drug use, elder abuse

(AAA: abdominal aortic aneurysm; CVA: cerebral vascular accident; DM: diabetes mellitus; HTN: hypertension; MI: myocardial infarct; TIA: transient ischemic attack)

Sources: Adapted from Aschkenasy MT, Rothenhaus TC. Trauma and falls in the elderly. Emerg Med Clin North Am. 2006;24(2):413-32; Sattin RW. Falls among older persons a public health perspective. Annu Rev Public Health. 1992;13:489-508.

Motor Vehicle Collision

Older patients are more likely to have more severe injuries at low-speed motor vehicle crash (MVC) and are to be admitted to the intensive care unit. Number of geriatric patient with motor vehicle collision are increasing and because of higher mortality in these patient, they require hospitalization in level-I trauma center with good rehabilitation facilities.

Pedestrian Struck

Approximately 20–30% of geriatric pedestrians are struck and killed by a motor vehicle. The most important risk factors for elderly pedestrian trauma are decreased visual acuity, slow reaction times, and difficulty ambulating as well as impaired judgment. Even with minor or low-energy trauma, elderly patients are more prone to serious injury and a higher incidence of death as compared with younger patients.

CLINICAL WORKUP

Triage/History of Present Illness

In both the prehospital setting and the ED, geriatric patients with trauma are frequently undertriaged. Certain risk factors such as age, female sex, and a fall-related injury may lead to undertriage. In geriatric patients, due to common underlying comorbidities, use of certain medications can mask the physiologic effect of the trauma or exacerbate vital signs. General prehospital triage guidelines may be ineffective or unreliable. The risk of death increases with even minor deviations in normal vital signs. Heart rate (HR) >150 beats per minute and a systolic blood pressure of 90 mm Hg carry a higher risk of mortality. Even small changes in the Glasgow Coma Scale (GCS) score of 14 in geriatric trauma patients after TBI are associated with significantly higher mortality in comparison to younger adults with a similar GCS. Elderly

patients with trauma should be evaluated at a trauma center and the trauma team should be activated.

Injury Severity Score

Trauma severity scores are used to correlate injury with mortality in the elderly. Trauma score (TS) and revised trauma score (RTS), the two most useful scores, are used. In the ED, the TS is assessed on the basis of blood pressure, respiratory rate, respiratory effort, GCS, and capillary refill (score of 0–16) while RTS does not use respiratory effort or capillary refill (score of 0–8). In the triage of elderly trauma patients, RTS and TS may be useful tools although studies are mixed regarding their use. ISS is also used to predict mortality. It is a common practice to use ISS in triage but its applicability to elderly patients is debatable. Even minor trauma in elderly patients is extremely susceptible to the adverse outcome, so history should be taken very carefully. There is no consensus of using the triaging scale in geriatric trauma so the combination of TS and RTS can be used along with clinical impression age, and other physiologic parameters should be taken into account. Certain underlying disease processes include heart disease, peripheral arterial disease, coagulation disorders, malignancy, and obesity and affect clinical outcomes in geriatric patients with multitrauma.

Past Medical History/Medications and Reversal Agents

When taking the history, it is important to note the medications such as β-blocker and OAC that are used before a traumatic event. Patients taking a drug combination of β-blockers, calcium channel blockers, and an angiotensin-converting enzyme inhibitor or angiotensin receptor binding agent can mask hemodynamic responses to trauma. The elderly who are on antihypertensive and sedatives increase the risk of trauma, due to falls. Many common conditions, including atrial fibrillation, stroke, thromboembolism, and medical management, after cardiac revascularization require OACs such as warfarin, rivaroxaban, apixaban, dabigatran, clopidogrel, and aspirin prescription for a longer duration. Patients who are on OACs are at a greater risk of intracranial hemorrhage following head injuries and increased risk of hemorrhage after intra-abdominal injuries. In the setting of intracranial or intra-abdominal hemorrhage, rapid reversal of the international normalized ratio (INR) slows the progression of the bleed and reduces mortality.

INITIAL MANAGEMENT AND RESUSCITATION

As in any other patient, initial resuscitation should begin with ABCs (airway, breathing, and circulation). Supplemental oxygen should be placed in all trauma patients to preoxygenate, and endotracheal intubation becomes necessary for an apneic patient. Various physiologic and structural changes with increasing age like rigid cervical spine, poor dentition, and high Mallampati score makes the bag mask ventilation and endotracheal intubation difficult. Degenerative changes of jaw causes incomplete opening of the mouth which makes intubation further more difficult. Mechanical ventilation also become difficult due to decreased functional reserve. Rapid-sequence intubation (RSI) medicine doses should be adjusted in the elderly if intubation is required (**Table 2**). To decrease the hemodynamic effects of benzodiazepines and etomidate, doses should be reduced by approximately 20–40% in the elderly. Ketamine should be used with caution in patients with ischemic heart disease because it increases myocardial oxygen demand. Complete exposure of the patient and a quick neurologic assessment should be performed under the secondary survey. Due to decreased pain perception and cognitive decline, physical and abdominal examination may be more difficult and unreliable in elderly patients. Similarly, underlying dementia or altered mental status from other causes, such as infection or stroke, make neurologic examination complicated. Thus, even with minor trauma, liberal use of CT scans is appropriate.

TABLE 2: Rapid-sequence induction medications and suggested dose adjustments.

Medication	*Adjustment*
Succinylcholine 1.5 mg/kg IV	No change
Etomidate 0.1–0.2 mg/kg IV	Decreased from 0.3 mg/kg IV
Midazolam	Decrease 20–40%
Fentanyl	Decrease 20–40%
Ketamine	Should be avoided secondary to cardiac effects

Do-not-resuscitate Status

It is critical to consider the patient's wishes; during resuscitation, consider the possible futility of such resuscitation but age alone should never be used as the sole determinant to limit care. The risk of mortality increases with the presence of certain risk factors, including hypotension, age >74 years, and higher ISS.

Assessment for Unstable Patients

In all unstable elderly patients with trauma, aggressive resuscitation should be initiated. All elderly should be considered unstable if they present with persistently abnormal vital signs or are not responsive to resuscitation efforts and those who have evidence of active hemorrhage or deteriorating mental status. Apparently stable geriatric trauma patients should be thoroughly evaluated for occult life-threatening injuries. In elderly patients with trauma, abnormal values of the serum lactate level and base deficit indicate impending deterioration and may predict mortality. After initial resuscitation, persistently abnormal values of serum lactate and base deficit values should be repeated. Hemodynamic monitoring in the elderly patients with trauma is essential. Ultrasonography and echocardiography have widely replaced the use of pulmonary artery catheters. Even slight changes in hemodynamic (HR, blood pressure) in geriatric trauma may signify occult injury and should be investigated thoroughly.

Reversing Anticoagulants

A patient's INR, activated partial thromboplastin time, and prothrombin time should be assessed and reversed promptly if any abnormalities are found in the geriatric trauma patient. Fresh frozen plasma (FFP) or prothrombin complex concentrate

TABLE 3: Anticoagulants and potential reversal agents.

Anticoagulation agents	*Mechanism of action*	*Potential reversal agents*
Warfarin	Vitamin K antagonist	FFP, PCC, vitamin K
Dabigatran	Direct thrombin inhibitor	Idarucizumab
Rivaroxaban	Factor Xa direct inhibitor	PCC
Apixaban	Factor Xa direct inhibitor	PCC
Enoxaparin	Antithrombin III inhibitor	Protamine (partially effective)
Heparin	Antithrombin III inhibitor	Protamine

(FFP: fresh frozen plasma; PCC: prothrombin complex concentrate)

(PCC) and vitamin K may be used for rapid reversal in patients with an increased INR. Normalization of prothrombin time or INR does not always correlate with decreased bleeding. The newer anticoagulants such as rivaroxaban, apixaban, and dabigatran do not yet have proven reversal agents; however, some studies show that PCC may be a reasonable choice with life-threatening bleeding (**Table 3**). Monoclonal antibody reversal agents for rivaroxaban, apixaban, and edoxaban are being investigated. Idarucizumab, a monoclonal antibody, for the reversal of dabigatran in the setting of an acute bleed has been recently approved by the US Food and Drug Administration.

DIAGNOSTIC EVALUATION

Neurologic or cardiac events are more common in the elderly population; thus, thorough assessment of the fall is critical. In the event of geriatric trauma, environmental factors, substance use, acute or chronic medical conditions, medications, and the patient's baseline functional capacity should also be assessed and investigated carefully. An appropriate investigation like electrocardiogram plain films or CT scanning of the affected organ systems should be done in all elderly patients with trauma. Elderly patients do not always experience the same degree of pain relative to the severity of injury; thus, radiology use should be liberal. In elderly patients with trauma with moderate-to-severe mechanisms, FAST (focused abdominal sonogram in trauma) examination is quick and easy to perform. Elderly patients should undergo whole-body CT scan when there is evidence of multisystem involvement.

Head Injuries

The TBI is the fifth leading cause of death in the elderly and as a result of low impact, ground-level falls. Geriatric patients with TBI require longer hospital admissions and more intense rehabilitation after discharge after a head injury as compared with young patients. Even minor changes in GCS of 14 have 10–15% mortality in a geriatric patient; any patients >60 years of age with loss of consciousness or who are taking an OAC should undergo a brain CT scan. Elderly patients with minor head injury who are taking OACs and have a normal brain CT scan may be safely discharged because of the low risk of bleeding but they should be given clear instructions.

Cervical Spine Injuries

Similarly, elderly patients after trauma are at an increased risk of cervical spine fractures. As a result of degenerative changes and stiffening of the cervical spine in the elderly, cervical spine (C1–C2) and odontoid fractures are twice as likely to have a cervical spine injury (CSI) as younger patients with the same mechanism of injury. Geriatric patients may have CSI with lower energy mechanisms of injury so application of the National Emergency X-radiography Utilization Study (NEXUS) decision rule in the elderly has been debated. It is recommended that a CT scan of the cervical spine be obtained if CT scan of the brain is ordered because the concomitant risk of CSI is high.

Thoracic Trauma

Even with isolated rib fractures, blunt thoracic trauma in the elderly carries a significant risk of complications and mortality. Pneumonia and pulmonary contusions are the most common complications following thoracic trauma in the elderly. Factors helpful in predicting adverse outcomes are age >85 years, initial systolic blood pressure of <90 mm Hg, three or more unilateral rib fractures, or the presence of pneumothorax, hemothorax, or pulmonary contusion. Dispositions should be carefully considered in an elderly patient with one or more rib fractures because of the high risk of mortality.

Musculoskeletal Injuries

Musculoskeletal injuries carry a risk of osteoporosis, and subsequent fractures are very common in elderly patients with trauma. A geriatric patient with fracture negatively affects both the patients' quality of life and the society at large. Forearm fractures are the most common, with hip fractures a close second in the geriatric population. A dedicated orthogeriatric team approach with early surgical repair, balanced with medical optimization, significantly improves the chance of patients in returning to their previous functional states and may improve outcomes for these patients.

Elderly patients with pelvic fractures and lateral compression fractures are likely to require angiography and blood transfusion due to the increased risk of hemorrhage. In older patients with pelvic fractures, even with appropriate treatment and disposition, mortality remains high so these patients should be aggressively resuscitated.

SPECIAL SITUATIONS

Elder Abuse

Elder mistreatment or abuse can be defined as intentional actions that cause harm or create a serious risk of harm, whether or not intended, to a vulnerable elder by that person's caregiver or by a trusted person in relation to that elder. Failure

of the caregiver to satisfy the elder's basic needs or to protect that person from harm is also considered as elder abuse. Nearly one fourth of elders are affected by psychological abuse. An emergency physician should ask about the potential abuse of elderly patients because they often report it if asked.

Risk factors and types of elder abuse: Elder abuse is a global problem. Dementia is one of the greatest risk factors for elder abuse. Older women with disabilities are at a significant risk for interpersonal violence. Financial, emotional, and both physical neglect and sexual abuse are also other types of elder abuse.

Health impact of elder abuse: Geriatric population has a higher incidence of bone and joint disorders, digestive problems, depression, anxiety, chronic pain, increased blood pressure, and a heart problem; thus, even modest abuse has an increase in risk of death compared with nonabused.

Management principles: *Assessment—a*n emergency physician should ask few screening questions to the elderly related to managing their daily lives or any psychosocial stress while performing daily activities because this is a risk factor for abuse. Ideally, the patient should be interviewed alone. Caregiver fatigue should also be assessed by taking his interview because this can increase the risk of elder abuse. The cognitive and functional status of the patient should be assessed; this should be addressed before discharging the patient. Until a preliminary investigation is conducted, there should be a low threshold for admitting these patients to get them out of their potentially abusive environments. If it is determined that the patient is experiencing abuse, a social worker should be involved, the case should be reported, and a safe environment should be established. Also, clinicians must try to facilitate treatment of the underlying disease, e.g., anxiety and depression, causing the patient at risk for abuse by caregivers.

DISPOSITION

A multidisciplinary approach should be taken while discharging or admitting patients. History of multiple falls, impaired mobility, poor strength, and depression increase the risk of a recurrent fall; thus, the involvement of social work, family members, and the patient's primary care physician is important. Acute underlying conditions should be evaluated and managed promptly before discharge. Several factors must be considered before discharge, including the cause of the injury, the patient's home environment, availability of helpers at home if the patient needed, and who will follow up with the patient. Admission should be considered to facilitate coordination of an appropriate care plan if a definitive discharge plan is not available.

SUMMARY

Geriatric patients with trauma will become increasingly common as the population ages. Mechanism of injury, injury types, morbidity, and mortality are unique in the geriatric population; if not treated aggressively, they are likely to have poor outcomes. Emergency medicine physicians and trauma surgeons should be familiar with the physiologic changes of aging and effects of potential underlying comorbidities on geriatric trauma and maintain a high index of suspicion for serious injury for all geriatric patients with trauma. Emergency physicians should be liberal with the use of laboratory and diagnostic imaging studies in geriatric trauma patients and should have a low threshold to admit elderly patients with trauma. Geriatric trauma patients deserve a more aggressive approach than younger patients who have similar mechanisms during their initial emergency management because aggressive care and resuscitation have a dramatic effect in improving outcomes in these patients.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Approach to Pediatric Trauma

Nisreen Hamza Maghraby, Mohye Al Wahas, Samar Ahmad Al Nahash

INTRODUCTION

Injury remains the most common cause of death and disability in childhood. Each year, more than 10 million children—nearly one of every six children—in the United States require emergency department (ED) care for the treatment of injuries. Each year, more than10,000 children in the United States die from serious injury. Injury morbidity and mortality surpass all major diseases in children and young adults, making trauma the most serious public health and healthcare problem in this population. The mechanism of trauma is divided broadly into blunt and penetrating. As in adults, blunt trauma is more common. It results from falls, sports-related injuries, and motor vehicle collision (MVC). Most injuries are accidental, but nonaccidental traumas must not be missed. Clues include but not limited to history, physical examination, a changing history, bruises of different ages and bruises in <1 year of age; remember "if you cannot cruise, you should not bruise."

Evaluating the pediatric population is challenging, as they might not directly communicate with strangers. It is very important to be observant of what they can and cannot do on initial visual assessment.

It is important to understand that children will not move if the movement induces pain, so if they are brought in by emergency medical services (EMS) and strapped down on a board, they cry to get out. You can simply bring in the parents and start unbundling the child, being observant and supportive at the same time.

It is also important not to forget to offer parents to come in and observe the resuscitation efforts and to assign a member from the team to support them by explaining each intervention that is taking place. Studies have shown that it helps parents to accept the outcome and eases grief.

ANATOMICAL AND PHYSIOLOGICAL DIFFERENCES

Pediatric are not just small adults. There are multiple anatomical and physiological differences. The most relevant differences that must be understood when managing a pediatric trauma patient are as follows:

- Greater physiological reserve, so they are able to maintain blood pressure, despite 25–30% blood loss, and look for subtle changes in heart rate, blood pressure, and extremity perfusion always refer to the normal range according to age.
- Airway interventions could be challenging due to relatively larger tongue, floppy and U-shaped epiglottis, anterior/cephalad larynx, shorter tracheal length, and the cricoid ring being the narrowest portion.
- Serious head injuries are a result of greater head to body ratio and thinner cranial bones, and the brain is less myelinated.
- Intrathoracic injuries are more likely as the ribs are more compressible dissipating the force of impact and decreasing the likelihood of bony injuries.
- Solid organs (liver and spleen) are less protected by muscle mass, are more anteriorly placed, and have less subcutaneous tissue thus making them prone to injuries, but the protective elastic capsule around both these solid organs leads to subcapsular injuries/hematomas and less lacerations with free fluid (blood) in the abdomen.
- Kidneys are susceptible to deceleration injuries, as they are less protected and more mobile; despite that, 15% of pediatric patients with hematuria post-trauma have congenital anomalies.
- Multiple traumas are common due to small body size leading to greater distribution of the injuries.
- Greater relative body surface area relative to the weight lead to greater heat loss and predispose them to hypothermia.
- Extremity fractures could possibly result in limb-length abnormalities as the growth plates are not closed and the most common fractures are Salter-type fractures.
- Higher caloric and energy requirements are a result of higher oxygen consumption and glucose utilization.
- Age- and weight-adjusted fluid and medication doses should be considered and clinicians should be familiar with length-based resuscitation tapes and their uses.

EVALUATING A PEDIATRIC TRAUMA PATIENT

A complete trauma evaluation has three surveys, each with a separate goal:

1. *Primary survey*: To identify the killers. Follow the evaluate, identify, and intervene approach.

2. *Secondary survey*: To identify major musculoskeletal (MSK) injuries or dislocations.
3. *Tertiary survey*: Final review of the laboratories and radiological imaging and screening before the patients are cleared to go home.

Prevent and Identify the Killers in Trauma

The killers can be described by two different approaches:

- *Physiology*—lethal triad of trauma (**Fig. 1**) prevent hypothermia, acidosis, and coagulopathy.
- Pathology—the HOTT mnemonic (**Fig. 2**), identify and treat these: H: Hemorrhage, O: Oxygenation, T: Tension pneumothorax, T: Tamponade (pericardial hemorrhage).

Receiving the Patient

If the patient was brought by EMS, he/she is most likely to be on a backboard. This board must be removed immediately; backboards are for transportation only. They are not a benign intervention. They lead to pain, pressure, and wounds and are simply uncomfortable.

Before the paramedics leave, you must ask four main questions, which are summarized in the mnemonic MIST, M: Mechanism of injury, most importantly was the patient restrained or not, where was he/she found (ejection mechanism), blood or death on the scene; I: Injuries found or suspected; S: Vital signs on scene; and T: Treatments given, when and how much. The patient must be connected to a monitor immediately and undressed into a hospital gown to easily evaluate the patient. A line should be secured; the size of the line should consider the patient's situation (unwell large line, well no line or small line) and a venous blood gas (VBG) sent. Additional samples can be kept. Ultrasound (US) should be ready to be used for evaluation.

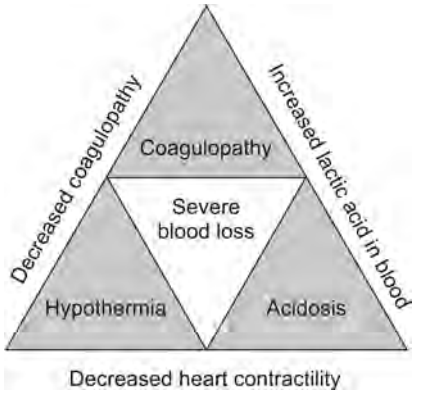
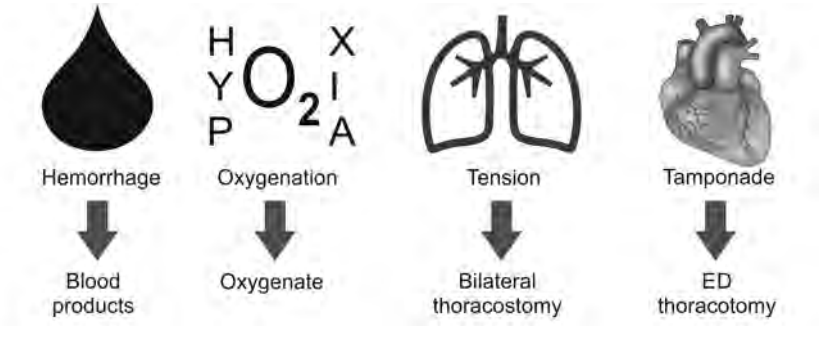


FIG. 1: Lethal triad.

PRIMARY SURVEY

The primary survey is a quick scan to evaluate the patient for the killers; your quick screen should follow the traditional airway, breathing, circulation, disability, exposure (ABCDE) approach:

- *A*: *Airway and C-spine precautions*—the airway must be evaluated immediately for possible airway obstruction or a pending obstruction. Look for blood in or around the mouth, look at the floor of the mouth for a hematoma, check the teeth for missing or loose teeth, check if there are any vomitus stains, check if the patient is controlling his saliva, and listen for gurgling sounds or any stridor. If you need to open the airway, perform a jaw thrust maneuver as it is less likely to lead to C-spine movements. Use airway adjuncts or apply oxygen via a face mask as needed. The main purpose of airway evaluation is to determine if the patient is able to protect the airway or not.
  Regarding the C-spine: Always attempt to clear the C-spine clinically whenever possible. Remember C-collars are again not a benign intervention. They lead to pain, discomfort, and predispose the patient to aspiration if they vomit and increase work on the nurses. There are a few clinical decision rules (CDR) to help clear the C-spine clinically. Nexus is the one that included pediatrics. If the C-spine could not be cleared clinically, then the imaging of choice is a computed tomography (CT) scan and not an X-ray and the patient must remain in the C-collar until the report is negative for any C-spine fractures. The patient may be kept in a reverse Trendelenburg position for comfort. After that, the patient must be re-evaluated by passively allowing the patient to rotate his head to evaluate the range of motion to roll out ligamentous injuries. During this re-evaluation, there is no role in palpating the C-spine as palpation is an indirect sign to assess for bony injuries and they have already been rolled out by a gold standard test (CT scan). If the patient is unable to rotate his/her neck, then he/she must remain in a collar and be referred to neurosurgery for magnetic resonance imaging (MRI) to roll out ligamentous injuries. Spinal cord injury without radiographic abnormality (SCIWORA) is the term used to describe spinal cord injuries without radiographic abnormality. It is suspected in patients with neurological deficits, including transient paresthesia, numbness, or



(ED: emergency department)

FIG. 2: Approach to cardiac arrest.

paralysis, without any radiological finding, more common in <8 years of age; in this case, MRI is the best diagnostic modality. *Endotracheal* (*ET*) *intubation is indicated mainly for*: Oxygenation, ventilation, and protection of the airway from an anticipated deterioration in the clinical situation. Indications for intubating pediatric trauma patients are:

- Glasgow Coma Scale (GCS) score <8
- Inadequate oxygenation or ventilation—poor effort or color
- Inability to maintain or protect airway—gag reflex not especially helpful because it does not correlate with GCS
- Inability to ventilate by bag-valve-mask (BVM) or need for prolonged control
- Severe head injury
- Potential for clinical deterioration (thermal inhalation injuries)
- Respiratory failure from flail chest
- Decompensated shock resistant to initial fluid resuscitation.

Few anatomic differences should be kept in mind while dealing with pediatric airway (**Table 1**).

Selection of the ET tube size should be determined by a length-based resuscitation tape or age-based calculation: Uncuffed: 4 + 1 (age in years/4), Cuffed: 3.5 + 1 (age in years/4)

- *B*: *Breathing*—breathing is evaluated by looking at the oxygen saturation and the respiratory rate (RR), auscultating the chest, and observing chest wall movements. A fast RR may be an indirect sign of occult shock. The chest must be palpated, looking for any pain or grimacing that might be generated in addition to palpating for any subcutaneous emphysema. If the patient was identified to need intubation during the assessment of airway, preparation must be done immediately, but not performed until breathing is evaluated. We must make sure that the patient does not have a pneumothorax that could be converted into a tension pneumothorax with positive-pressure ventilation. Point-of-care lung US [extended focused assessment with sonography in trauma (eFAST)] should be done to mainly look for lung sliding, which is more sensitive than a chest X-ray. Never the least, a chest X-ray is still required to look for lung contusions and for follow-up and documentation. It is important to remember that hypoxia produces agitation and hypercarbia leads to central nervous system (CNS) suppression (drowsiness). *Surgical airway* (needle cricothyroidotomy in small children and infants, surgical cricothyroidotomy in >12 years of age) *is indicated in cases of failure of ventilation and intubation*.
- *C*: *Circulation*—evaluation of circulation is mainly done to identify hemorrhage that may lead to hemodynamic instability. Multiple data points must be collected as the gold standard to identify hemorrhage is a CT with contrast (trauma protocol). This leads to a large radiation and contrast exposure; timely identification is important before major compromise in blood pressure occurs as it will be an unsafe transport to the CT scan department at that point. Multiple data points that could determine possible hemorrhage include tachycardia, tachypnea, cold/clammy, prolonged capillary refill, confusion, shock index > 0.9, or a delta shock index > 0.1 (difference between SI on scene and in the ED) and a negative base access on the VBG. It is also important during this time to check on the size and site of intravenous (IV) access. The patient must be exposed down to the skin, to look for any signs of trauma indicating a concerning mechanism. It is during this time that any pressure dressings applied prehospitalization can be removed as before inserting an IV line or checking the blood pressure, it could be unsafe, especially if it was controlling an active hemorrhage and suddenly without preparation it starts to bleed. IV access in antecubital area is the preferred site and if it fails the intraosseous route can be used. The pelvis should be examined for any instability; if unstable, it should be wrapped immediately. An eFAST scan is then performed to look for free fluid in the abdomen. It is important to remember that a focused assessment with sonography in trauma (FAST) scan is only able to identify hemorrhage intra-abdominally. We have mentioned that a CT scan is the gold standard to identify injuries. In pediatric age group if child is complaining of abdominal pain, the ultrasound abdomen can be done before requesting a CT scan. As mentioned above, subcapsular hematomas in solid organs are common in pediatric and can be evaluated by a formal US. It is important to mention that if a trauma patient requires fluids, blood is the fluid of choice. One bolus of crystalloid might be given till blood arrives.
- The areas where a patient might bleed (chest, abdomen, retroperitoneal, and long bone fracture) which lead to hemodynamic instability are summarized in a mnemonic (four plus the floor), but in the <1-year-old population the head is an additional area (due to the ability of the skull to expand and accumulate enough volume).
- *D*: *Disability and dextrose*—despite being the last component of the primary survey, attempting to sedate and intubate a patient should never be done before evaluating the level of consciousness and looking for lateralizing signs. This can be done by asking the patient to simply passively move both his upper and his lower extremities or by applying a painful stimulus if the patient is not responding. The level of consciousness can be evaluated using the GCS (pediatric version) or the alert, voice, pain, unresponsive (AVPU) scale. Attention to the pupils (size/reactivity) should not be overlooked. It is important to take

TABLE 1: Anatomic difference of pediatric airway.

Airway differences	*Interventions*
Prominent occiput	Use a rolled towel under the shoulders
Larger tongue, larger adenoid tissues	Optimize head positioning, jaw-thrust position, use of an oropharyngeal airway
Floppy, U-shaped epiglottis	Use of a straight blade
Larynx more anterior	Positioned yourself closer to the patient at a 45° angle
The cricoid ring is the narrowest portion of the airway	Have a smaller sized tube ready because the larger sized tube may pass the cords but not the cricoid
Narrow tracheal diameter and distance between the rings	Must do needle cricothyrotomy rather than surgical
Shorter tracheal length resulting in frequent right-mainstem intubations or dislodgement	Use three times the tube size to estimate the accurate depth of placement, minimize head movement once placed

this chance and look externally at the head for any signs of head trauma. Generally, frontal hematomas are benign as the frontal bone is stronger due to a double cortex. Unlike temporal hematomas, frontal hematomas should be taken seriously for a possible significant head injury. The main concern after any head trauma is the likelihood of a significant head injury. That does not mean that a CT scan should be done for all head traumas. Again, there are a few CDRs to help guide that decision. Pediatric Emergency Care Applied Research Network (PECARN) is the most commonly used. Sharing the decision with the family is extremely important, but more important is to explain the benefits and risks to help them make an informed decision, in addition to providing them with a sheet for head trauma instruction if they decide to go home.

- *E*: *Exposure*—at the end of the primary survey, remember to expose the patient and perform a log role to make sure that there are no hidden injuries that have not been identified or no bandages or splints that have not yet been removed. Check a temperature, especially if the context of the situation has exposed the patient to possible hypo- or hyperthermia.

Adjuncts of the Primary Survey

Chest X-ray and VBG should be done and a Foley catheter should be inserted if the patient is intubated. Pelvic X-rays are not a routine requirement. If the patient has a GCS of 15, no distracting injuries or intoxication or no pain or tenderness, then a pelvic X-ray is not required.

TABLE 2: Indications of CT scan in pediatric trauma.

Pediatric age	*Indication of CT scan*
Children < 2 years of age	• Age < 3 months • Palpable skull fracture GCS < 14 • Agitation, irritability, somnolence, slow response • Scalp hematoma (temporal, parietal, temporal) • Loss of consciousness > 5 seconds • Fall > 3 feet, high-energy head impact • Motor vehicle collision with passenger ejection, rollover, or death of another passenger • Unhelmet pedestrian or on the bicycle
Children > 2 years of age	• GCS < 14 or any signs of altered mental status • Signs of basilar skull fracture • Battle sign—ecchymosis of the mastoid process • Raccoon eyes—periorbital ecchymosis • CSF otorrhea or rhinorrhea • Headache, vomiting, loss of consciousness • Fall > 3 feet, high-energy head impact • Motor vehicle collision with passenger ejection, rollover, or death of another passenger • Unhelmet pedestrian or on the bicycle

(CSF: cerebrospinal fluid; CT: computed tomography; GCS: Glasgow Coma Scale)

SECONDARY SURVEY

The secondary survey is basically a head-to-toe examination, palpating every single bone to identify injuries. It is important to range all joints in the range of motion, to roll out any dislocations. If a fracture is suspected, request an X-ray with a joint above and below. Confirm if there is any breakdown in the skin, as the management for an open fracture defers from a simple fracture. Check the pulse and evaluate the sensory and motor components of the nerve supplying that area, to confirm that neurovascularly the limb is intact. Address the pain and start with acetaminophen, nonsteroidal anti-inflammatory drug (NSAID) and then opioid if needed. If the patient has wounds, irrigate them, examine their size, and type of destruction to determine the need for antibiotics. Tetanus is usually not required in pediatrics, especially if their vaccines are up to date.

Children should not be exposed to unnecessary radiation. PECARN head injury guidelines were developed for obtaining a CT scan in the setting of pediatric head trauma based on symptomatology (**Table 2**).

Secondary Survey of Cervical Spine

Anatomic difference in the pediatric cervical spine: The pediatric age group is more susceptible to upper cervical injury because of certain anatomic differences. These anatomic differences of the cervical spine are as follows:

- Larger head size and weight compared with the neck and trunk
- Weaker C-spine musculature
- Increased laxity of the spinal ligaments
- Immature vertebral joints and ossification centers
- Increased elasticity of the spinal column
- Lack of uncinate processes until approximately 10 years of age.

Any child involved in a trauma with the potential for a C-spine injury should be treated as if the injury exists until proved otherwise, either by physical examination or by radiography. The C-spine should be adequately immobilized as soon as possible, ideally in a prehospital setting. The indications for spinal cord immobilization are given below:

- High-risk mechanism (MVCs, diving, contact sports, acceleration-deceleration injury)
- Altered mental status
- C-spine midline tenderness
- Decreased range of motion
- Neurologic deficits
- Distracting injury
- Multiple system trauma.

Secondary Survey of Cardiothoracic Trauma

Due to the differences in pediatric anatomy and physiology, injury patterns as a result of thoracic trauma in children are different from those seen in adults. Pediatric chest wall is able to absorb and distribute forces resulting in fewer rib fractures than the adult. But this compliance of pediatric chest wall may mask serious underlying chest injuries. Important features to look for in pediatric chest trauma are as follows:

- *Respiratory:* Abnormal rate, nasal flaring or retractions, paradoxical chest wall movement, chest wall injuries or defects, abnormal lung sounds on auscultation.
- *Cardiac*: Distant or muffled heart tones, murmur, irregular rhythm, distended neck veins.

- *Commotio cordis*: This condition is specially attributed to pediatric trauma. Commotio cordis is a combination of ventricular fibrillation and sudden cardiac death secondary to a sudden impact to the anterior chest wall.

Secondary Survey of Blunt Abdominal Trauma

Blunt trauma abdomen in the pediatric age contributes to significant mortality. The extent of injury in a child with blunt abdominal trauma is often difficult to determine. The intra-abdominal injury should be considered in any child with trauma until proved otherwise. The gold standard investigation after a trauma, for identifying intra-abdominal injury, is an abdominal CT scan with IV contrast in hemodynamically stable patients. The indications for obtaining an abdominal CT scan are as follows:

- History suggestive of severe intra-abdominal injury
- Physical examination concerning for intra-abdominal injury (i.e., abdominal tenderness, guarding, or rebound tenderness)
- Presence of the seat belt sign or other abdominal bruising
- Aspartate aminotransferase (AST) > 200 or alanine aminotransferase (ALT) > 125
- Decline in hemoglobin or hematocrit <30% from baseline
- Positive FAST examination
- Gross or microscopic blood on urine analysis [>50 red blood cells (RBCs)].

The majority of children with acute abdominal trauma are managed conservatively. Children with hemodynamic instability should be admitted to an intensive care unit for continuous monitoring and for volume resuscitation. A pediatric surgeon should be involved. Indications of emergency laparotomy after blunt abdominal trauma are given below:

- Intra-abdominal bleeding with persistent hemodynamic instability despite aggressive crystalloid and blood transfusion (transfusion > 20 mL/kg packed RBCs)
- Perforation of a hollow viscous injury leading to pneumoperitoneum
- Increasing abdominal tenderness or the development of peritoneal signs on examination
- Solid-organ injury with persistent bleeding
- Pancreatic injury with ductal disruption.

TERTIARY SURVEY

If the patient is intubated or will require admission, then the tertiary survey is deferred till predischarge. The aim is to make sure that the patient is able to function at baseline. All vital signs, laboratories, and imaging are reviewed; follow-up plans are set by the admitting team and any prescription, if required, is ready. The patient must be symptom-free, tolerating PO and ambulating at baseline. Clear discharge instructions must be given and what to expect. It is important to emphasize on the point that even if a CT of the abdomen was done, there are a few injuries that can be missed (mesenteric, bowel, diaphragmatic, and pancreatic). If the patient develops abdominal pain and fever and is unable to tolerate PO (vomiting), then they must return to the hospital immediately.

DISPOSITION

Most traumas are minor and patients are discharged from the ED. Others that are more severe are sent to the pediatric intensive care unit (PICU) for observation or postoperatively if an operation was required emergently. It is of note to mention that infants and children with moderate-to-severe injuries have improved outcomes in a PICU. So, if they were initially seen in an adult hospital, arranging for transportation should be considered. Remember that the role of an emergency physician is to evaluate and stabilize trauma patients prior to operating room (OR), PICU, or transfer to a tertiary care facility. Children with suspected abuse should not be discharged and involvement of concerned authorities should be done as they have high risk of fatalities.

SUMMARY

Various anatomical and physiologic differences are present between pediatric and adult population. These differences play a significant role while evaluation of a pediatric trauma patient. The emergency physician should be aware of these nuances while managing a pediatric trauma patient. A focused and structured approach should be used when dealing with children with traumatic injuries.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Trauma in Pregnancy

Wael Hakmeh, Mustafa Sabak, Behçet AL

INTRODUCTION

Though pregnant female trauma patients presenting to the emergency department are few, they are associated with high morbidity and mortality. In critically injured patients, morbidly obese, and the first trimester of pregnancy, immediate recognition of pregnancy is not always possible. All women of childbearing age who present after trauma must be considered pregnant until proven otherwise. There are very few presentations in emergency; complex pathophysiology of pregnancy and dealing with two patients (mother and fetus) simultaneously must involve trauma team of emergency medicine specialist, obstetrician, and neonatologist. The specialist team can also deal with emotional and social issues very effectively. Although trauma management prioritizes the mother, the fetus must also be taken into consideration. Physicians should understand and anticipate the anatomical and physiological changes and potential injury patterns that occur in pregnancy. Other challenges while dealing with a pregnant trauma patient are multidisciplinary approach, exposure to radiation and teratogens, and management of pregnancy-specific problems.

ETIOLOGY

Trauma is the leading cause of nonobstetric maternal mortality, occurring in approximately 7% of all pregnancies, more often in the third trimester. Most frequently, it is caused by domestic violence and traffic accidents such as motor vehicle collision (MVC). Other forms of injury include penetrating injuries, slips and falls, burns, unintentional poisoning, suicide, and homicide (**Table 1**).

ANATOMICAL AND PHYSIOLOGICAL CHANGES OF PREGNANCY

Knowledge of physiologic and anatomic changes in pregnancy and their clinical impact on symptoms and manifestation of traumatic injuries are important in management (**Table 2**).

- *Cardiovascular*: Cardiac output increases due to increased plasma volume, decreased vascular resistance, and increased maternal heart rate (an additional 10–15 beats/min). The supine positioning of pregnant trauma patient increases the risk of superior vena compression and 20–30% reduction in cardiac output due to gravid uterus particularly in second and third trimesters, particularly during the second and third trimesters (**Figs. 1A** and **B**). Blood pressure is lower than normal (5–15 mm Hg less than usual) in the second trimester, which causes difficulty in diagnosing hypovolemia secondary to bleeding but returns to near-normal levels at term.
- *Respiratory*: The airway diameter decreases due to laryngeal edema and increased mucosal congestion, rendering airway management more challenging. Rapid-sequence intubation medications are considered safe. The oxygen consumption is increased and the fetus is very sensitive to hypoxia. For this reason, it is important to keep oxygen saturation above 95%. Functional residual capacity decreases and hyperventilation leads to respiratory alkalosis due to increased pressure on the diaphragm in late pregnancy. Therefore, patients are expected to be hypocapnic [partial pressure of carbon dioxide ($PaCO_2$) ~30 mm Hg] during late pregnancy periods. A $PaCO_2$ closer to 40 mm Hg (the normal value in a nonpregnant patient) should alert the physician of impending respiratory failure.

TABLE 1: Prevalence of types of trauma mechanism in pregnancy.

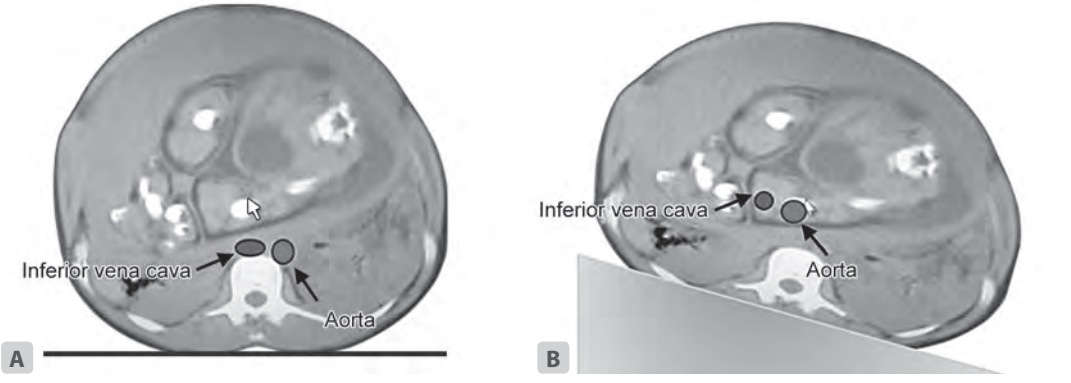
Domestic violence	8.307/100,000 live births
Motor vehicle collision	207/100,000 live births
Falls and slips	48.9/100,000 live births
Toxic exposure	25.8/100,000 person-years
Penetrating trauma	3.27/100,000 live births
Homicide	2.9/100,000 live births
Suicide	2/100,000 live births
Burns	0.17/100,000 person-years

Source: Mendez-Figueroa. Trauma in pregnancy. Am J Obstet Gynecol. 2013;209(1):1-10.

TABLE 2: Anatomic and physiologic changes in pregnancy.

Anatomic changes	*Clinical relevance*	*Physiological changes*	*Clinical relevance*
Edematous and friable airway	Difficult airway, may require smaller ETT	Increase in oxygen consumption	Require high-flow oxygen
Uterus extent beyond bony pelvis after 12 weeks, gravid uterus after 20 weeks	• Direct injury to the uterus • Supine hypotension due to compression of inferior vena cava	• Increase in plasma volume • Increase heart rate/low blood pressure	• Delay in the identification of shock • Poor marker of hemodynamic stability
Bladder moves superiorly	Direct bladder injury	Increase in the bladder and uterine blood flow	Increase in bleeding risk with direct injury
The diaphragm moves upward 4 cm	Pneumothorax, tension pneumothorax, tube placement 2–3 spaces upward	• Increase in renal plasma blood flow and GFR • Increase bicarbonate excretion	• Precaution with drugs which excrete through the renal system • Susceptible to acidosis
Small bowel moves up	Direct blunt/penetrating bowel injury	Decrease in platelets, PT, PTT increase in fibrinogen, d-dimer	Precipitates disseminated intravascular coagulation (DIC) early
Peritoneum-abdominal wall stretches with the progression of pregnancy	Poor assessment of organ injury intra-abdominal bleeding	Other hematopoietic changes in pregnancy are decrease in hemoglobin, hematocrit, and platelets, increase in white blood cell count, fibrinogen factors VIII and X	Awareness about these changes helps in resuscitation and anticipation of various complications

(ETT: endotracheal tube; GFR: glomerular filtration rate; PT: prothrombin time; PTT: partial thromboplastin time)



FIGS. 1A AND B: (A) Compression of the vena cava inferior in the supine position of the pregnant patient and (B) the disappearance of the compression with a tilt of about 15–30° on the right side.

Courtesy: Dr Fatma Sinem Samim.

Rates of hemothorax (Htx) and pneumothorax (Pnx) are unchanged.

- *Gastrointestinal*: Decreased lower esophageal sphincter tone from the effect of progesterone combined with increased intra-abdominal pressure can lead to esophageal reflux and aspiration. Because the uterus displaces the bowels cephalad and laterally in later gestational periods, it can interfere with the abdominal examination and clinical findings, particularly with upper abdomen penetrating injuries.
- *Hematologic*: The volume of plasma increases more than the increase in the number of red blood cells causing physiologic anemia. A mild leukocytosis and relative thrombocytopenia can develop. Coagulation factors [VII, VIII, IX, XII, fibrinogen, and von Willebrand factor (vWF)] increase from the effect of estrogen, and this is thought to increase physiologically to prevent excessive bleeding at delivery, although it may predispose to hypercoagulability during pregnancy.
- *Renal*: Renal plasma flow and glomerular filtration rate increase due to systemic vasodilation and increased cardiac output while blood urea nitrogen and creatinine levels decrease during pregnancy. Proteinuria may increase but levels >300 mg/dL are pathological, requiring consideration of possible preeclampsia. Hematuria is always pathological. Mild dilutional hyponatremia (130–135 mEq/L) can be observed.
- *Reproductive*: Because of its anterior position and size, the uterus is the most frequently injured organ in blunt abdominal trauma. Penetrating injuries to the uterus

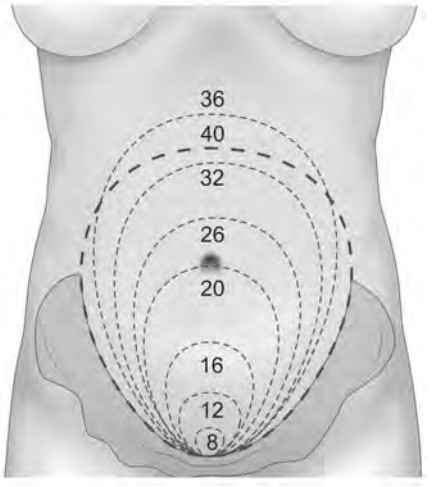


FIG. 2: Estimated pregnancy week based on fundal height.

Courtesy: Clinical Multimedia Unit, Metro North Hospital and Health Service, Queensland.

often result in fetal loss. Fundus height, tenderness, and shape and tone of the uterus must be evaluated. The uterus remains intrapelvic up to 12 weeks of pregnancy, then enters the abdomen, and reaches the umbilicus by 20 weeks and the costal margin (xiphisternum) by 34–36 weeks (**Fig. 2**). In case of decreased maternal blood flow, uterine blood flow decreases, and uterine vasoconstriction occurs. The whole blood volume of the mother passes through the uterus every 10 minutes. During maternal shock, blood flow is preferentially redirected to the maternal central circulation away from the maternal periphery and the uterus. This can lead to fetal distress while the mother remains in compensated shock with no obvious vital sign derangement, underscoring the need for fetal monitoring.

CLINICAL PRESENTATION

- *Blunt trauma* is the most common cause of injury, most often due to domestic violence and MVC. While the abdominal wall and uterus act as a buffer to protect the fetus, complications can include uterine rupture, uterine contractions, premature delivery, placental abruption (the most common cause of fetal loss from blunt trauma), fetomaternal hemorrhage (FMH), and direct fetal injury.
- *Penetrating injury* carries a higher risk of fetal mortality than blunt trauma. The trajectory of the wound must be examined via entrance–exit holes for the possibility of visceral organ injuries. Most stab wounds require extensive exploration.
- *Domestic violence* is the most common type of trauma in pregnant women (8,307/100,000 live births). Domestic violence should be considered with any injury in pregnant women. Risk factors include abuse, young age, poverty, level of education, unwanted pregnancy, and ethnicity. It is important to educate those who provide health services to pregnant women to detect and treat domestic violence. Each emergency department should have a written protocol for sexual abuse assessment.
- *Burns* are rare and the exact incidence is unknown. In severe burns, the mother and fetus are at risk for insensible fluid loss, hypoxia, and sepsis. In case of burns over 60% of the mother's total body surface area, fetal mortality is over 50%. In this case, the caesarean section should be considered as soon as possible.
- *Falls*: One in four pregnant women falls at least once during pregnancy. With the progression of pregnancy, the increased joint elasticity and weight gained in pregnancy may contribute to balance problems. Falls occur more often in the third trimester. Apart from minor lower extremity injuries, preterm labor, placental abruption, fetal distress, fetal hypoxia, uterine rupture, or even fetal death in pregnant women can occur.

EVALUATION

In the management of the pregnant trauma patient, the priority must be on the mother. Evaluation and management are guided by the severity of the trauma and influenced by the gestational age. Fetal evaluation should be done after the primary survey of the mother is completed. Conditions such as placental abruption, fetal trauma, fetal-maternal hemorrhage, Rh (rhesus) isoimmunization, and preterm labor should be evaluated while considering the physiological and anatomical changes in pregnant women. Employing a multidisciplinary approach that includes a trauma surgeon, obstetrician, and neonatologist may be beneficial.

Primary Survey

Every woman of childbearing age should be considered pregnant until proven otherwise. For pregnant patients after trauma, like other patients, ventilation and oxygenation should be optimized after the airway is secured, the bleeding focus should be controlled, and adequate circulation should be restored or maintained.

Airway: Laryngeal edema, mucosal congestion, decreased airway diameter, decreased residual capacity secondary to diaphragm compression, and decreased lower esophageal sphincter tone increasing the risk of aspiration may cause difficulty in airway management, especially after 20 weeks of gestation. In a study by McKeen, 5.7% of intubations were considered difficult. If intubation is pursued, it should be performed by an experienced person and a smaller sized endotracheal tube is preferred in anticipation of airway edema. Alternative airway techniques should be performed after two unsuccessful attempts. As with all trauma patients, it is important to protect the cervical spine if there is a concern for a possible spinal injury.

Breathing: Oxygen saturation should be kept above 95%. Chest tube insertion should be above 1–2 intercostal space higher than the typical fifth intercostal space due to diaphragm elevation during pregnancy.

Circulation: Two veins should be cannulated with a large caliber (14–16 gauge) catheter preferably cephalad to the diaphragm. Maternal hypotension should be treated aggressively; otherwise, it may cause fetal distress. Vital signs may not change until 15–20% of the total blood volume is lost. If transfusion is necessary, crystalloid fluid and blood products (preferably O negative in an emergency situation) should be given initially. Massive transfusion, if indicated, should be administered in a 1:1:1 (fresh frozen plasma, platelets, and packed red blood cells) ratio.

The use of vasopressors is discouraged in resuscitation because they reduce fetal blood flow from vasoconstriction of uteroplacental vasculature. Vasopressors should only be used if there is a transient need to stabilize blood pressure during volume resuscitation. The uterus should be positioned to the left side either manually or by providing a 15–30° tilt to the right side of the patient due to the vena cava vein compression, especially in the second and third trimester; laying in the left lateral recumbent position is also reasonable. *Tranexamic acid* is safe for the fetus in severe bleeding but has not been found to reduce maternal mortality.

In some studies, *viscoelastic assay thromboelastography (TEG)* and *rotational thromboelastometry (ROTEM)* tests have been shown to increase survival for the severely injured patient, provide guidance for blood component transfusion in trauma, and decrease postpartum hemorrhage compared to massive transfusion. Fetal well-being must be evaluated before the secondary survey.

Cardiopulmonary Resuscitation

Pregnant cardiac arrest cases require a multidisciplinary approach. The obstetric and neonatal team should be involved if possible. If the gestational age is over 20 weeks, the uterus should be positioned to the left. Chest compression, ventilation, and defibrillation techniques are unchanged. Cardioversion is considered safe in pregnancy.

Perimortem Cesarean (Resuscitative Hysterotomy)

Perimortem cesarean or resuscitative hysterotomy is a rarely performed yet potentially life-saving procedure in the resuscitation of a pregnant woman and fetus (over 20–24 weeks gestation) in cardiac arrest. Aortocaval pressure from uterine compression begins after the 20th week) potentially disrupting the mother's hemodynamics. If the spontaneous circulation of the pregnant cannot be achieved within 4 minutes, the newborn should be delivered by cesarean section within the next minute (within 5 min of cardiac arrest). Cardiopulmonary resuscitation should be continued without interruption. The chance of spontaneous circulation increases when blood flow is redistributed centrally to the mother away from the uterus. Therefore, early resuscitative hysterotomy is recommended to increase survival for both mother and fetus.

Secondary Survey

Once the patient is stabilized, the head-toe secondary survey should be conducted. Use of a seat belt (directly over the abdomen? no restraints?) should be asked. *C*omplications of pregnancy, *o*bstetric history, *d*ating method and estimated due date, and *e*vent details (e.g., bleeding, fetal movement) (*CODE*) should be questioned.

Physical Examination

- *Gestational age* can be assessed using bedside ultrasound (biparietal diameter or femur length), patient history, medical record, or measuring the distance from the symphysis pubis to the top of the fundus *(1 week/cm)*. On bedside ultrasound, a femur length ≥ 4 cm suggests fetal viability (4 cm correlates with 22–24 weeks gestational age).
- *Abdominal examination* can be unreliable in pregnant patients because of changing organ positions and a lower likelihood of exhibiting peritoneal signs because the uterus can stretch the abdominal wall, further distancing sources of inflammation from the peritoneum. Evaluating for uterine tenderness, vaginal bleeding, and contraction frequency can be helpful. Uterine tenderness and rigidity may be a sign of *placental abruption*, or intermittent pain may also be a precursor of possible labor. In the case of *uterine rupture*, fetal parts may be palpated and the uterus may be tender. However, it may not be detected during an abdominal examination.
- *Vaginal examination* can help identify pathologies such as an open pelvic fracture (concomitant vaginal laceration), placental abruption or pelvic fractures (vaginal bleeding), or rupture of membranes (clear fluid). Initially, the vagina should be examined externally (laceration, ecchymosis, etc.). The physician should avoid frequent examinations. The bimanual examination should evaluate for bleeding from the vagina or uterus, injury to the pelvic bone, and amniotic fluid leakage. Caution should be exercised when evaluating pelvic bony fractures to avoid harm to the examiner. To prevent massive exsanguination, pelvic examination after 20 weeks' gestation should not occur prior to ruling out placenta previa by ultrasound.

Fetal Assessment

Gestational age should be estimated because preterm births under 23 weeks will most likely result in fetal death or severe neurocognitive delays. Presumed viability is generally considered ≥24 weeks. Fetal heart rate (FHR) is important for assessing fetal well-being and the adequacy of maternal blood flow. Abnormal FHRs can occur with maternal hypotension or compensated maternal shock, maternal hypoxia, placental abruption, uterine rupture, or direct fetal injury. It is sufficient to document the FHR before 23 weeks of gestational age. Continuous FHR monitoring and uterine contraction monitoring should be performed in pregnancies 23 weeks onward for at least 4 hours. It is important to recognize that fetal distress may be the first and only presenting sign of material distress.

INVESTIGATIONS

Laboratory Tests

Laboratory tests for pregnant patients are similar to those of other trauma patients and include coagulation studies and type and screen (which evaluates Rh status). All at-risk pregnant women should be given Rh-negative 300 μg anti-D Ig (which protects against 30 mL fetomaternal hemorrhage) within 72 hours. If the mother is Rh-negative, the *Kleihauer–Betke (KB) test* may be performed to determine the amount of FMH and correct dose of Rh immunoglobulin (IG) (in rare cases, the patient may require >300 μg of Rh IG).

Diagnostic Imaging

- *Ultrasound* is inexpensive, reproducible, easily performed at bed side with no radiation exposure to mother or fetus. Ultrasound can be useful in detecting intraperitoneal bleeding after trauma using the FAST (focused assessment with sonography for trauma) exam. It allows evaluation of FHR (normal 110–160 bpm), gestational age, placenta location (previa?), placenta abruption (sensitivity: 24%; specificity: 96–100%), and fetus presentation as well

(cephalad, breech). Ultrasound does not reliably rule out placenta abruption. The use of ultrasound (abnormal FAST exam) may obviate the need for diagnostic peritoneal lavage or the harmful ionizing radiation from computed tomography (CT).

- *Computed tomography*: While the biggest concern is the radiation exposure to the fetus, in the setting of trauma, CT should not be delayed for this reason. Many guidelines report that <50 mGy is not associated with any fetal loss or abnormality during pregnancy although it may cause a 2% increased risk of cancer in the fetus. CT can be used to detect complicated bone fractures, organ and vascular injuries, and placenta abruption which are difficult to detect with ultrasound. The use of contrast is not contraindicated for either mother or fetus. Like ultrasound, limitations of CT include missing diaphragm and hollow viscous injuries. However, unlike ultrasound, a CT scan can identify specific organ injuries and can identify pathology in the retroperitoneum and pelvis.

Magnetic resonance does not cause radiation exposure and may be preferred in case of placenta abruption and evaluation of intrauterine pathologies in stable patients, but its use is limited because of availability and the time required to obtain study away from the emergency department.

PREGNANT PATIENTS NEEDING FETAL MONITORING

Trauma is common in pregnancy. Maternal injuries are mostly due to falls, assaults, and road traffic accident. Fetal death is more frequent than maternal death due to trauma. Observing the pregnant patient in emergency and fatal monitoring is beneficial. A multidisciplinary team in the observation unit is required to care for the mother as well as the fetus. The initial findings due to trauma may be detected within 2 hours or may require admission for prolonged observation. During observation, any vaginal bleeding uterine tenderness or contractions should be noted. These findings may adversely affect the pregnancy. Fetal death after trauma is mostly due to placental abruption.

Cardiotocographic Monitoring

Cardiotocographic monitoring (CTM) should be started soon after trauma to a pregnant woman. Even after minor injuries to the mother, CTM should be initiated as soon as possible. Any changes in the fetal physiology should be noted. The American College of Obstetricians and Gynecologists and Eastern Association for the Surgery of Trauma (EAST) guidelines recommend CTM in all pregnant women greater than 20-week gestation who suffer trauma. CTM should be for a minimum of 6 hours. Monitoring parameters should include FHR, vaginal bleeding, uterine tenderness, significant maternal injury, or rupture of the amniotic membranes. Initially, a patient's CTM should be done for 4–6 hours; if no maternal obstetric symptoms have developed and CTM is reassuring, traumatic complications to the fetus can be ruled out with high sensitivity. CTM should be extended for 24 hours if nonreassuring, and the following features are noted:

- Significant abdominal pain
- Uterine tenderness
- Vaginal bleeding
- Contraction frequency >1/10 minute (during the first 6 h of monitoring)
- Rupture membrane
- Abnormal FHR pattern
- High-risk mechanism of injury
- Serum fibrinogen < 200 mg/dL.

The FHR monitoring is largely used as a screening tool to indicate when more definitive instigations are required, such as nonstress test or biophysical profile. Normal FHR tracing is associated with a good outcome, but abnormal FHR does not always indicate fetal injury. If CTM findings are nonconclusive, ultrasound can assist in the diagnosis of abruption and evaluate fetal well-being. Fetal ultrasound is helpful in direct visualization of the heartbeat, gestational age, presentation, amniotic fluid volume, placental integrity, biparietal diameter, abdominal circumference, and femur length, allowing gestational age and weight to be estimated, essential for planning if delivery is considered. Factors that should be taken into consideration when deciding to observe an injured pregnant patient are the severity of the injuries, gestational age, and viability of the fetus. Maternal health should always take priority over interventions for the fetus.

SPECIFIC CONDITIONS OF PREGNANCY TRAUMA

- *Uterine rupture* is rarely seen after trauma (0.6%), most often after motor vehicle accidents from pelvic fractures hitting the uterus, and considered in the case of abdominal pain, vaginal bleeding, fetal death or abnormality in the FHR, palpation of the fetal parts, or maternal shock. The treatment is primary closure of the laceration or laparotomy depending on severity.
- *Placental abruption* involves disruption of the placenta from the uterus. It is the leading cause of fetal death after trauma. Because placental abruption can occur from deceleration injuries, it may occur in the absence of signs of physical trauma to the abdominal wall. Placental abruption is a clinical diagnosis, not dependent on ultrasound findings, and should be suspected in pregnant women with vaginal bleeding, tenderness in the uterus and abdomen after abdominal trauma, or nonreassuring fetal heart monitoring which is the most sensitive predictor. Vaginal bleeding may not be present. Placental abruption can result in leakage of thromboplastin into the maternal circulation leading to disseminated intravascular coagulation.
- *Preterm labor* refers to delivery before 37 weeks. Preterm labor should be considered in case of symptoms such as four uterine contractions per hour with cervical changes, cramp-like abdominal pain, pressure sensation in the pelvic area, and vaginal bleeding.
  - *Antenatal steroids* are recommended in pregnant women with gestational age of 34 weeks up to 36 weeks 6 days with preterm labor risk or rupture of membranes to accelerate fetal lung maturation.
  - *Tetanus-diphtheria-acellular pertussis (Tdap)* is not contraindicated in pregnancy.

SUMMARY

Management of trauma in pregnancy needs awareness of anatomic and physiologic changes. A team of relevant specialists is required with exceptional coordination. The salient points of management are described below and shown in **Flowchart 1**.

- Anatomic and physiologic changes develop during pregnancy.
- The most common causes of trauma are domestic violence and MVC. Domestic violence should always be considered in pregnancy.
- All patients of childbearing age should be considered pregnant until proven otherwise and managed accordingly.
- The priority is to stabilize the mother. Consultation with obstetrician and neonatologist is recommended.
- Aspiration risk is higher in pregnant women. Edematous mucous membranes can make airway management challenging. The insertion of a nasogastric/orogastric tube should be considered for unconscious patients in the absence of contraindications.
- Oxygen saturation should be maintained >95%.
- If indicated, chest tube insertion should be at the third or fourth intercostal space.
- The uterus should be shifted to the left to prevent compression on the inferior vena cava in pregnancies >20 weeks.
- In patients with gestational age ≥23 weeks, after stabilization, the FHR should be evaluated and monitored for at least 4 hours with obstetrician consultation in case of uterine tenderness and abnormalities in contractions, abdominal pain, vaginal bleeding, rupture of amniotic membrane, abnormality of FHR, or high-velocity trauma.
- In pregnant trauma patients with concern for injury, a CT scan should not be postponed for concern of fetus radiation exposure.
- If the spontaneous return of circulation cannot be achieved within 4 minutes and if the estimated gestational age is ≥20–24 weeks, the perimortem cesarean section should be performed within 5 minutes of arrest.
- Anti-D IG should be given to all Rh-negative pregnant trauma patients.
- Tetanus prophylaxis should be updated, if indicated.

Assessment of maternal status

Stable?
Airway secure? Hemodynamically stable?
Normal mental status?

Yes

Follow ATLS algorithm

Major injury

Yes

- Consult OB
- Get history of the patient
- Do physical examination including pelvic
- Estimate gestational age
- ≥ 23 weeks fetal heart monitoring (at least 4 h)
- UC ≥6/h consider admission
- Do imaging and labs tests
- Check the specific injuries (such as preterm labor, uterine rupture, FMH, etc.)
- Consider anti-D immunoglobulin if the patient is Rh negative, tetanus prophylaxis

No

- *Ex*: Bruising, laceration, etc. (ISS:0)
- Assess the fetus
- Can be evaluated without imaging and laboratory tests
- Consider anti-D immunoglobulin if the patient is Rh negative and tetanus prophylaxis

Admission Criteria
- Vaginal bleeding
- Hypovolemia
- Abdomen tenderness, pain or cramping
- Uterine tenderness
- Abnormality of fetal heart rate
- Leaking of amniotic fluid

No

Start Advanced Trauma Life Support
- Airway-cervical protection
- Breathing ... Maintain >95% ... insert chest tube into the 3rd-4th intercostal space if Ptx or Htx
- Circulation-bleeding control—manually displace the uterus
- Disability
- Exposure
- Call trauma team, OB, neonatologist as soon as possible
- IV access (two lines with 14–16 gauge), give IL lactated ringers, Rh negative blood product, if needed
- Early MTP activation, if needed
- FAST examination
- If >23 week + no ROSC within 4 minutes, PMCD during CPR
- After stabilization check the fetus viability

Secondary Survey
- Assess all injuries in detail
- Detemine gestational age
  >23 week continue fetal heart rate and uterine contraction monitoring (if the patient stable and normal CFHR ...4 hours if not admitted to the hospital)
- Perform pelvic examination (for vaginal bleeding, rupture of membranes, cervical dilatation and effacement, fetal presentation...)
- Do the diagnostic tests and treatment without concern about the fetus
- *CODE*: Complication of pregnancy, obstetric history, dating method and estimated due date, event details (e.g., bleeding, movement)
- *Lab*: CBC, coagulation tests, type and match cross, fibrinogen
- Consider anti-D immunoglobulin if the patient is Rh negative, tetanus prophylaxis

(ATLS: advanced trauma life support; CBC: complete blood count; CFHR: continuous fetal heart rate; CPR: cardiopulmonary resuscitation; FAST: focused assessment with sonography for trauma; FMH: fetomaternal hemorrhage; Htx: hemothorax; OB: obstetrician; MTP: massive transfusion protocol; MVC: Motor vehicle collision; PMCD: perimortem cesarean delivery; Ptx: pneumothorax; ROSC: return of spontaneous circulation; UC: uterine contraction)

FLOWCHART 1: Summary of management of trauma in a pregnant patient.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Basics of Wound Management

Sukhdeep Singh, Aditya Agarwal, Devendra Richhariya

INTRODUCTION

One of the most common problems seen and treated in the emergency department (ED) is traumatic lacerations of the skin. Because of 24-hour access, the ED remains the most reliable place for effective, safe, and clinically competent wound care. Avoidance of infection and esthetically appearing repair are the most desired outcomes by the physician as well as by the patient. A disciplined approach to wound management will improve patient care and satisfaction. This chapter describes the current and fundamental aspects of basic wound management, which include a focused history, methodical physical examination, meticulous wound preparation, effective wound closure techniques, and pertinent postrepair care instructions

What is a Wound?

A wound is a discontinuity and breakage of the normal structure and function of the skin. An acute wound has normal wound physiology and the healing follows the normal stages of wound healing, whereas a chronic wound does not heal in an orderly manner and is physiologically impaired.

CLASSIFICATION OF WOUND

Acute wounds heal as anticipated and proceed through a normal, orderly, and timely reparative process that results in sustained restoration of anatomic and functional integrity. Chronic wounds do not heal as anticipated and fail to proceed through this process or proceed through the process but fail to establish a sustained anatomic and functional result. Chronic wounds may get stuck in any of the phases of wound healing for greater than 6 weeks.

Acute Wounds

Lacerations are usually caused by a simple shearing force (e.g., from a knife or glass). This is a simple dividing of tissue. There is little kinetic energy imparted to the tissue, so the surrounding tissue injury is minimal, although glass injuries can cause significant damage to soft tissues. Partial avulsion lacerations are complicated lacerations in which the dermis has undergone a significant separation from the superficial fascia, creating a "flap of dermis." This wound can compromise the flap of tissue because its remaining blood supply is derived from the intact dermal portion at the base of the flap. In random flaps, clinical experience has resulted in the observation that the ratio of flap length to width is critical for complete flap survival. This rule varies from anatomic site to anatomic site. Tension injuries are a result of a blunt or a semiblunt object striking the skin at an angle. Often a triangular flap is created, and the blood supply is interrupted on two sides of the flap. Crushing or compression injuries occur when a relatively blunt object strikes the skin at a right angle. These lacerations often have ragged or irregular edges, and a significant amount of kinetic energy is transferred to the surrounding and underlying tissue. Shearing force is a mechanical force that is parallel rather than perpendicular to an area. This may cause a triangular-shaped flap or tunneling.

Puncture Wounds

Puncture wounds account for 3– 5% of all traumatic injuries presenting to pediatric emergency rooms. Most are on the plantar aspect of the foot. Puncture wounds are commonly caused by nails but can also occur via envenomation, human and animal bites, iatrogenic causes, and foreign bodies such as wood, metal, glass, and plastic. One must be vigilant to suspect a retained foreign body if the mechanism of injury suggests it.

Bite Wounds

Bite wounds are one of the most common types of trauma. The majority of such wounds are caused by dogs, cats, and humans and often involve young children. The mechanism of injury can frequently cause crushing, tearing, or avulsion of tissue and cause devitalized tissue with significant bacterial contamination.

Abrasions

Abrasions are skin wounds caused by a tangential force to the epidermis and dermis. The skin surface is forced against a resistant surface and essentially scraped away. Varying thicknesses of the epidermis and/or dermis can be lost, and deeper abrasions can occur. Abrasions can cover a significant amount of the total body surface area and are frequently impregnated with grass, asphalt, and dirt.

Burns

A burn is a damage to the skin and underlying structures caused by excessive heat or caustic chemicals. Burns are usually divided into three depths of tissue injury. Superficial or epidermal burns, typified by the common sunburn, are confined to the epidermis. Partial-thickness burns involve the epidermal layer and part of the dermal layer (formerly referred to as second-degree burns). This can further be divided into two depths of partial-thickness burns: superficial partial thickness and deep partial thickness. Superficial partial-thickness burns involve destruction of the epidermis and the upper one third of the dermis. Blisters form in this type of burn. Deep partial-thickness burns destroy the epidermis and most of the dermal layer. As a result, the wound is white and dry. Full-thickness burns are burns in which the epidermis, dermis, and epidermal appendages have been destroyed. This burn is waxy and white. Subdermal burns involve the destruction of the outer epidermis and dermis and extend to the tissue below, including fat, tendon, muscle, and bone. Burn severity is determined by the depth of burn, total body surface area burned in percent, location of the burn, and patient age. The rule of nines is a commonly used tool to divide the surface of the body into segments of 9%. Age is a major factor in determining the prognosis of the burn, with infants and elderly individuals at higher risk for a mortal event. The depth of heat or caustic injury depends upon the quantity of heat exposure and depth of heat penetration. Location of the burn with respect to anatomic function and depth of overlying skin also play a role in the severity of the burn. Initial evaluation of a burn patient in the emergency department may underestimate the severity of the burn. The wound may involve deeper structures than can be estimated upon primary evaluation. Burns are dynamic and can evolve into deeper wounds over time depending upon the initial injury and subsequent environmental insults.

Chronic Wounds

Chronic wounds arise from acute wounding if appropriate interventions are not initiated or if factors known to delay healing predominate. Chronic wounds often occur in individuals who have underlying comorbidities, including advanced age, peripheral vascular disease, malnutrition, diabetes, chronic steroid use, or other chronic diseases that impair tissue healing. Chronic wounds do have differences at the cellular level that distinguish them. Chronic wounds do not have clot formation, which diminishes the growth factors present in platelets and "primes the wound for healing." Debridement can improve healing by exposing viable tissue. Most chronic wounds are colonized with bacteria and thus require more macrophages and immune response to be mounted to clear away debris, contributing to prolonged healing time. Increased epithelialization, which increases scar friability and the need for increased angiogenesis, can also prolong wound healing. Chronic wounds generally have extensive tissue loss and extensive tissue remodeling.

Pressure Ulcers

A pressure ulcer is a disruption of the normal anatomic structure and function of skin that results from an external force associated with a bony prominence that does not heal in an orderly and timely fashion. Pressure ulcers can be categorized according to the National Pressure Ulcer Advisory Panel definitions.

- *Stage 1*: An observable pressure-related alteration of intact skin, with indicators such as an adjacent or opposite area on the body, which may include changes in one or more of the following: skin temperature (warmth or coolness), tissue consistency (firm or boggy feel), or sensation (pain, itching). In lightly pigmented skin, the ulcer appears as a defined area of persistent redness, whereas in darker skin tones, the ulcer may appear with persistent red, blue, or purple hues.
- *Stage 2*: Partial-thickness skin loss involving the epidermis, dermis, or both
- *Stage 3*: Full-thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to but not through the underlying fascia
- *Stage 4*: Full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures

Diabetic Foot Ulcers

Diabetic foot ulcers typically occur on the plantar aspect of the foot in areas prone to excessive pressure. They generally present as symmetric, round, puncture-appearing wound cavities with a clean wound bed and callous around the wound. The atherosclerotic occlusive disease is a factor in the development of malperforate ulcers; however, the combination of autonomic neuropathy, infection, and autonomic dysfunction, which produces anhidrosis and hyperkeratosis, also contributes to the development of this wound. Diabetic patients typically manifest lesions in the distal popliteal and tibioperoneal arteries, with usual sparing of the dorsal foot.

Venous Insufficiency Ulcer

Venous insufficiency ulcers are typically partial-thickness wounds resulting from chronic venous insufficiency. They are usually located between the mid-calf and malleolus. They have shaggy, irregular borders and often have heavy exudates. There is a brownish pigmentation of the skin secondary to extravasated hemoglobin and loss of subcutaneous fat, leading to lipodermatosclerosis. Although there is a unanimous agreement that venous ulcers are due to venous stasis and back pressure, there is less consensus as to the exact pathophysiology that leads to ulceration and impaired healing.

Ischemic Wounds

Ischemic wounds are generally atrophic and can lead to necrosis of the affected part. The wounds are generally shallow, painful, have a pale base, and are usually caused by a decrement in blood supply to the affected body part. The wounds are commonly present on the most distal portions of the extremities, although more proximal locations are encountered. Other signs of peripheral ischemia, such as dryness of the skin, hair loss, scaling, and pallor, can be present. The occlusive disease is often manifested in the superficial femoral system, often in the adductor hiatus or Hunter's canal. This brief introduction of the anatomy and types of wounds will help in the evaluation of wounds seen in the emergency department. Knowledge of skin structure can help to define the

depth of injury and informs the clinician of the extent of repair that must occur to restore tissue health.

WOUNDS COMMONLY MANAGED IN EMERGENCY

Clean lacerated wound or simple laceration: These are clean-cut wounds with clean margins; no dirt or contamination is present in these wounds. These could be superficial (involving the superficial layers of the skin) or deep (involving all layers of the skin). Simple lacerations may be cleaned and closed primarily with tapes, staples, or sutures (**Fig. 1**).

Complicated laceration: These lacerations involve deeper layers of tissue such as muscle, tendon, joints, nerves, or blood vessels. Complicated lacerations may need cleansing and debridement of the wound. It is not uncommon for the irregular skin edges or skin at sites where such lacerations meet to break down, and therefore plastic surgical techniques may be needed to provide an acceptable cosmetic and functional result (**Fig. 2**).

Contaminated laceration: These may be simple or complicated lacerations that are contaminated with dirt or saliva (bites), foreign bodies, and other contaminants. These wounds have the potential to become infected or result in post-traumatic tattooing (**Fig. 3**).

Large-tissue defect: This can result from traumatic wounds or the need to remove devitalized tissue due to infection (e.g. Fournier's gangrene). Once the debridement is completed, the wound needs special care until the wound bed allows for skin graft or flap closure.

ASSESSMENT OF THE WOUND

After the initial evaluation of vitals, the assessment of lacerations includes determination of time and mechanism of injury, a history of allergies, the status of immunization (tetanus, hepatitis, and others), the extent of the wound, and the presence of a foreign body and the type of injury—simple or complicated (**Table 1**). The parameters given below may impact the plan for wound repair and its final outcomes and must be evaluated carefully prior to initiating the management of the laceration.

Location and time of injury: In the case of head and facial injuries, the healing is relatively independent from the time of injury to the time of repair. They can be closed up to 24 hours later if the injury is reasonably clean. There is no ideal time between injury and time of laceration, but a repair must be attempted at the earliest.

Mechanism of injury: Understanding the mechanism of injury helps to define the type of laceration (simple or complicated), the presence of a foreign body (contaminated), and thus the prognosis for the development of infection or scarring. Injuries such as those caused by compressive trauma may have a component of crush injury and thus have the highest risk of infection. Other considerations include:

- Bite wounds which must be evaluated for associated injuries and risk of infection
- Crush injuries which may involve devitalized tissue that must be debrided to decrease the risk of infection
- Stab wounds which should be evaluated for depth; surgical consultation may be necessary if the underlying structures (e.g., fascia) have been penetrated or damaged.

FIG. 1: Clean lacerated wound on the forehead. ***(For color version, see plate 43)***

FIG. 2: Complicated laceration of the face. ***(For color version, see plate 43)***

FIG. 3: Post-traumatic tattooing due to inadequate removal of foreign bodies. ***(For color version, see plate 44)***

Presence of foreign body: Identifying and removing foreign bodies are important because retained foreign bodies increase the risk of delayed wound healing and infection. Any foreign body that can be easily seen should be removed. If the object can be reliably palpated, the wound should be explored to make an attempt to remove it, provided there is no risk to underlying critical structures. A nonirritant foreign body, such as glass or metal, that is not in a critical area (e.g., a joint space) or adjacent to a vital structure (e.g., major blood vessel) and not causing any ongoing irritation may be left in place if unable to be removed, and the wound sutured. Irritant material, such as wooden splinters, can be a source of later infection and should be removed even if it requires exploration of the base of the wound. Direct wound inspection may fail to detect all foreign bodies, particularly if the base of the wound cannot be seen. Deep wounds, wounds on the head or foot, and wounds due to trauma in a motor vehicle accident or due to glass cut injuries are more likely to contain retained glass. Radiologic evaluation by a plain X-ray is helpful if the foreign body is radiopaque and should be considered as an adjunct to visual inspection if history indicates a possibility of a foreign body or debris (**Figs. 4A** to **C**).

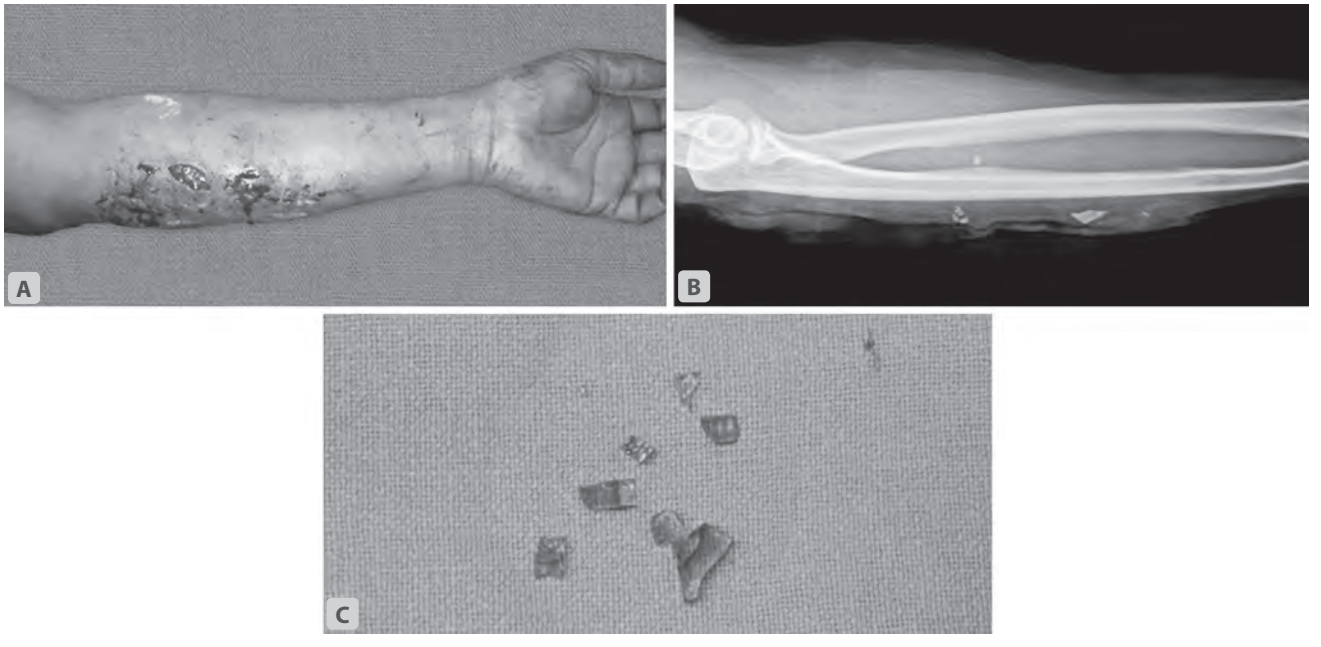
Extent of wound: The base of the wound must be identified whenever possible. Injury to underlying structures, such as a fracture beneath a laceration or penetration of joint space in a finger laceration, has significant implications for management and must therefore be identified.

Neurovascular or tendon injury: Careful assessment of circulation and sensation, including two-point discrimination in hand injuries, will identify the neurovascular injury. Any wound overlying a tendon should be assessed for tendon function and the base of the wound should be carefully explored, with a tourniquet and loupes if necessary, to identify an injured tendon. Tendons must be explored in movement or as the position of the body during the injury, i.e., an injury might be missed if a laceration occurred with the finger in flexion and the wound is inspected only with the digit in extension. Similarly, the ends of a tendon that has been completely severed may retract from view. Wounds that involve joints, nerves, tendons, and major blood vessels require operative exploration.

Investigations: Investigations are needed if there is an underlying deeper tissue injury or nonvisualization of the base of the wound which may need operative exploration. These investigations may include complete blood counts, coagulation profile, viral markers, a plain X-ray, CT scan/MRI scan of the local region to evaluate and exclude fractures, neurovascular injuries, and any foreign body.

TABLE 1: Clinical evaluation of a patient with a laceration

History	*Clinical examination*	*Local examination*
Time of injury	Vitals	Depth of laceration, and extent of the wound
Mechanism of injury	Obesity	Neurovascular or tendon injury
Immunization status for rabies and tetanus	Peripheral arterial disease	Visualization of the base of the laceration
Allergies to antibiotics, anesthetics, latex, and other drugs	Malnutrition	Presence or absence of foreign body
Ongoing medical therapy and concomitant illnesses	Hypertension, chronic renal failure	Special considerations (injury near/to eye, animal bites)
Any implants (for imaging purposes)	Tendency to form keloids	Cosmetic significance of the wound



FIGS. 4A TO C: (A) Patient involved in road traffic accident with multiple cut injuries to the forearm with retained glass pieces; (B) X-ray showing multiple radiopaque shadows suggestive of retained glass particles; (C) Multiple glass pieces removed from the wound. ***(For color version, see plate 44)***

WOUND PREPARATION

The management of lacerated wounds has two primary aims: (1) *A good approximation to give a functional and cosmetically acceptable resultant scar* and (2) *minimizing infection.* Once the patient has been examined and necessary investigations conducted, the next steps include:

Irrigation: It is an important means of minimizing wound infection as it washes out any soil or small foreign bodies that may remain and reduces the bacterial load. However, irrigation is not mandatory and may be avoided in low-risk wounds, especially those in well-vascularized locations. Irrigation should be performed after adequate local anesthesia has been administered or peripheral nerve block has been performed. Consideration must be given to the irrigation solution, pressure, and volume. Isotonic (normal) saline is frequently used for uncomplicated wounds, when easily available; warmed saline may offer a comfort advantage to room-temperature irrigation. Other antiseptic solutions such as chlorhexidine and hydrogen peroxide are no longer used as they may be toxic to wound tissue, impede wound healing, or have other adverse effects.

Hair removal: Hair does not need to be shaved in most cases and is best trimmed to avoid interference with wound closure or knot formation. Lubrication to comb the hair away from wound margins or simple clipping with scissors is all that is necessary in most cases. Shaving flush to the skin level increases the risk of infection. In case of lacerations around the eyebrow, great care must be taken to maintain the hairline of the eyebrow to ensure cosmesis and this hair must not be shaved.

Preoperative antibiotics and immunization: For clean lacerated wounds stitched within the first 6 hours of injury, no oral or injectable antibiotics are needed. In the case of contaminated wounds, broad-spectrum coverage for both gram-positive and gram-negative bacteria should be given.

Tetanus toxoid: Tetanus immunization must be done, especially for patients who have either never been vaccinated (250 U of intramuscular human tetanus immune globulin) or did not have tetanus shots in the last 10 years [intramuscular or subcutaneous tetanus toxoid (0.5 mL)] (**Table 2**).

Rabies: If the laceration is due to the bite of a wild animal, administer rabies prophylaxis. If a domestic animal is the reason, check the rabies immunization status and quarantine the animal for 10 days.

Pain relief: The author suggests the use of local anesthetic agents such as xylocaine to improve patient cooperation and minimize patient discomfort during examination and surgical procedure (**Table 3**). Procedural or conscious sedation should be considered for the repair of wounds in areas that require the patient to be still (e.g., wounds that are near the eye or mouth) or in patients whose inability to cooperate jeopardizes the adequacy of repair (**Table 4**).

TABLE 2: Tetanus prophylaxis in routine wound management (>18 years)

Tetanus immunization	*Clean minor wound*		*All other wounds*	
	Td	*TIG*	*Td*	*TIG*
<3 dose or uncertain	Yes	No	Yes	Yes
>3 dose				
Last dose within 5 years	No	No	No	No
Last dose within 5–10 years	No	No	Yes	No
Last dose >10 years	Yes	No	Yes	No

Note: All other wounds—contaminated wounds (feces, dirt, saliva, soil), puncture wounds, avulsions, burns, crush injuries, and frostbite

(Td: tetanus-diphtheria toxoid; TIG: tetanus immune globulin)

TABLE 3: Agents used for local anesthetic.

Agent	*Onset of action*	*Duration of action*	*Dose*
Lidocaine	Fast	1–2 h	4.5 mg/kg of 1%
Lidocaine with epinephrine	Fast	2–4 h	7 mg/kg of 1%
Bupivacaine	Intermediate	4–8 h	2 mg/kg of 0.25%
Bupivacaine with epinephrine	Intermediate	8–16 h	3 mg/kg of 0.25%
Procaine	Slow	15–45 min	7 mg/kg
Procaine with epinephrine	Slow	30–60 min	9 mg/kg

TABLE 4: Agents for procedural sedation.

Medication	*Dose*	*Route*
Fentanyl	1–2 µg/kg	Intravenous
Midazolam	0.02–0.1 mg/kg (adult); 0.05–0.15 mg/kg (child)	Intravenous
Ketamine	1–2 mg/kg (IV); 2–4 mg/kg (IM)	Intravenous/ intramuscular
Propofol	1 mg/kg	Intravenous
Etomidate	0.1–0.2 mg/kg	Intravenous

MATERIALS USED FOR CLOSURE OF LACERATIONS

Sutures

Sutures may be monofilamentous (Prolene or Ethilon) or multifilamentous (silk). The designation for suture strength is the number of zeros. The higher the number of zeros (1-0 to 10-0), the smaller the size and the lower the strength. They can also be defined as absorbable (dissolve within 14–180 days) or nonabsorbable. Types of suture material used in laceration are summarized in **Table 5**.

Staples

Staples can be used best in clean lacerated wounds of the scalp, trunk, arms, and legs, especially in a mass causality situation. They are best avoided on the face or the neck due to poor approximation of the edges and thus poorer cosmetic

TABLE 5: Choosing appropriate suture material for body region and their removal.

Body part	*Suture material (skin)*	*Suture material (deep)*	*Closure*	*Suture removal*
Scalp	3-0 or 4-0 NA	4-0 SA	Single tight layer	7–12 d
Ear	6-0 NA	5-0 SA	Interrupted	4–6 d
Eyebrow	6-0 NA	4-0 or 5-0 SA	Layered closure	4–6 d
Eyelid	6-0 NA	–	Single-layer horizontal mattress	4–6 d
Lip	6-0 NA	4-0 silk/SA (mucosa)	Three-layer closure	4–6 d
Oral cavity	–	4-0 SA	Layered closure if tongue muscles are involved	7–8 d
Face	6-0 NA	4-0 or 5-0 SA	Layered closure if full-thickness laceration	4–6
Neck	5-0 NA	4-0 SA (subcutaneous)	Two-layer closure for best cosmetic results	4–6
Trunk	4-0 or 5-0 NA	4-0 SA (subcutaneous)	Single or layered closure	7–12
Extremities	4-0 or 5-0 NA	3-0 or 4-0	Splint if wound over the joint	7–12
Hand and Feet	4-0 or 5-0 NA	–	Only skin closure	7–12
Nailbed	5-0 SA	–	Replace nail until the cuticle	Allow to dissolve

[NA: nonabsorbable suture (nylon, polypropylene); SA: synthetic absorbable suture]

results. In patients who may need computed tomography or magnetic resonance imaging as part of their care, staples are best avoided for scan artifacts and possible avulsion by the powerful magnetic field.

Many stapling devices are commercially available. Units that hold between 5 and 25 staples can be purchased. The 10-staple unit suffices for most lacerations. The stapling is done after approximation of the adjacent skin margins with eversion of the skin edges using toothed forceps (forceps with teeth) or the thumb and forefinger. The stapler is placed firmly on the skin without indenting it, aligned with the center of the wound, and gently squeezed to eject the staple onto the skin, ensuring proper apposition of the wound margins. Staples can be removed within 5–7 days by positioning the staple remover under the staple and depressing its handle to ease the staple out of the skin.

Tissue Adhesives (Cyanoacrylates) and Tapes

Cyanoacrylate tissue adhesives are liquid monomers that upon exposure to moisture (e.g., on the skin surface) change to polymers that form a strong tissue bond.When applied to a laceration, the polymer binds the wound edges together and permits normal healing of the underlying tissue.

Once applied, the maximum bonding strength is achieved within 2 minutes of application. The tissue adhesives form a barrier to moisture and microbes over the wound with longer side chain adhesives taking longer to set. The bonded adhesives spontaneously slough off within 5–10 days. Compared with wounds closed with either absorbable or nonabsorbable sutures, the tensile strength of wounds closed by tissue adhesives is less at the time of initial application but equalizes by 1 week after repair.

We suggest that patients with short (<5 cm) traumatic skin lacerations that are clean have good wound approximation, are under low wound tension, and undergo repair with tissue adhesives rather than sutures. Clinical experience indicates that scalp wounds can also be closed with tissue adhesive, but the hair around the wound needs to be trimmed prior to closure. Adhesives are also helpful for closure of skin tears and flaps in patients with fragile skin that cannot be easily sutured (e.g., elderly patients). When wounds are under tension, the placement of subcutaneous sutures can often reduce the tension sufficiently to permit the use of tissue adhesives for skin closure.

Tissue adhesives have the following advantages for the repair of short, clean, straight, traumatic lacerations with low wound tension when compared with sutures:

- Less painful procedure
- More rapid repair time
- Creation of a waterproof and antimicrobial barrier
- Better acceptance by patients
- No need for suture removal or follow-up
- Cosmetically similar results at 12 months postrepair

Evidence suggests that wound dehiscence occurs more frequently with tissue adhesives but that the frequency of dehiscence in properly selected wounds is low (baseline frequency 4%). Tissue adhesives are not thought to prevent the formation of keloids but may promote less tissue reaction than sutures when performing closure of small lacerations in susceptible patients.

Tissue adhesives should not be used in:

- Wounds under tension, unless subcutaneous sutures can be placed to lessen tension and permit good wound approximation
- Complex stellate lesions, crush wounds, or other lacerations with poor wound approximation
- Wounds on the hands, feet, or over joints unless the affected areas are immobilized because repetitive movements could cause the adhesive bond to break before sufficient tensile strength is achieved
- Oral mucosa or other mucosal surfaces (e.g., vagina) or areas of high moisture, such as the axillae and perineum
- Wounds in hairy areas unless the hair is trimmed
- Wounds requiring a high level of precision (e.g., hairline or vermilion border)

- Bite wounds and other wounds at increased risk of infection (e.g., puncture wounds, wounds with devitalized or contaminated tissue).
- Allergy to adhesives (or formaldehyde)

Caution should be used when applying them to wounds in conditions that may delay wound healing such as diabetes mellitus, chronic vascular disease, peripheral vascular disease, decubitus ulcers, and prolonged steroid use.

Ocular exposure to cyanoacrylates: The eyes should be well protected during the repair of adjacent lacerations. If adhesive gets into the eye, under the eyelid, or glues the eyelashes together, generous amounts of ophthalmic antibiotic ointment should be placed within the eye and on the eyelid to break down the adhesive. Gentle manual traction typically permits the reopening of eyelids that have been glued shut. If manual traction is unsuccessful, an ophthalmologist should be consulted. Once the eyelids are reopened, the patient should be assessed for a corneal abrasion.

Surgical tapes, such as "*steri-strips*," may be used directly in the case of small clean superficial lacerations and in areas of low skin tension, and are a useful alternative to staples. However, tape alone is usually not effective and should be used in conjunction with adhesives, such as tincture of benzoin. Unfortunately, local skin reaction occurs due to tincture of benzoin. Surgical tape is typically placed perpendicular to the wound and in strips parallel to each other. It has been noted, however, that in certain wounds on the back and chest, this method can lead to blistering secondary to an increased shearing effect of the surgical tape. Blistering was not present when the surgical tape was placed parallel to the wound edges on wounds in the same anatomical locations. The tape should be left in place until it falls off. Disadvantages with this method of closure include the inability to place the tape on areas with significant hair as well as the inability of the patients to get them wet. Tissue adhesive steri-strips are useful for facial lacerations in the pediatric population as per recent studies.

TYPES OF WOUND CLOSURE

Wound closure can be divided into three types: *primary*, *secondary*, and *delayed.* When the wound closure is done before the formation of granulation tissue, it is known as *primary closure*. This is generally done in all clean wounds but not in the puncture wound because this wound cannot be irrigated adequately. Contaminated wounds, noncosmetic animal bites, abscess cavities, and wounds presenting after a delay should be irrigated, hemorrhage controlled, and debrided. When the wound closure is performed after 3–5 days, it is termed *delayed primary closure.* This allows the patient's defense system to decrease the bacterial load. The bacterial load will be at its lowest approximately 96 hours after the time of initial impact. Secondary closure is healing by granulation tissue. Partial-thickness avulsions (i.e., fingertip injuries), contaminated small wounds (i.e., puncture wounds, stab wounds), and infected wounds closure is done by *secondary closure*.

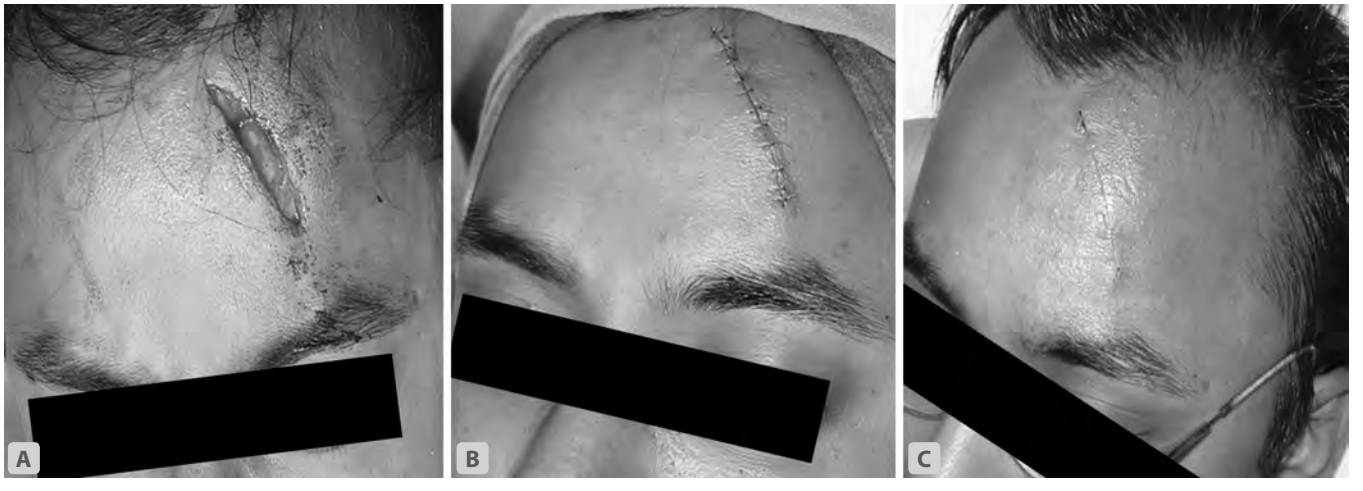
WOUND CLOSURE

Clean lacerated wounds: *Primary closure*—clean lacerated wounds may undergo primary closure at the earliest any time up to 12–18 hours after injury; location on the trunk or proximal extremity and the patient's lack of other risk factors favor success in closure. The wounds of the head and neck have rich vascularity and may be primarily closed up to 24 hours postinjury (**Figs. 5A** to **C**).

Contaminated or complicated lacerations: *Primary closure* is done only in the case of a noncontaminated injury that is recent in origin (<12–18 hours) Absolute contraindications to a primary wound closure are signs of inflammation (redness, warmth, swelling, pain). In the absence of these findings, the decision to suture is based upon clinical judgment. *Closure by secondary intention*: Indications for secondary closure (i.e., by granulation and wound contraction) include:

- Deep stab or puncture wounds that cannot be adequately irrigated
- Contaminated wounds
- Small noncosmetic animal bites
- Abscess cavities
- Presentation after a significant delay (i.e., >24 hours)

Delayed primary closure: This is considered for uncomplicated wounds that present after the safe period for primary closure. It involves initial cleaning and debridement followed by at least a 4- to 5-day waiting period. Consideration of the relationship of the laceration to the relaxed/resting skin tension lines (RSTL) is essential. Lacerations that are oblique or perpendicular to



FIGS. 5A TO C: (A) Clean lacerated wound of the forehead; (B) Primary closure of the wound; (C) Postoperative results after 4 weeks. ***(For color version, see plate 44)***

these lines are at an increased risk of scarring. Therefore, any excision should be parallel to the RSTL. A jagged laceration in which some of the components are parallel to the RSTL may result in a better cosmetic repair than a wound that has been excised.

Technique of wound closure and cosmetic concern: The major consideration while selecting the technique of wound closure is scarring (cosmetic concern). When the goal is to obtain the best function, the laceration should be closed in a single layer with the least number of sutures. When cosmetic is the most important concern, a multiple-layer closure should be used. **Table 6** summarizes the wound factors associated with cosmetic concerns. All wound heals with the scar, but patient factors, wound factors, and technical factors influence the final appearance of scar. Wound factors include the nature of the wound (elective or traumatic), location and orientation of the wound, vascularity of the tissues, elasticity and tension of soft tissues, and degree of contamination. Technical factors include the handling of tissues, debridement, sutures used, and method of wound repair. Avoiding rough tissue handling and the use of crushing instruments are important in preventing tissue ischemia, which leads to necrosis and poor scarring.

TABLE 6: Factors contributing to scar visibility.

Factors associated with scarring	*Measure to minimize scarring while closure*
Direction of wound perpendicular to lines of static and dynamic tension	Layered closure; proper direction in elective incisions
Wounds infection requiring removal of sutures and healing by secondary intention	Proper wound preparation; irrigation and use of delayed closure in contaminated wounds
Wide scar secondary to tension	Layered closure, proper splinting, and elevation
Suture marks	Remove all percutaneous sutures within 7 days
Uneven wound edges	Careful, even approximation of wound superficial layer to prevent differential swelling of edges
Inversion of wound edges	Proper placement of simple sutures or use of horizontal mattress sutures
Tattooing secondary to retained dirt or foreign body	Proper wound preparation and debridement
Tissue necrosis	Use of corner sutures on flaps, splinting, and elevation of wounds with marginal circulation or venous return; excision of nonviable wound edges before closure
Compromised healing secondary to hematoma	Use of properly conforming dressing and splints
Hyperpigmentation of scar or abraded skin	Use of sun block with a sun protection factor R15 for 6 months
Superimposition of blood clots between healing wound edges	Proper hemostasis and closure; proper application of compressive dressings
Failure to align anatomic structures (e.g., vermilion border) properly	Meticulous closure and alignment: use of regional blocks

Source: Adapted from Markovchick V. Suture materials and mechanical after care. Emerg Med Clin North Am. 1992;10:676.

ANTIBIOTICS IN WOUND CARE

The use of prophylactic antibiotics in wound care is controversial. Various studies do not show any benefits of using prophylactic antibiotics in a simple laceration. Evidence supports the use of antibiotics in hand injuries involving fractures, contaminated wounds, crush injuries, animal bites, and human bites. In dog bite wounds, debridement is more effective than prophylactic antibiotics in reducing infection. Prophylactic antibiotics are beneficial in puncture wound as it could not be irrigated thoroughly and chances of infection are higher. In general, antibiotics are recommended for contaminated wounds or wounds that cannot be adequately debrided or irrigated. Also, antibiotics need to be considered in patients who are more prone to infection including diabetics. Each wound needs to be considered individually, and the patient should have good follow-up, especially when the clinician decides not to provide antibiotics in potentially high-risk wounds (**Table 7**).

Indications of antibiotic prophylaxis following dog bites wounds are as follows:

- Hand wounds
- Deep puncture wounds
- Wounds requiring surgical debridement
- Wounds in older patients
- Wounds in immunocompromised patients
- Bite wound near or in a prosthetic joint
- Bite wound in an extremity with underlying venous and/or lymphatic compromise

AFTER-CARE INSTRUCTION

If possible, wounds should be covered with a nonadherent dressing for 24–48 hours. This period allows enough epithelialization to protect the wound from contamination. Compression dressings should be applied to wounds with the potential for hematoma formation. This dressing is left in place for 24– 48 hours. After this time period, dressings should be removed, and wounds should be cleaned three to four times a day to minimize coagulum between wound edges. Thereafter, patients should be advised to administer a sun-blocking agent with a sun protective factor of 15 to the wound to prevent hyperpigmentation from exposure to sunlight. This process should be continued for 6 months. Tissue adhesives do not require removal and will slough off over 5–10 days with wound epithelialization. Sutures and staples require removal on an average of 7 days after placement. Facial sutures can be removed in 3–5 days to avoid the formation of sinus tracts.

TABLE 7: Antibiotic prophylaxis and therapy—post-wound care.

Conditions		*Antibiotic recommendation*
Open fracture wounds	Types I and II fracture wound (adult)	First-generation cephalosporin, cefazolin 1–2-g IV 8 hourly (for 24 hours after wound closure)
	Type III fracture wound (adult)	First-generation cephalosporin + Gentamycin (1.5–3 mg/kg IV 8–12 hourly) (continue after 72 hours after wound closure)
	Farmyard injury (fecal, clostridial contamination)	Add high-dose penicillin
Human bite	High risk and hand bite	First-dose IV ampicillin-sulbactam or cefoxitin 1 g, then oral antibiotic amoxycillin-clavulanate for 5 days (if the first dose of injectable antibiotic is not possible, continue amoxycillin-clavulanate for 5 days)
	Infected human bite	First-dose IV ampicillin-sulbactam (3 g IV 6 hourly) or cefoxitin 1 g IV 8 hourly or ertapenem 1 g/d followed by amoxycillin-clavulanate (875 + 125) orally 12 hourly—continue for 5 days
Dog/cat bite	High-risk dog bite/all cat bite	First-dose IV ampicillin sulbactam (3 g IV 6 hourly) or imipenem (meropenem 1 g IV) followed by amoxycillin-clavulanate (875 + 125) orally 12 hourly—continue for 5 days
	Infected bite	First-dose IV ampicillin-sulbactam (3 g IV 6 hourly) or cefoxitin 1g IV or piperacillin-tazobactam 3.375 g IV followed by amoxycillin-clavulanate (875 + 125) orally 12 hourly—continue for 5 days
Plantar puncture wound		Ciprofloxacin
Underlying immunocompromised status (HIV, uncontrolled diabetes, chronic steroid use)		Amoxycillin-clavulanate or second-generation cephalosporin
Alters local defense (peripheral arterial disease)		Amoxycillin-clavulanate

- Alternative antimicrobial recommendations: Clindamycin/clindamycin fluroquinolones
- If first parenteral antibiotic therapy is not possible, then continue amoxycillin-clavulanate for 5 days

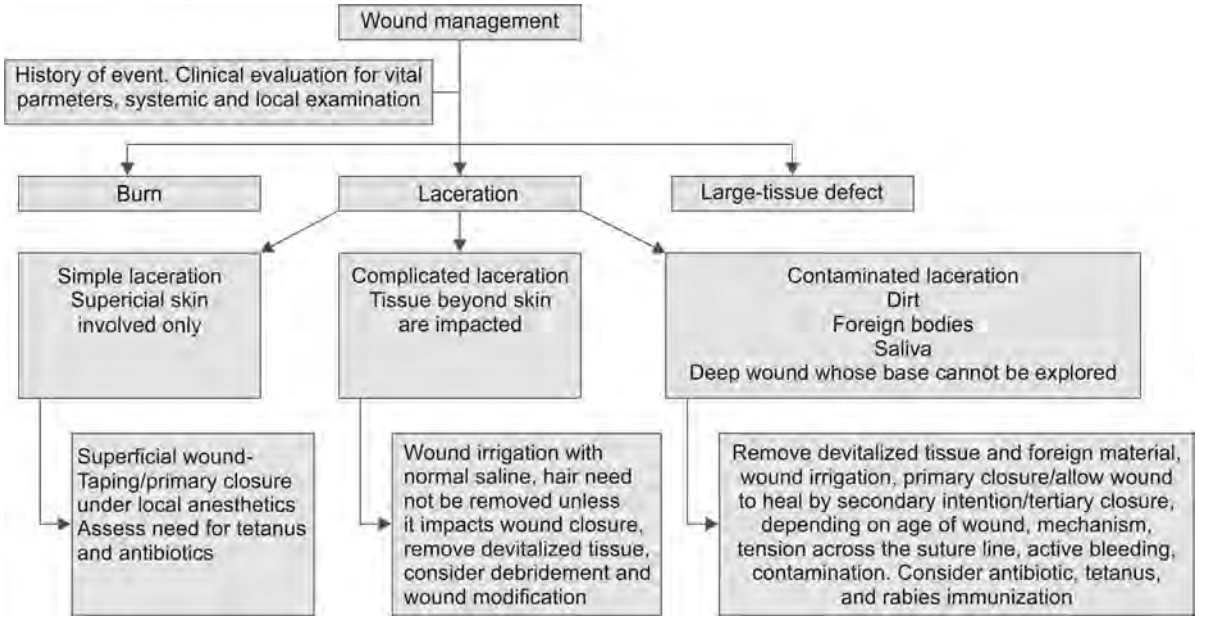
TABLE 8: Postclosure wound care and follow-up.

Type of wound	*Dressing*	*Follow-up*
Simple laceration/ abrasion	Topical antibiotics/ sunscreen/Vaseline/ clothing if exposed to sun	Not required
Complex laceration and wound healing by secondary intentions or delayed primary closure	Topical antibiotics and simple nonadherent dressing	5 days
Complex hematoma/ contusion	Gentle compression and elastic wrap	1 week
Puncture and bite wound	Topical antibiotics and nonadherent dressing	5 days
Abscess	Loose packing/ nonadherent dressing	24–48 hours

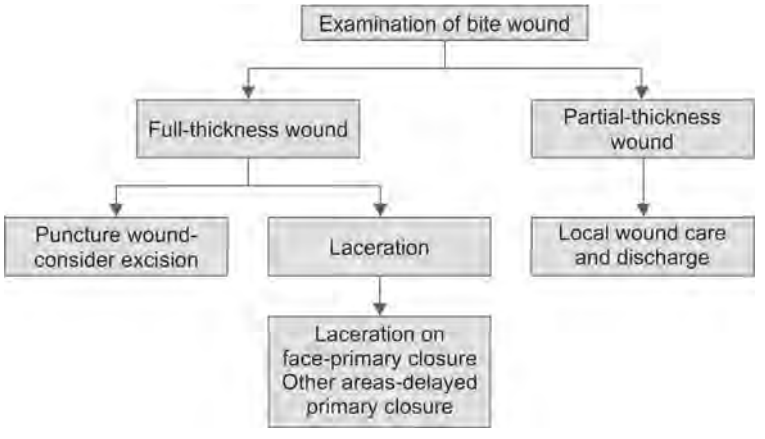
Sutures over joints or areas with a lot of movement should stay in for 10–14 days. Also, lacerations overlying joint surfaces should be splinted in the position of function for up to 10 days (**Table 8**).

SUMMARY

To treat wounds properly, the emergency physician needs knowledge of basic wound physiology along with host and wound factors affecting healing. Although many types of wound closure techniques are available, the choice of closure needs to be appropriate for the wound (**Flowchart 1**). Wound and host factors affect the type of closure that is best for different types of wounds. Bite wound is managed as per **Flowchart 2**. To obtain the ideal functional and cosmetic result without complications should be the ultimate goal.


Wound management
History of event. Clinical evaluation for vital parmeters, systemic and local examination
Burn
Laceration
Large-tissue defect
Simple laceration Supericial skin involved only
Complicated laceration Tissue beyond skin are impacted
Contaminated laceration Dirt Foreign bodies Saliva Deep wound whose base cannot be explored
Superficial wound-Taping/primary closure under local anesthetics Assess need for tetanus and antibiotics
Wound irrigation with normal saline, hair need not be removed unless it impacts wound closure, remove devitalized tissue, consider debridement and wound modification
Remove devitalized tissue and foreign material, wound irrigation, primary closure/allow wound to heal by secondary intention/tertiary closure, depending on age of wound, mechanism, tension across the suture line, active bleeding, contamination. Consider antibiotic, tetanus, and rabies immunization

FLOWCHART 1: Algorithm for managing wound.



FLOWCHART 2: Algorithm for managing bite wound.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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237 CHAPTER

Advanced Laceration Management

Aditya Agarwal, Sukhdeep Singh

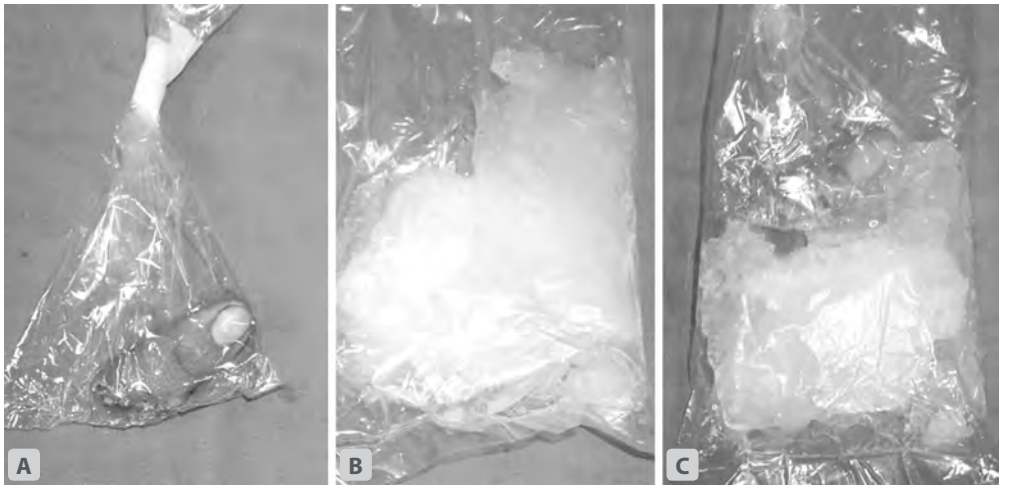
INTRODUCTION

Many lacerations which are specifically based on anatomic location require specific management in the emergency department. Advanced management techniques are required to manage for the repair of complex lacerations of the fingertip, ear, nose, lip, tongue, and eyelid. Since these lacerations are complex and aesthetically important, to avoid any further litigations it is important for the emergency clinician to know when specialist consultation is appropriate for treatment. In addition to routine triage of lacerations described in the previous chapter, some special considerations are needed while handling lacerations including ones that are periorbital, ear, nose, lips, tongue, and scalp. This chapter includes initial management, methods of repair, technical tips to facilitate repair, appropriate consultation, and postoperative care for these complex lacerations.

INITIAL MANAGEMENT

Initial treatment includes resuscitation of both airways and circulation. Any active vascular hemorrhage can initially be controlled by direct digital pressure; clamps may then be applied if the vessel can be clearly visualized. Blind clamping of a bleeding vessel is not recommended due to the risk of damaging adjacent tissue, especially nerves. Tourniquets are best avoided in routine due to the risk of compression injury to nerves, occlusion of veins resulting in the compartment syndrome, and increased chances of venous thrombosis yet maybe lifesaving in some cases. After identification of the vascular injury, a management strategy should be developed consistent with the clinical condition of the patient, severity of the injuries, and resource availability. In case the patient has to be moved to another center, cooling the ischemic limb will minimize warm ischemia time. For this to be accomplished, the limb is wrapped in towels, and ice in plastic bags is applied around the limb, avoiding direct contact of the ice to the limb, which can result in cold ischemic injury (frostbite) (**Figs. 1A** to **C**).

Wound care: Injured patients present with a myriad of different wounds depending upon the injury mechanism. Upon admission, the location and size of each wound should be documented. Deep and more extensive wounds, particularly



FIGS. 1A TO C: Dry cooling for transfer of the amputated part. (A) Finger in a clean plastic bag; (B) Ice in a separate plastic bag; (C) Bag with a finger placed such that the finger does not have direct contact with the ice. ***(For color version, see plate 45)***

those in proximity to major vessels, should be explored in the operating room where lighting is optimal, debridement can be undertaken, and any disrupted vessels can be managed in a controlled fashion. Individual wounds are managed with moist dressings and closure or coverage, as indicated.

DIAGNOSTIC WORKUP

Investigations needed will include complete blood count, renal function tests, coagulation parameters, and serum lactate level (as a marker of end-organ perfusion) that can serve as a guide for ongoing resuscitation.

Other investigations that may be needed include the following:

- *Plain radiography*: Plain radiographs of the affected extremity to detect fractures, joint penetration, and foreign bodies
- *Hand-held Doppler and ultrasound*: In case pulses are not palpable in an injured extremity
- *Ankle-brachial index and arterial pressure index*: In an effort to improve on the accuracy of physical examination without relying on expensive and invasive tests such as arteriography, the use of blood pressure in the injured versus the uninjured extremity [arterial pressure index (API)] or the blood pressure in an injured leg at the ankle compared with brachial artery pressure [ankle-brachial index (ABI)] was developed and validated in numerous studies as an accurate means of detecting vascular injury.
- *Computed tomography and magnetic resonance imaging*: *Computed tomography* (CT) with contrast enhancement [computed tomography angiography (CTA)] has become the standard of care for the detection of peripheral vascular injury in most trauma centers. Magnetic resonance imaging (MRI) is contraindicated in the presence of iron-containing metallic foreign bodies.
- *Arteriography*: Arteriography and digital subtraction angiography (DSA) may be used for assessing vessels before any surgical exploration.

SELECTION OF SUTURES AND SUTURING METHODS

Sutures may be monofilamentous (prolene or ethilon) or multifilamentous (silk). The designation for suture strength is the number of zeros; the higher the number of zeros (1-0 to 10-0), the smaller the size and the lower the strength (**Table 1**). They can also be defined as absorbable (dissolve within 14–180 days) or nonabsorbable. Pediatric injuries are managed similarly but may require general anesthesia.

PERIORBITAL WOUND

Eyelid lacerations should be carefully evaluated for the involvement of the lid margin and any tissue loss. They tend to follow relaxed skin tension lines. Management includes:

- Careful evaluation excluding any for any injury to the globe
- Protection of the cornea
- Excluding the presence of any foreign body
- Minimizing the risk of infection
- Optimizing cosmesis

History of the Injury

In addition to standard information, carefully ascertain the presence of any foreign body and tissue loss. Animal or human bite wounds may result in infection and should be appropriately managed for rabies, human immunodeficiency virus (HIV), and hepatitis. In cases of small penetrating lid lacerations, maintain a high index of suspicion for underlying globe trauma. Document carefully the prior visual acuity. Patients who are inebriated or children may not be good historians and one should be essentially careful while evaluating them.

Examination of the Eye

Look for any gross injury. Evert the lids only in the absence of globe rupture and flush the fornices. Palpate and examine the lids for foreign bodies, including contact lenses. Examine the

TABLE 1: Sutures and suturing methods for advanced laceration.

Laceration parameters	*Type of needle*	*Type of suture*	*Special suturing techniques*
Superficial facial lacerations	Reverse cutting	Prolene or ethilon (6-0)	Simple interrupted skin sutures
Deep facial lacerations (layered closure)	• Reverse cutting • Reverse cutting	• 5-0 PDS or Monocryl • Prolene or ethilon (6-0)	• Subdermal interrupted sutures • Simple interrupted skin suture
Tongue	Taper cut	4-0 or 5-0 Vicryl	Vertical mattress sutures
Oral mucosa	Taper cut	4-0 or 5-0 Vicryl	Vertical mattress sutures
Eyelid	Taper cut	6-0 silk or prolene	Simple interrupted skin sutures
Nailbed	Reverse cutting/taper cut	6-0 or 7-0 plain catgut	Simple interrupted sutures
Limbs and torso	Reverse cutting	4-0 or 5-0 ethilon or prolene	Simple interrupted sutures or vertical mattress sutures
Suture removal: The timing of suture removal varies with the anatomic site. • *Eyelids*: 2–3 days • *Neck*: 3–4 days • *Face*: 5 days • *Scalp*: 7–14 days • *Trunk and upper extremities*: 8–10 days • Lower extremities: 8–10 days			

(PDS: polydioxanone)

cornea for any lacerations, tears, or foreign bodies. Carefully observe all ocular movements including intrinsic and extrinsic muscles of the eye. Damage to the tarsal plate, ptosis, injuries to the lacrimal duct system, canthi, or lid margins should be referred to an oculoplastic surgeon for repair.

Preclosure Workup

Investigations in addition to the routine ones must include HIV, hepatitis serology, and when needed a CT scan to exclude foreign bodies, retrobulbar hemorrhage, globe rupture, or an orbital fracture. Antibiotics and tetanus prophylaxis may be given as previously discussed.

Anesthesia and Pain Relief

Most adults can be operated for lid repair under local anesthesia (topical anesthetic drops and topical lidocaine gel, anesthetic with epinephrine) in the emergency itself, yet uncooperative patients or children may require general anesthesia. A loupe magnification is useful in wound exploration and repair.

Surgical Management

Assessment and management of eyebrow lacerations are shown in **Figures 2A** and **B**. A careful inspection of the orbital rim and palpation of the circumference can help to identify underlying fractures and displacement of the rim. The eyebrow should never be shaved because the hairline cannot be visualized and that is critical for the correct alignment and additionally regrowth of the hair is unpredictable (**Figs. 3A** and **B**).

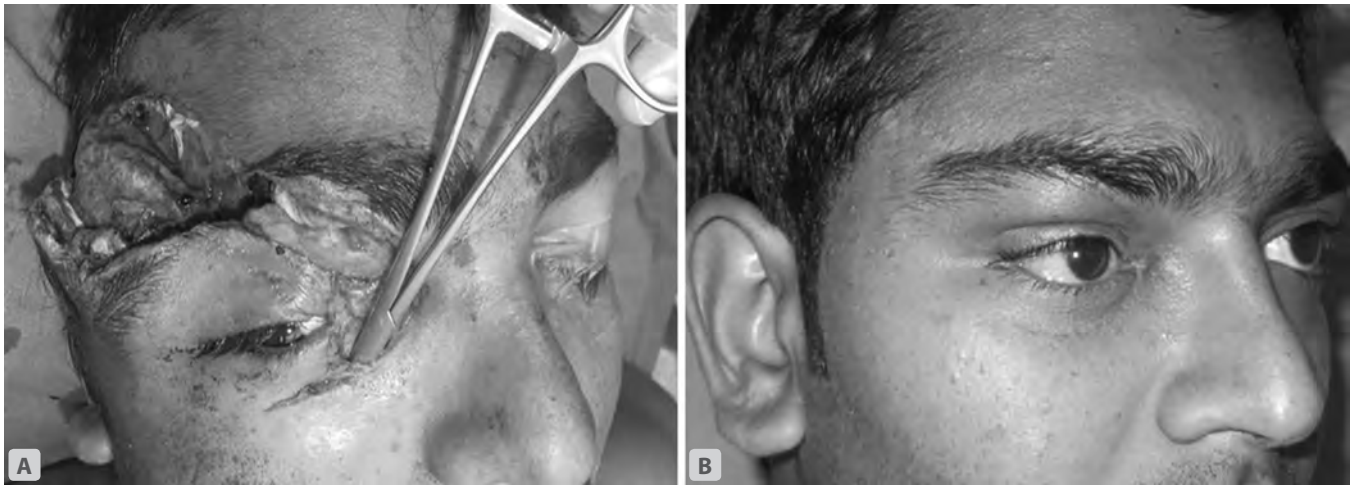
Combined Injuries

If a patient has a ruptured globe and a lid laceration, the globe rupture must be repaired first (**Figs. 4A** and **B**). If the lid repair must be delayed in favor of more life-threatening injuries, ensure adequate corneal lubrication and consider systemic antibiotic coverage. It is beneficial to try and save all lid tissue as the ocular adnexa has a good blood supply, and even ischemic-appearing tissue will often heal.

FIGS. 2A AND B: (A) Clean lacerated wound of the right eyebrow (no need to shave the hair); (B) Good eyebrow alignment after 1 week. ***(For color version, see plate 45)***

FIGS. 3A AND B: (A) Clean lacerated wound of the forehead and eyebrow; (B) A single stitch taken to align the eyebrow prior to a primary repair of the remaining wound. ***(For color version, see plate 45)***

FIGS. 4A AND B: (A) Complex periorbital laceration involving the eyebrow, lid, and lateral canthus; (B) Results after 6 months—careful anatomical alignment maintained during the repair. ***(For color version, see plate 46)***



FIGS. 5A AND B: (A) Complex periorbital injury showing disruption of the medial canthus with nasolacrimal duct injury and facial skin avulsion following a road traffic accident; (B) Late postoperative (6 months) results of a primary repair and fixation of underlying fractures. ***(For color version, see plate 46)***

NASOLACRIMAL DUCT INJURIES

Suspect these in cases of lacerations near the medial canthus of the eye. Once identified, these need to be repaired under magnification, which is best done by an oculoplastic surgeon (**Figs. 5A** and **B**).

CHEEK LACERATIONS (ZYGOMA)

Deep lacerations to the cheek, just anterior to the ear, have the potential to injure the parotid gland or the facial nerve. If the parotid gland is injured, bloody fluid can be seen leaking from the parotid duct via the buccal mucosa at the level of the maxillary second molar (**Fig. 6**).

EAR LACERATIONS

Wound closure on the ear can proceed in a standard fashion when the cartilage is not involved. The cartilage should not

FIG. 6: Poorly stitched oblique cheek laceration with parotid duct injury. The wound was re-explored and the parotid duct repaired. ***(For color version, see plate 46)***

be sutured if at all possible, because of the risk of infection. If suturing is necessary, the perichondrium must be included in the stitch in order for it to hold. The goal in repairing a wound with exposed cartilage is to cover it with skin as completely as possible. Blunt trauma may cause perforation of the tympanic membrane and a high degree of suspicion must be kept to exclude the same (**Figs. 7A** and **B**).

NOSE LACERATIONS

An injury to the nose is fairly obvious due to deformity of the nose or epistaxis. Performing an adequate and thorough nasal examination is difficult without epistaxis control. The origin of most nosebleeds is the vascular area on the anterior septum. Once the bleeding is controlled, by pinching the same or nasal packing, an intranasal inspection using a nasal speculum should be performed. The nasal septum (for hematomas), turbinates, and inferior meatus should be visualized bilaterally. Mucosal lacerations may be the sign of underlying fracture and should be carefully noted. Cerebrospinal fluid (CSF) rhinorrhea should be suspected in case of significant trauma. Septal hematoma if not identified in time can result in a continuous pressure on the septal cartilage resulting in necrosis and deformity (**Figs. 8A** to **C**). Septal hematoma is best managed by decompression (by a large gauge needle or by incision and drainage) followed by bilateral nasal packing.

SCALP LACERATION

As it is a highly vascular structure, the bleeding may be disproportionate to the size of the injury. After cleaning the wound, hemostasis with direct pressure application must be done to stop the bleeding before further evaluation should be attempted with direct pressure (**Figs. 9** and **10**).

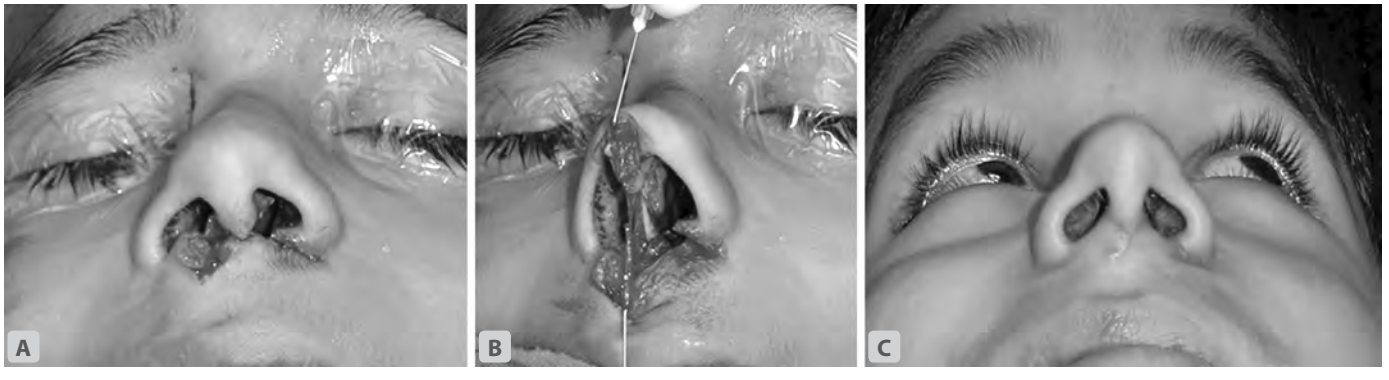
LIP LACERATION

It is especially critical that lip lacerations are repaired correctly to preserve the cosmetic appearance and functionality of the lip. Disruption of the vermilion border should be noted as a failure to do so can lead to do a significant cosmetic deformity. A step-off of the vermilion border as small as 1 mm is apparent at a close distance. Inspect inside the mouth and lips in case of every facial injury for any through-and-through wound, carefully evaluating the parotid duct area and inspecting for any disrupted teeth and hematomas (**Figs. 11A** and **B**).

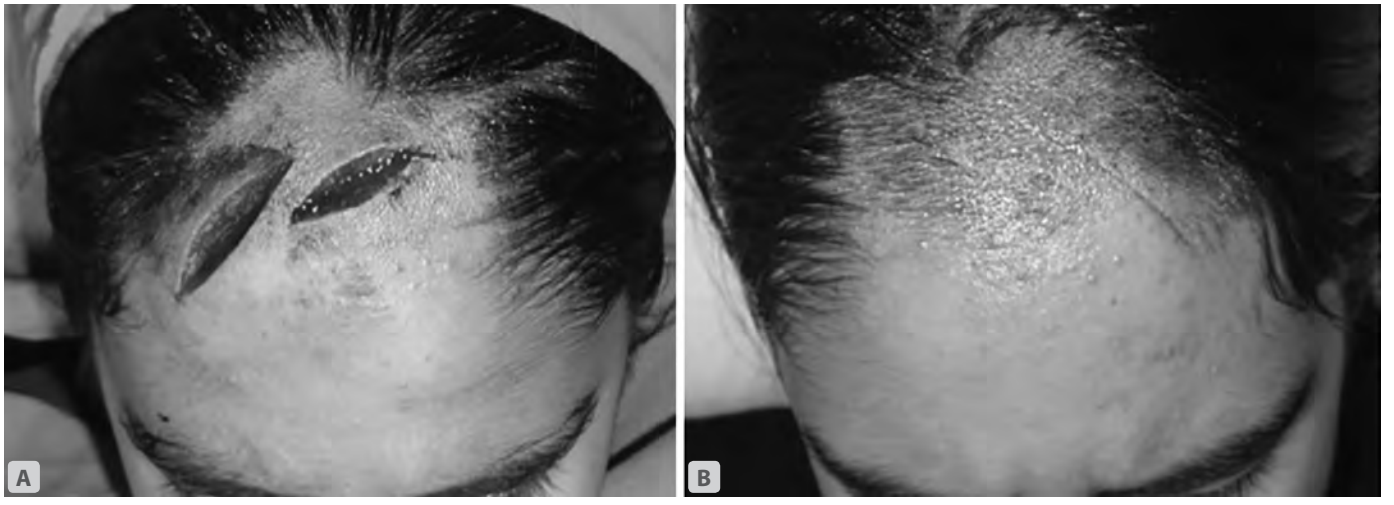
Complex Lip Laceration

Unlike the cosmetically important facial lacerations that are almost always closed primarily, certain small intraoral lacerations may be left open and will heal well without repair. Intraoral closure is needed when the mucosal laceration

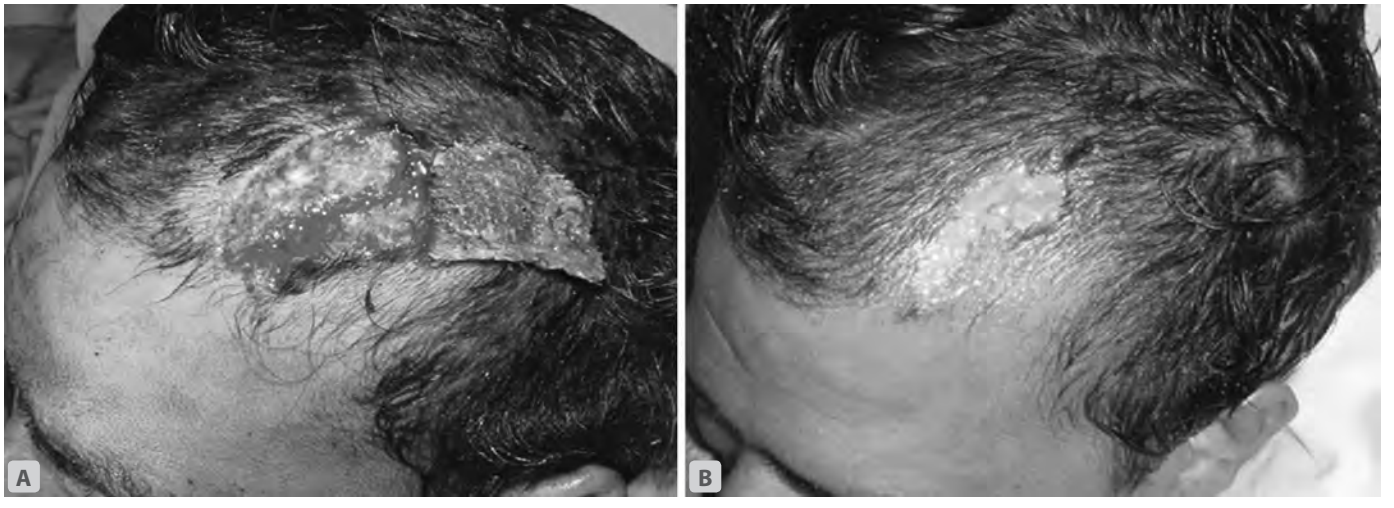
FIGS. 7A AND B: (A) Complex ear laceration with exposed cartilage; (B) Well-aligned repair with good healing on postoperative day 7. ***(For color version, see plate 47)***



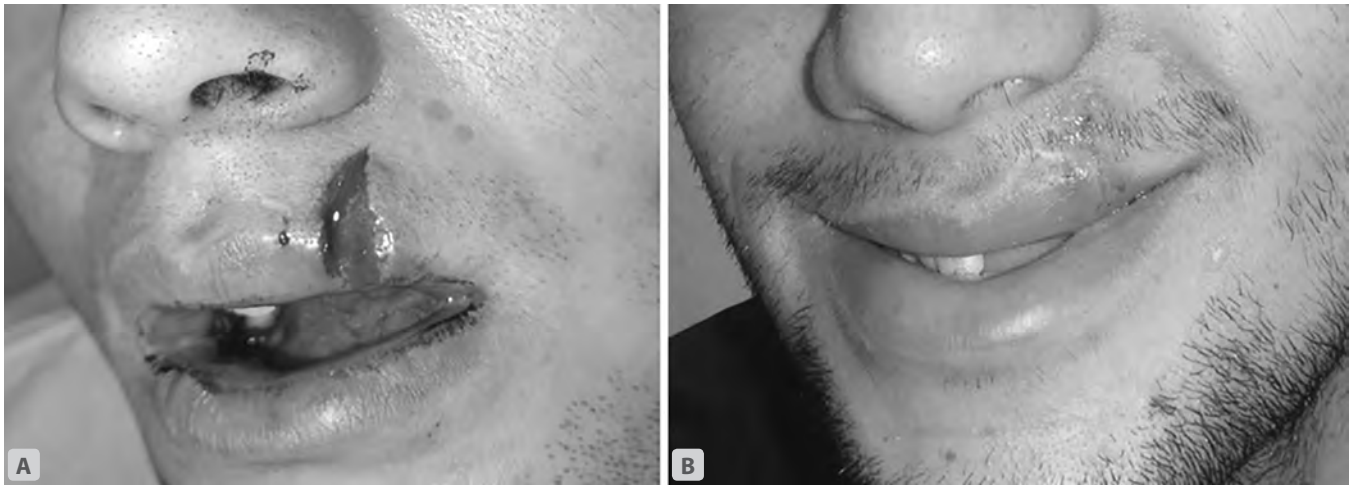
FIGS. 8A TO C: (A) Complicated nasal injury following a fall on a sharp object; (B) Identifying the injured structures—septal cartilage, columella, upper lip, and nasal floor; (C) Postoperative (day 30) picture showing good anatomical alignment. ***(For color version, see plate 47)***



FIGS. 9A AND B: (A) Patient referred from a primary health center with shaved scalp hair (avoid shaving unless grossly contaminated); (B) Wound on postoperative day 10. ***(For color version, see plate 47)***



FIGS. 10A AND B: (A) Scalp avulsion following a road traffic accident—needed removal of the avulsed skin flap and split skin graft; (B) Postoperative results on day 15. ***(For color version, see plate 48)***



FIGS. 11A AND B: (A) Upper lip clean laceration involving the vermilion border—repaired with careful white roll alignment of the vermillion border; (B) Postoperative day 10 results. ***(For color version, see plate 48)***

creates a flap or is large enough to trap food particles or is longer than 2 cm (**Figs. 12A** and **B**).

Vermilion border: If the vermilion border is involved, approximate it with the first suture placed on facial skin. Use 6-0 ethilon/prolene suture. In young children, consider using absorbable sutures for the repair of these lacerations.

Intraoral skin: It may be closed either before or after the facial skin. Approximate the buccal wet mucosa with simple interrupted absorbable sutures (4-0 or 5-0); absorbable sutures fall out or absorb and do not require removal. However, do not use fast-absorbing sutures on mucosal surfaces. Secure each stitch with four or more knots to ensure that the stitches are not untied by the tongue. These sutures can be continued onto the wet and dry vermilion surface of the lip. Silk is best avoided in the mouth, as it can irritate mucosal tissues. Any small intraoral flaps may be excised. If a patient with a lip or oral laceration also has a newly chipped tooth, search diligently for tooth fragments in the oral mucosa because if these are not removed, they may cause wound infections. *Facial skin*: Using 6-0 sutures, approximate the skin with simple interrupted sutures. This suture material can be continued onto the lip. Many prefer absorbable sutures on the dry vermilion surface.

TONGUE LACERATION

All tongue lacerations will not need a repair but must be carefully evaluated for depth of the injury and any foreign bodies. An exception is the complete anterior laceration, which should be repaired properly else it can result in a bifid tongue (**Figs. 13A** and **B**).

FACE LACERATION

In the case of any traumatic accidental injury, the face should be inspected and palpated for any asymmetry. The facial expressions and the related nerves should be evaluated by raising eyebrows, closing eyes, smiling, and frowning (**Figs. 14A** to **D**).

Repair: Superficial wounds may be repaired in a single layer, but deeper wounds should be repaired in layers. If muscle

FIGS. 12A AND B: (A) Complex lip laceration following a road traffic accident showing a through-and-through avulsion of the lower lip with other facial injuries. A three-layer repair (mucosa, muscle, and skin); (B) Results on postoperative day 30. ***(For color version, see plate 48)***

FIGS. 13A AND B: (A) Deep through-and-through laceration of the tongue that was repaired by a layered closure with a 5-0 Vicryl; (B) Intraoperative results. ***(For color version, see plate 49)***

FIGS. 14A TO D: (A) Patient reported with a facial nerve palsy following facial laceration repair at a primary care unit; (B) Operative picture showing the exploration of the wound and identification of the facial nerve injury; (C) Gradual recovery of the repaired facial; (D) Complete recovery. ***(For color version, see plate 49)***

layers are not repaired, they may result in puckering and scarring. When performing a two-layer closure, the deeper layers should be closed with absorbable sutures and the skin with a nonabsorbable monofilament suture. *Dermal adhesives* have shown equivalent efficacy for simple clean wounds as sutures. The advantages of dermal adhesive use include a shorter repair time, less pain, and no need of follow-up stitch removal. The disadvantages are that they cannot be used on the lips or mucous membranes. *Staples* may be conveniently used in scalp lesions, need a shorter repair time, and have similar rates of infection. Disadvantages include the lack of precision in alignment of the wound edges, thus limiting the use to of the scalp.

HUMAN BITES

Human bites have a preponderance to become infected due to the bacterial inoculum in the saliva and the fact that most injuries involve the hands and hand wounds have a higher rate of infection regardless of etiology. Recognition of the risk of infectious complications and early aggressive treatment are the thumb rules to prevent serious wound infection.

Human bite wounds occur as two separate entities: (1) *Clenched-fist injuries and* (2) *occlusive bites.*

Clenched-fist injury: These occur when a closed fist strikes the teeth of another individual with force enough to create an injury. The injury usually occurs over the dorsal surface of the third and fourth metacarpophalangeal (MCP) or proximal interphalangeal joints of the dominant hand. As the skin in these areas is thin, there may be penetration of joints and injuries to extensor tendons.

Occlusive bites: These occur when there is sufficient bite force to break the skin. Such injuries to the hand/finger when a finger is bitten must be carefully evaluated to rule out deeper tendon injuries. Bites to the head and neck can result in avulsion, laceration, and crushing of the tissues. Such injuries in small children must be reviewed carefully for depth of injury beyond the obvious in addition to legal considerations of suspected abuse.

Wound characteristics: Assess all bites for location, shape size, depth, associated laceration, avulsion, crush, or any retained foreign or particulate matter Additionally, note for any neurovascular or tendon injury.

FIG. 15: Soft-tissue deficit of the upper lip following a human bite, which will require an expert plastic surgical repair. ***(For color version, see plate 49)***

Puncture wounds: These are the most common around the head and are difficult to clean due to the depth of the wound. Explore the depth by extension of the neck, irrigation, and investigations such as X-ray or CT scans to identify the presence of any debris. They are best left open and secondarily closed. As they are prone to infections, appropriate antibiotics are a necessity.

Ear bites: Ear wounds are also common due to their prominent location. Small bites may be closed primarily and bigger ones may need a wedge excision. It is important to cover any exposed cartilage and restore its original shape.

Nose bites: Nose wounds and resultant nose reconstruction can be challenging and may need plastic surgeon's opinion for the same. Bites to the ear or nose or lips—are best closed in consultation with a plastic surgeon (**Figs. 15** and **16**).

Wound closure: In general, we do not primarily close deep puncture wounds, hand wounds, or wounds older than 12 hours. They may be closed secondarily or revised at a later date. Clean and uncontaminated head and neck wounds less than 12 hours of age may be closed primarily and heal well due to excellent blood supply. Antibiotic prophylaxis is mandatory in patients with bite wounds. Ensure closure in a simple interrupted fashion with good edge approximation and

yet allowing drainage. Tetanus prevention is recommended as previously discussed.

SPECIAL CONSIDERATIONS FOR ANIMAL BITES (DOG AND CAT)

As with human bites, primary closure is suggested only in facial wounds younger than 8 hours. Puncture wounds or contaminated wounds or those older than 12 hours may be better left open for healing with a delayed closure (**Figs. 17A** to **C**). Treatment with prophylactic antibiotics for 3–7 days is recommended. Tetanus immunization is recommended as previously discussed

Rabies immunization: If the laceration is due to the bite of a wild animal, complete rabies prophylaxis must be given. If a domestic pet was the culprit, check the pet's rabies immunization status and quarantine the animal for 10 days. In case it is not possible to quarantine the animal, the bite victim should receive the rabies immunization. Rabies immunization should begin within 48 hours after the bite and consist of active immune cover with a vaccine and passive immune cover with rabies immunoglobulin.

FIG. 16: Human bite on the nose with subtotal nasal loss which will require a complex plastic surgical repair. ***(For color version, see plate 49)***

LIMB INJURIES

Injuries to limbs may be simple or complex with neurovascular or deeper tissue They may be caused due to blunt or penetrating trauma or a combination of blunt and penetrating trauma (such as bull goring injuries) (**Figs. 18A** and **B**).

Evaluation of Limb Injury

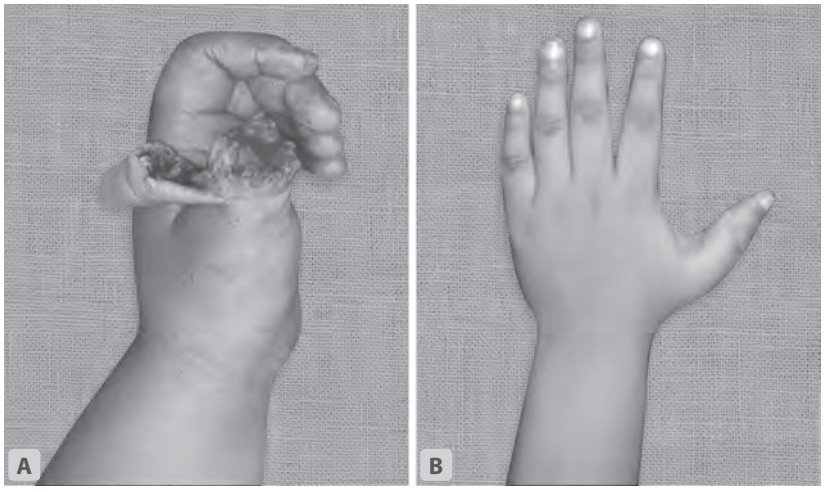
History: Note carefully the time of injury (to evaluate the warm ischemia time) and the types of injury: Crush or bites are more prone to infections and any coexistent medical conditions (such as diabetes, immunocompromise, and vascular insufficiency that can impair wound healing). Open avulsion injuries of limbs are severe because the skin is the last structure to tear much later than vessels and nerves. The vascular injury also should be suspected in patients with massive soft-tissue avulsion or crush injury, displaced long-bone fractures, electrical or lightning injuries, and severe burns as well as in those with compartment syndrome from trauma or prolonged immobilization as a result of stroke, coma, drug overdose, or other causes. Large animal bites are particularly prone to arterial injury and wound complications.

Physical examination: Careful physical examination including palpation of the peripheral pulses and recording blood pressures in both affected and unaffected limbs is important in the diagnosis of nonobvious vascular injury (**Table 2**). *The classic findings of vascular injury* include pulsatile bleeding, loss of distal pulses, audible bruit, or palpable thrill. Findings such as pallor, cyanosis and cold extremities, and distension of superficial veins may indicate an arteriovenous (A-V) fistula. Wounds that are close in proximity to neurovascular bundles must be carefully evaluated to rule out vascular injuries. Detection and management of vascular injuries are done in accordance with established principles of trauma care with the resuscitation of the patient. Once the source of bleeding is identified, it is compressed with digital pressure.

CRUSH INJURIES

In recent years, physicians have seen an increase in the number of crush injuries. Larger population densities coupled with impoverished conditions result in large groups of people living in close proximity in buildings with poor structural integrity.

FIGS. 17A TO C: (A) Pet dog bite with a through-and-through disruption of the upper and lower lips (front view); (B) Pet dog bite with a through-and-through disruption of the upper and lower lips (lateral view); (C) Results at postoperative day 30. ***(For color version, see plate 50)***



FIGS. 18A AND B: (A) Table fan injury with devascularized left thumb, requiring neurovascular and tendon repair; (B) Postoperative month 3 results. ***(For color version, see plate 50)***

TABLE 2: Clinical evaluation of a limb injury.

Upper limb		***Lower limb***	
Palpate peripheral pulses	Compare strength and quality on both sides	Palpate peripheral pulses	Compare strength and quality on both sides
Movement	• Across all joints • Flexion and extension	Movement	• Across all joints • Flexion and extension
Sensation	Compare sensory deficit on both sides	Sensation	Compare sensory deficit on both sides
Suspect missed injuries	Blunt arterial injury, intra-abdominal, diaphragmatic, pulmonary, and intracranial injuries	Suspect missed injuries	Blunt arterial injury, intra-abdominal, diaphragmatic, pulmonary, and intracranial injuries

Modern warfare and large-scale natural disasters, such as earthquakes or tsunamis, can be an inciting event. Collapsing structures result in a large number of people being trapped by rubble, and thus we have seen an increase in the number of crush injuries from these events. Crush injury-related renal failure and wound infection are complications that can be treated with the appropriate resources and training.

Pathophysiology: Crush syndrome was first described in the literature by Bywaters and Beall in 1941. Their observations came from taking care of soldiers who were crushed during bombing raids in London during the Blitz. It was recognized during this time period that myoglobin deposition in the kidneys was responsible for renal failure. Since that time, numerous observations have been made regarding crush syndrome demonstrating the involvement of many organ systems.

Complications secondary to crush syndrome: Limb injury, amputation, acute renal failure, acute respiratory distress, disseminated intravascular coagulation, bleeding and hypovolemic shock, cardiac failure, arrhythmias, electrolyte disturbances, psychologic trauma

Following the initial insult to muscles various processes occurs during crush syndrome. After a muscle cell is crushed or stretched, potassium and myoglobin are released from the damaged cell. Also, damaged cells absorb water, calcium, and sodium from the extracellular space through leaky sarcolemma. A large efflux of potassium from these cells can result in hyperkalemia and the secondary cardiotoxicity that results from it. The myoglobin is released from the cells along with urate and phosphate, which precipitates in the distal convoluted tubules and forms casts leading to obstruction. Metabolic acidosis and hypovolemia potentiate this problem in the renal tubules. Acidemia causes myoglobin to form a gel, which leads to decreased urine output and acute renal failure. Oligemia, hyperkalemia, hypocalcemia, and uremia progress to death in 3–7 days, if untreated. In addition to the renal disaster, there are other medical issues in patients involved in significant crush injuries. There is the risk for infection and subsequent sepsis from the initial crush injury and also from fasciotomy sites. Patients are also susceptible to acute respiratory distress syndrome following such a systemic insult. Additionally, if crush injuries result in bony abnormalities, fat embolism syndrome must be considered in the differential diagnosis.

Prehospital care: This is of great importance in patients involved in significant crush injuries. The rate of complications, such as renal failure and compartment syndrome, is inversely proportional to the elapsed time from injury to prehospital medical care. Primary management of airway, breathing, and circulatory issues must be addressed before transport. Normal saline should be administered to these patients because of the risk for worsening pre-existing hyperkalemia and the inability to accurately monitor urine output in these patients. The eventual goal is to maintain urine output at 1–2 mL/kg/h. Hemorrhage must be controlled, and some would argue for the early administration of antibiotics in these patients.

Hospital management: These patients arrive with multiple issues that need to be addressed. Specifically, primary trauma can result in issues regarding hemorrhage, pneumothoraces, and unstable fractures that need to be managed concurrently. Some patients require fasciotomies, whereas some have already received such therapy in the prehospital environment.

Fluids: Fluids are a key component to resuscitation in an effort to maintain peripheral organ perfusion and specifically preserve renal function. Initially, normal saline can be used, but eventually, potassium- and glucose-containing solutions are needed. Many suggest alternating between normal saline and a glucose solution in an effort to keep as many electrolytes in balance as possible. Large amounts of fluid can be required, sometimes upward of 12 L in the first 48 hours. A reasonable goal is to maintain urine output at 200–300 mL/h.

Alkalinization: Alkalinizing the urine of patients undergoing rhabdomyolysis secondary to crush syndrome has been a proven technique for some time. Urinary alkalinization increases the solubility of myoglobin and minimizes the formation of gel that causes tubule obstruction and subsequent oliguria. There are numerous suggested regimens in the literature to achieve urinary alkalinization. One such model is to add 50 mmol bicarbonate to the initial fluid boluses with a goal of keeping urine pH greater than 6.5.

Mannitol: Although somewhat controversial, many authors suggest that the use of the osmotic diuretic mannitol as an adjunctive therapy in crush injury patients improves outcomes. The suggested dose is 1–2 g/kg of 20% solution administered over a 4-hour period. It is believed that this creates a forced diuresis, thereby increasing urine output and helping to wash out tubular myoglobin. Mannitol also has the potential benefit of reducing intracompartmental pressures (which could potentially decrease the need for fasciotomies) and protecting the kidneys from oxidative injury by acting as a free radical scavenger. As an intravascular volume expander, it must be monitored closely and should not be given until urine output is established in the patient. Electrolytes, osmolarity, and urine output must be monitored closely while administering mannitol.

Renal failure: Despite physicians' best efforts, some patients succumb to acute kidney injury. Patients who have complete failure of their kidneys need dialysis. Patients with crush syndrome who require dialysis should continue this therapy for 13–18 days.

Compartment syndrome: This results when injured muscle cells increase in size with intracellular fluid uptake while total space remains constant. This swelling results in increases in intracompartmental pressures. As pressure increases, blood flow to the damaged tissue decreases resulting in tissue ischemia and eventual necrosis. It is classically taught that increased pressures resulting in tissue ischemia for >6–8 hours result in permanent damage. The treatment for compartment syndrome is fasciotomy. This procedure allows the swelling muscle to expand outside of its compartment, thereby preserving afferent blood flow. Fasciotomy continues to be a controversial subject in the realm of crush syndrome management. Some authors argue that this is a lifesaving intervention that also decreases the risk for complications related to crush syndrome. Other studies have not shown such profound benefits with fasciotomy. The benefits of fasciotomy must be compared with the outcomes related to localized wound infection, sepsis, subsequent amputations, and increased mortality.

Additional treatment modalities: In general, surgical amputation is not a recommended course of action in patients who have crush syndrome and should be considered a last resort in all patients. Even consensus statements recommend this only as a last resort because many severely crushed limbs can return to near or full function. There is some evidence that exposing crush injuries to subatmospheric pressures lowers serum myoglobin levels. Further research involving human subjects is needed to quantify when this therapy should be initiated in patients. Additionally, hyperbaric oxygen (HBO) could be an effective adjunctive therapy for crush injury patients.

Infections and wound management: These are concerns for the provider when patients make it out of the acute phase in which renal failure predominates. These patients who have crushed extremities have varying severity of wounds, but the one common feature is that they are all dirty wounds. Both endogenous and exogenous bacteria are introduced into an open wound site following these types of injuries. This, combined with the loss of the protective skin barrier, makes these patients susceptible to infection, sepsis, and risk for death. Also, the main site of infection risk is the fasciotomy site following a few days of hospitalization. The use of fasciotomies, especially in the prehospital environment, remains controversial and this study demonstrates the increased infection and mortality complicated by this surgical procedure.

SUMMARY

Advanced and difficult wounds constitute a significant amount of the morbidity and mortality emergency physicians face on a daily basis. There are specific traumatic and atraumatic wounds that are difficult to manage and have a high risk of complications. Emergency physicians must be able to identify these high-risk wounds and patients and take steps to mitigate further morbidity and mortality.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Burns

Gaurav B Shetty, Sahanya Ramesh Shetty

INTRODUCTION

According to the World Health Organization, about 3,22,000 die after fire-related burns every year throughout the world. This is still an underestimate of the actual deaths caused by burns in developing countries which accounts for more than 95% of these deaths. Factors attributing to increased incidence of burns in developing countries are illiteracy, high population intensity, poverty, and unsafe cooking methods. The management and treatment of burns are not always easy. However, the points to be taken into consideration are that the initial 24 hours are critical and are linked to morbidity and mortality. In order to initiate adequate and optimal care to burn victims, health care personnel need to understand the pathophysiology of burn injuries, their classification, and the appropriate use of surgical treatment. This knowledge is deemed to be important as there is a small window of opportunity to revive a burnt patient. Depending upon the severity of the condition, some patients may be treated in the hospital emergency department, while others may require transfer to a tertiary burn care center after initial stabilization and resuscitation.

What factors influence outcome?

A study of survival data from patients of burn-related injuries from the Massachusetts General Hospital revealed three factors that cause death: (1) Age above 60 years, (2) burn surface area above 40%, and (3) smoke inhalational injury (SII).[2] As the outcome of survival has improved with decreased mortality to about 5–6% in resourced centers, the assessment of outcome has shifted from mortality to quality of life. Hence, the main agenda for burn patients involves preservation of function, reconstruction, and rehabilitation. The pathophysiological process which is responsible for outcome is shown in **Flowchart 1**.

ETIOLOGY

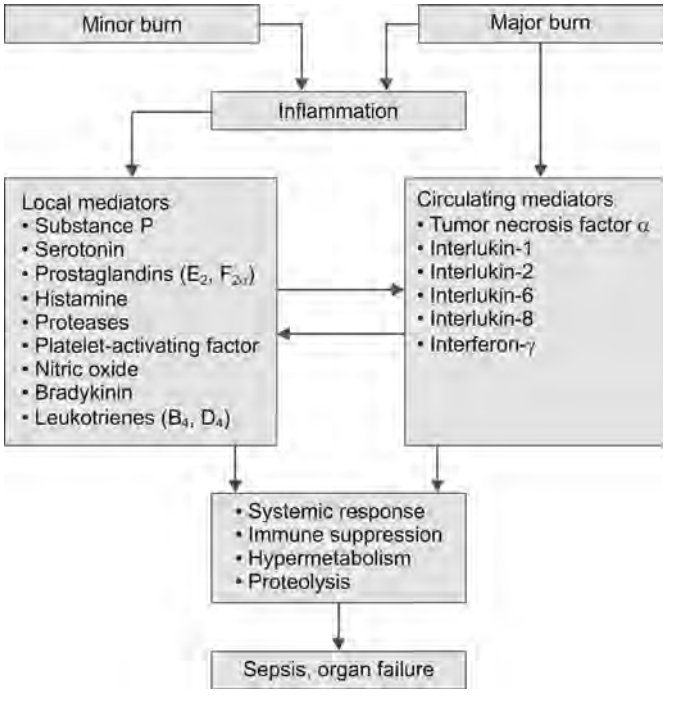
- Flame burns (thermal burns)
- Scalds (hot liquids)
- Steam
- Contact burns (hot objects and articles)
- Chemicals (acids or alkalis)
- Electrical burns (high and low voltage)
- Sunburns
- Friction burns
- Radiation burns
- Burns from a lightning strike

DETERMINING THE SEVERITY OF BURN: CLASSIFICATION

Determining burn severity depends on the involvement of the total body surface area (TBSA) and depth of the burn.

Severity on the basis of TBSA involvement: *TBSA*: The estimation of adult burns by *Wallace's "rule of nines"* (**Fig. 1A**):

- 18% each for back, chest, and legs (individually)
- 9% for each arm and head, 1% for perineum
- Though being an efficient tool to evaluate the percentage of burn over body surface, it overestimates the area by 3%.



FLOWCHART 1: Pathophysiology of burn.

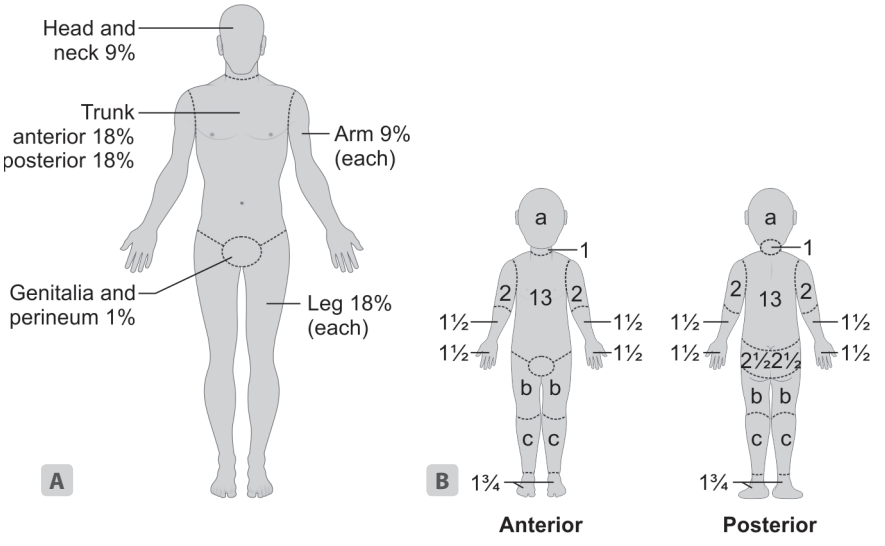
Lund and Browder's chart: It takes into account changes in body surface area with age and growth. It is helpful in the estimation of burns in all age groups (**Fig. 1B**). Another modality to estimate surface area is by the area on the volar aspect of hand inclusive of fingers. This is essential in determining small burns (<15%) or large burns (>85%). In larger areas of burn, the total area affected can be calculated by estimating the areas not burnt and then subtracting it from 100. One of the pitfalls is the addition of the erythema, which will present an overestimate of the calculation.

Severity on the Basis of Depth of the Burn

Clinical estimation of burn depth is often subjective. An independent blinded comparison among experienced surgeons showed only 60–80% concurrence. Burn wounds are dynamic and need reassessment in the first 24–72 hours because depth can increase after the injury as a result of inadequate treatment or superadded infection. Burn wounds can be superficial in some parts but deeper in other areas (**Figs. 2A** and **B**).

First degree: These consist of an intact epidermis in the presence of erythema, e.g., sunburn.

Second degree: The integrity of the epidermis is intact. When the extent of burn is limited to the upper layers of dermis, it is a superficial second degree. Burns progressing toward deeper reticular layers are termed a deep second-degree burn. In contrast, superficial burns are more painful, while deeper second-degree burns have decreased pain and a blunt pressure feeling in affected areas.



Relative percentage of body surface area (% BSA) affected by growth

	Age				
Body part	**0 years**	**1 years**	**5 years**	**10 years**	**15 years**
a = 1/2 of head	9 1/2	8 1/2	6 1/2	5 1/2	4 1/2
b = 1/2 of 1 thigh	2 3/4	3 1/4	4	4 1/4	4 1/2
c = 1/2 of 1 lower leg	2 1/2	2 1/2	2 3/4	3	3 1/4

FIGS. 1A AND B: (A) Rule of nine for adult; (B) Lund–Browder chart for children for estimating the extent of the burn.

FIGS. 2A AND B: (A) Partial thickness with partial thickness superficial burn noted on abdomen and bilateral thighs having partial-thickness superficial burns; (B) Flame burns: Upper extremity circumferential burns, causing a tourniquet effect on the distal forearm and hence predisposing to compartment syndrome. ***(For color version, see plate 50)***

Third degree: These involve all layers of the dermis. The skin may present as dark, dry, hard and painless. Thrombosis is present inside the blood vessels along with a typical eschar formation.

Fourth degree: These include all layers of skin with subcutaneous fat and deeper tissues. There is a carbonized appearance with muscles and tendons involved.

Superficial burns: The extent of injury involves minimal or no dermal injury. They consist of superficial second-degree burns and first-degree burns. They usually heal within 3 weeks without any sequelae.

Deep burns: The injury involves the dermis completely or partially. They consist of deep second-, third-, and/or fourth-degree burns, depending on the extent of the dermal injury and underlying deep tissues. The healing process involves a period of >3 weeks and may require surgical intervention.

Some characteristic features of burns of varying depths are summarized in **Table 1**. The terms "partial-thickness" or "full-thickness" burns describe the level of burn injury and indicate the likelihood and estimated duration for healing to occur.

INITIAL MANAGEMENT OF BURN

Burn Care in a Prehospital Setting

- Circulation, airway, and breathing are examined at first. In a patient sustaining multiple trauma injuries, one must apply the "forget the burn" principle; resuscitation of life-threatening injuries is a priority.
- The victim should be rescued from the site and extinguished of the fire.
- For minimal burns, it should be kept under running tap water for the initial 20 minutes, in order to alleviate the ensuing thermal damage and cease the process of further thermal damage.
- In cases of hot liquid burns, all wet clothes need to be removed.
- *Flame burns*: The idea is to move the patient away from the source. If not possible, fire is extinguished. Assessment for carbon monoxide and smoke inhalation is essential. Early administration of 100% oxygen is beneficial. If required in extreme cases, endotracheal intubation is done.
- In electrical burns, there are three types of injuries possible: (1) Electrocution, (2) Flash burns, and (3) arc Burns. One must ensure that electricity is turned off and the patient is moved away from the source of electric current. Assessment for need of cardiopulmonary resuscitation is evaluated. Check for multiple traumas, including blunt or penetrating injuries.
- In chemical burns, all dry chemicals need to be brushed off and rinsed under running water angulated at a tangent to the skin until the pain is relieved (this could take 60 min). However, care must be taken to prevent hypothermia. In most cases, neutralizing agents are contraindicated due to exothermic reactions. Avoid immersing the patient in a tub of water.

TABLE 1: Classification of burns on the basis of extent and depth.

		Second degree			
		Partial thickness			
Degree of burns	***First degree***	***Superficial***	***Deep***	***Third degree***	***Fourth degree***
Depth of burn	Epidermal	Superficial dermal	Deep dermal	Full thickness	Deep organ involvement
Sensation	Painful	Painful	Painful (varied sensation)	Insensate	Insensate
Clinical features	Blisters – Blanches +	Blisters+ (blanching + on unroofing the blister)	Blisters ± Blanching –	Blisters – Blanching –	Blisters – Blanching –
	Erythematous, red, glistening	Erythematous, pink + (on unroofing the blister)	Pale +, molting +, white +	Leathery Dry –, brown/black white +, leathery +, eschar +	Involves bone/ fat/ muscles
	Moisture + Exudates +	Moisture + Exudates +	Moisture + Exudates +	Moisture – Exudates –	Moisture Exudates
Examples	Sunburn	Scald injury	Hot grease injury	House fire, sustained burn	Electrical burn and extensively sustained burn
Healing	Scar less healing within 7–14 days	2–4 weeks	• 3–8 weeks • Severe scarring +, needs grafting	Needs grafting	4–11 weeks
Intervention		• Heals without grafting • Collagen application	Tangential excision + split-thickness skin grafting	Tangential excision + split-thickness skin grafting	Needs grafting/soft-tissue cover

- Establish a large intravenous access for major burns, and the choice of fluid should be Ringer's lactate solution for resuscitation. Observation of circulation, urinary output, and respiration is essential. The complete picture of the event and medical conditions of the patient should be obtained. In cases of transfer to other burn centers, one must provide detailed information of the severity of burn and the medical condition of the patient prior to transfer.
- One must anticipate edema formation in larger burns. Hence, removal of jewelry including rings, chains, necklaces, and bracelets is done. This is done for two reasons as these metals are heated and then dissipate a latent heat and the other reason being the edema that ensues making it difficult later on to remove these constricting articles. Covering the wound with a clean sterile cloth will prevent risks of infection and is sufficient during transfer to the nearest emergency center. If possible, burn wounds can be externally applied with medical coolants. The areas of the body that are unburned need to be covered in order to prevent systemic hypothermia.

BURN CARE IN THE EMERGENCY DEPARTMENT

Treatment protocol: Remove all clothing immediately. Areas exposed to the source of burns should be washed with water at 20–25°C temperature to avoid hypothermia. This is continued for a period of 60 minutes. Do not expose the surface to any neutralizing agents, as they may further increase the chances of reaction either directly or by the generated heat. These will cause deepening of burns.

Chemical powder should be initially brushed off with a sterile and clean brush or dry cloth. Once the exposed area is devoid of irritant particles, it is irrigated generously with running water. The applications which should be attempted in the emergency department are summarized below:

Circulation, Airway, and Breathing

A burn patient is treated as any trauma patient. Treatment guidelines should be followed as per advanced trauma life support (ATLS) protocol. Primarily, endotracheal intubation should be done where it is suspected or needed. In a worst-case scenario, tracheostomy must be done to secure airway at the earliest and ensure oxygen supply.

Establish an Intravenous Access

In cases of larger surface area burns, it is imperative to secure a "central" catheterization. It is better to access the subclavian vein than the femoral vein. The same norm holds good for children where one or two peripheral intravenous lines are established.

If the burn wound is extensive involving the central catheterization designated sites as mentioned, then it is mandated to introduce the catheter through the burn wound with the obvious risk of infection in mind but the only parameter that can tide over the crisis is adequate resuscitation and hence this has to be performed after thorough deliberation by the treating doctor. *In children younger than 6 years of age*, if central catheterization is difficult, a 16–18-gauge needle (spinal needle is compatible) is approached from the distal femoral or proximal tibial bone marrow under local anesthesia. Precise and careful attention should be paid to the epiphysis plaque. Intravenous fluid can be initiated at 100 mL/h. During this, other sites for peripheral access can be established by other medical emergency department (ED) personnel.

Avoid Systemic Hypothermia

In order to prevent this, intravenous fluids need to be administered at temperature closer to body temperature.

Polytrauma

In a higher percentage of burns, the victim is likely to endure other injuries, in some cases due to subsequent fall or trauma associated with the event. Serial examinations of upper and lower limbs, along with traumatic brain injury, must be carried out. If any concomitant injury is present, the designated department should be involved. A burns surgeon needs to be followed up with for management of burns. *Ocular injury*: Both eyes are irrigated well to remove all irritants, dust, and debris. The ophthalmologist is consulted for further treatment.

Maintaining Analgesia for the Burns Patient

- Exposed areas are kept under running water for both pain relief and also because it prevents further heat to be dissipated to the underlying tissues.
- In order to prevent hypothermia, the patient needs to be covered well even in unburnt areas. Avoid using ice coolants for local application.
- Pain relief is administered immediately to relieve anxiety and stress. Intravenous administration is preferred due to vasoconstriction as compared to intramuscular or subcutaneous routes (**Box 1**).
- Steady increments of morphine on an hourly basis are preferred to establish the most preferred method of pain relief. In a patient with associated respiratory injury, opioids can only be used with close monitoring of ventilation.
- Careful and precise titration of drugs on infusion should be done. One must look out for respiratory and hemodynamic changes.
- In order to perform escharotomy/fasciotomy, it is done ideally in the burns center. Analgesics such as tramadol and ketamine are most used in these surgical approaches.
- General anesthesia is preferred for children or stressed adults for surgical interventions.

Fluid Resuscitation

This should be initiated based on the total burned surface area involved, >10% in children and >20% in adults. Fluid administration is a crucial effort in recovering the depleted fluid loss in tissues and muscles. **Figure 3** is of paramount importance. It is Jackson's Thermal Wound Theory which comprises three zones of a burn wound signifying three regions with a Zone of Coagulation at the Center which is the tissue that cannot be rescued; following it concentrically in a circumferential manner is the Zone of Stasis and Zone of Hyperemia that can be salvaged. The Zone of Stasis is the tipping point between these two zones; if the dimension of this zone is not maintained then the Zone of Coagulation will encroach on it, whereas if the dimension of the stasis zone is not just maintained but expanded, then the stasis zone expands and undergoes a transition into the Zone of Hyperemia which

BOX 1: Pain management in a burn patient.

- *Analgesics for acute pain relief (intravenous dosage)*:
  - *Tramadol (>12 years of age)*: Every 4–6 h a dose of 1 mg/kg
  - *Ketamine*: Every 15–25 min a dose of 0.2–0.5 mg/kg
  - *Morphine or diamorphine*: Every 4–6 h a dose of 0.03–0.1 mg/kg
  - *Child*: Every 4–6 h a dose of 0.1 mg/kg
  - *Fentanyl*: Every 45–60 min a dose of 1–1.5 µg/kg
  - *Child*: Every 45–60 min a dose of 1 µg/kg
  - *Meperidine*: Every 2–4 h a dose of 0.5–1 mg/kg
- *Suggested combinations therapy for pain management*:
  - *Adults/children*: Combination of fentanyl 0.5–1 µg/kg/h and midazolam 0.03 mg/kg/h is preferred
  - *Children (<12 years age)*: Slow intravenous dose of ketamine at 0.5 mg/kg and fentanyl 1 µg/kg/h infusion is ideal
  - *Children (>12 years age)*: Appropriate dose of ketamine 0.5 mg/kg slow intravenous + tramadol 100 mg/2–4 h infusion
  - *Adults with unstable respiration*: A slow delivery of ketamine 0.5 mg/kg is followed by infusion of tramadol 100–150 mg/2–4 h during transportation

Repeat of doses should be maintained at a 15–20-min interval prior to the end of analgesic time.

- *Outpatient analgesics to be prescribed*:
  - *Children*: Paracetamol (preferably syrup, per oral)—10–15 mg/kg
  - *Ibuprofen*: (>2 years age, per oral) 20 mg/kg/day for 3–4 times a day
  - *Adult*: NSAIDs such as naproxen, oxicam group are preferred

(NSAID: nonsteroidal anti-inflammatory drug)

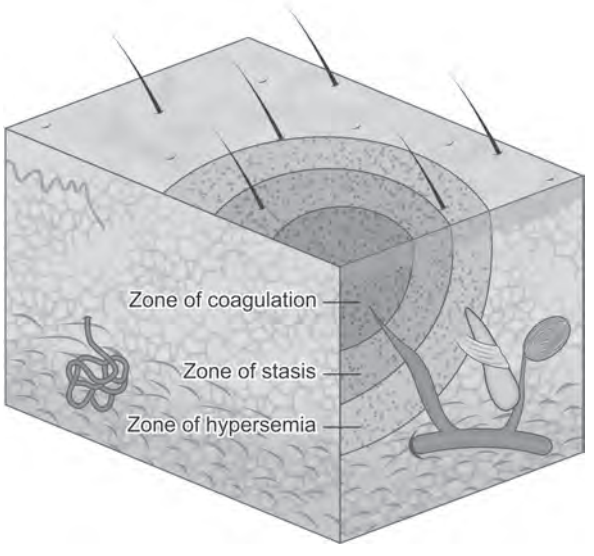
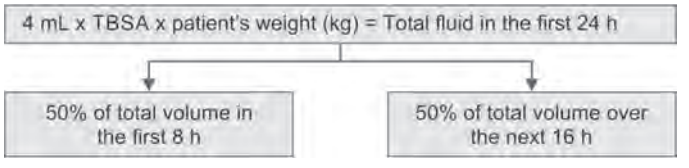


FIG. 3: Three zones of burn wound.

is the requirement in any burn wound. The only parameter that can keep a check on the limits of the Zone of Stasis to remain static is resuscitation and the only parameter that can expand the Zone of Stasis into the required Zone of Hyperemia is

TABLE 2: Pathophysiologic changes in three zones of burn wound.

Zone of coagulation	• Early protein denaturation • Irreversible destruction of protein architecture • Coagulation
Zone of stasis	• Compromised cells • Progressively impaired circulation • Can convert to full cellular necrosis • Platelet microthrombus • Neutrophil adherence to vessel wall • Fibrin deposition • Vasoconstriction • Endothelial edema • Occurs from 2–48 hours' postburn • Recovers in 1 week under optimal conditions • Will still have extensive epithelial cell loss • Tissue tenuous, susceptible to additional insult (dehydration, pressure, hypovolemia, over-resuscitation, infection)
Zone of hyperemia	• Minimal cellular injury • Prominent vasodilation (due to vasoactive mediators from the inflammatory response) • Complete cellular recovery


4 mL x TBSA x patient's weight (kg) = Total fluid in the first 24 h
50% of total volume in the first 8 h
50% of total volume over the next 16 h

(TBSA: total body surface area)

FLOWCHART 2: Distribution of adequate fluid resuscitation over 24 hours.

adequate resuscitation. This is the reason resuscitation takes precedence in burn management (**Table 2**).

The following formulas are recommending guidelines, for estimating the fluid requirement in a burn patient; however, fluid therapy can be modified according to the condition of the patient and prognosis of the injuries.

Adult: Fluid requirement is calculated for the initial 24 hours from the onset of burns by the Parkland formula given below and total fluid is given over 24 hours as shown in **Flowchart 2**.

Parkland formula: Lactated Ringer's solution, 4 mL/kg of body weight × % TBSA

Modified Brooke's formula: 2 mL/kg of body weight/% TBSA

Children: Based on the weight of the child, fluid to be administered using the *Galveston formula* is = 2,000 mL/m^2 body surface area + 5,000 mL/m^2 of TBSA (Ringer's lactate solution).

Special emphasis on the Parkland formula: This is the formula that is being used widely by all the medical personnel, be it resuscitation on the scene of the incident by the paramedics

or by the doctors at the emergency room (ER) once the patient is received. The formula has gained popularity for its simplicity and feasibility making it easy to calculate resuscitation rates. This was a formula devised by Dr Charles F Baxter during his tenure at the Parkland Memorial Hospital. He was one of the doctors at the trauma department who unsuccessfully tried to save the US President John F Kennedy after he was shot in Dallas, Texas, in 1963. It is pertinent to know that the new ATLS guidelines for Parkland formula have a change in the numerical corresponding to the Ringer's lactate. This discrepancy has been mentioned in **Table 3**. The decision on the transition to the new formula is widely accepted by many, but burn specialists believe of falling back on to the old formula, especially if the patient has arrived at the ER with a delay after the burn injury or the patient has been bought early but has not received any fluids in transit to the ER. Otherwise, the new ATLS formula holds well if the resuscitation has commenced within minutes of the incident or has been instituted by a paramedic at the scene of the incident. As this has been a conflict of interest, the author has left the decision to the reader to follow the old/new guideline based on the protocol of the department that he/she is working in.

In certain cases of associated injuries, fluid administration must be increased based on associated injuries. For example:

- Patient under the influence of alcohol or recreational drugs
- *Associated injuries to limbs or viscera*: These may lead to muscle breakdown further adding on to the fluid demand
- Injuries due to inhalational burns
- Delayed onset of resuscitation or signs of dehydration
- Electrical burns

In cases of a larger surface area of burns and/ perineal burns, urinary catheterization is an essential indicator of urinary output. Urinary output should be maintained at a target of 30–50 mL/h in adults and of 1–2 mL/kg/h in children. Urinary density is to be at 1015.

Note: *Inhalational and electrical injuries*—The targeted urinary output should be two-fold the values mentioned above. Local application of creams or pomades for pain relief is contraindicated.

Chemical Burns

The active process of burning continues till the substance is in contact with the surface of the skin. Once completely undressed, the patient is placed under running water at body temperature. Avoid placing the patient in a tub, as this may cause hypothermia. Some chemical burn agents are as follows:

- *Dry lime burns*: Initially, the chemical agent is brushed off and then placed under running water at body temperature.
- *Mercury compounds*: Unroofing of blisters containing mercury is done.
- *Tar burns*: Apply ice cubes on the tarred surface for 10–20 minutes. Tar forms a crusty layer and that eventually peels off.
- *Hydrofluoric acid*: It damages the epidermis of the skin and penetrates into the underlying tissues till it reaches the bone. Even small burns like 10% may be fatal. Hypocalcemia may cause derangement in cardiac activity. Treatment is to apply calcium gluconate gel over the affected area immediately and administration of calcium gluconate intravenously is indicated.

Radiation Burns

High radiation (8–10 Gy of radiation) causes injuries that prolong from few days to few weeks, unlike thermal burn injuries. Pain is usually intractable and progressive in nature.

Investigations

In cases of extensive burns involving a larger TBSA, chemical substance burns and/or electrical burns, it is evident that the patient requires to be admitted in a tertiary burn care center. Arterial blood gas analysis along with serum electrolytes is essential to rule out early signs of metabolic imbalance. Further, serial ECGs and cardiac monitoring should be done, in order to detect preventricular complexes and arrhythmias. In the early minutes of arrival in the ER, it is expected to administer 50 g of mannitol and two ampoules of sodium bicarbonate intravenously. In low-voltage electrical burns, atrial fibrillation with high ventricular response is the most encountered rhythm disorder and cause of death. Therefore, every patient with an electrical burn should have an ECG test. Cardiac monitoring and, if possible, serum creatine phosphokinase-myocardial band (CPK-MB) testing are indicated. Cardiac muscle necrosis may occur, especially in a high-voltage injury, and troponin-1 levels should be examined. If the electric flow trace crosses the heart, 24-hour cardiac monitoring is indicated. Circulation disorder or severe muscle damage may occur in the extremities. Developing edema can cause compression of the muscles and necrosis (compartment syndrome). In such a case, escharotomy is insufficient and fasciotomy is indicated (**Table 4**).

Systemic Examination and Supportive Therapy

Strong contraction of electricity may result in muscle avulsion or shearing. Bone fractures or joint dislocations may be seen. Intra-abdominal visceral damage may also occur. Progressive development of edema and/or eschar tissue formation is present in most cases of larger TBSA burns. Therefore, careful inspection of thorax, abdomen, extremities, and neck should be done, in order to anticipate the need for escharotomy or

TABLE 3: Fluid resuscitation in thermal and electric burn.

	Thermal burns		***Electrical burns***	
	Old ATLS	***New ATLS***	***Old ATLS***	***New ATLS***
Adult	TBSA: % × 4 mL × Weight (kg)	TBSA: % × 2 mL × weight (kg)	TBSA: % × 7 mL × weight (kg)	TBSA: % × 4 mL × weight (kg)
Child	TBSA: % × 4 mL × Weight (kg)	TBSA: % × 3 mL × weight (kg)	TBSA: % × 4 mL × weight (kg)	TBSA: % × 4 mL × weight (kg)

(ATLS: advanced trauma life support; TBSA: total body surface area)

TABLE 4: Surgical procedures of escharotomy and fasciotomy in burns.

Points	*Escharotomy*	*Fasciotomy*
Depth of surgical intervention	Superficial	Deep
Most commonly in	Common in thermal burns	Common in high-voltage electrical burns/other trauma
Intervention relieves	Extrinsic compression	Intrinsic compression
Indications	Circumferential/ near circumferential burns	Brawny edema on palpation
	Signs of impaired perfusion in parts distal to eschar	Signs of impaired perfusion even proximally
Treatment	Anesthesia—not required	Underappropriate anesthesia
	Up to subcutaneous tissue	Through the deep fascia
	Incision on neutral lines	Incision based on compartments

fasciotomy. In cases with >30% TBSA along with a decreased level of consciousness, there is an increased risk of paralytic ileus and gastroparesis. This indicates the need of nasogastric decompression when necessary. Treatment with a H2 receptor antagonist as prophylaxis for acute mucosal lesion is started. In children with good oral tolerance, there is no requirement to start on enteral (EN) nutrition.

Moderate or large TBSA burns: These patients along with a comorbid medical condition need to be evaluated at the earliest. Investigations such as complete blood count (CBC), blood glucose, serum electrolytes, renal function test, liver function test, CPK-MB, and urine for myoglobinuria and/ hemoglobinuria need to be done. Imaging is required in case of deformities, dislocations, or tenderness at joints in order to determine fractures. In case of extensive burns (>30% TBSA), prophylaxis for deep vein thrombosis is started with heparin or low-molecular-weight heparin. General tetanus prophylaxis protocols need to be carried out for all patients.

NUTRITION IN BURNS

Burns is a state of stress of causing a hypermetabolic response. Hypermetabolism means there is a heightened state in the levels of catecholamine, cortisol, and other glucocorticoids concomitant of adrenaline and noradrenaline. This hypermetabolic state lasts 9–12 months after a burn and it alters the metabolism of carbohydrates, proteins, and lipids; hence, knowledge of the same and the supplementation required are essential to be borne in mind while treating the burnt patient.

Glucose metabolism: Hypermetabolism translates its effects on glucose metabolism. The burn have implications on glucose metabolism with accelerated gluconeogenesis from alanine and other amino acids, there is an increase in glucose oxidation and plasma clearance of glucose. The blood glucose levels increase due to insulin resistance and breakdown of glycogen stores and simultaneously glucagon excretion by the liver increases initially after the burn and slows down as the wound heals. Carbohydrates are good sources for protein sparing, especially for nitrogen retention. High carbohydrates can contribute to hyperglycemia in which case a diet can be altered to increase fat in the diet. Recommended 60% of the calories should be from carbohydrates, not surpassing 400 g/day or 1,600 kcal/day.

Protein metabolism: Protein catabolism increases in burn patients leading to protein losses of 260 mg protein/kg/h. The basic unit of proteins being the amino acids, it is quintessential for collagen synthesis and in turn for wound healing, hence mandating a 1.4–2.2 g/kg protein requirement for burns. This exogenous protein intake is important for maintaining visceral protein for organ function, especially for immune systems and also for the muscle mass of the diaphragm and intercostal muscles for adequate respiratory efficiency. It is to be borne in mind that any trauma patient may lose 20–25 g of lean body nitrogen daily and this loss is exponential as a urinary nitrogen loss in patients with burn injury. So, keeping these losses in mind, the protein requirement estimate is calculated by combining 24-hour urinary nitrogen loss, 2–4 g of nitrogen for fecal loss, and 45 g/day for anabolism. Convert each gram of nitrogen to 6.25 g of protein. Patients are likely to miss feedings if in surgery frequently, so they should be given high-protein formulas between surgeries. Be aware of uremia—increase the free water intake. Generally, 20–25% of calories are derived from protein.

Lipid metabolism: Lipid stores are critical for long-term fuel after major thermal burns; fat oxidation is higher in hypermetabolic patients than in normal patients. Fat consumption should not exceed 30% of the diet to avoid diarrhea. Lipid intake is beneficial because fat is a more concentrated form of energy; lipid is available in the form of vegetable oil and contain essential fatty acids and fat-soluble vitamins. It is recommended that 12–15% of calories should be lipids.

Types of Nutrition Therapy in Burns

Oral: The first step in assessing nutrition care is to determine if oral care is appropriate. Natural digestion is preserved when eating orally. Consuming food provides micro- and macronutrients as well as phytochemicals and antioxidants. Nutrients and phytochemicals from food aid in wound healing and overall health of the patient.

Enteral: EN feeding is initiated when 80% of caloric and protein needs cannot be met. An appropriate step may be to administer night feedings so that appetite and oral intake during the day can be stimulated. Early administration of a feeding tube has shown positive effects on wound healing and diminishing gut bacterial translocation.

Parenteral (PN)*:* PN feeding is administered via the modality known as total parenteral nutrition (TPN) which is the last option for nutritional support. If no other means is acceptable, TPN may be administered. The characteristic features of oral, enteral, and parenteral modes of nutrition are given in **Table 5**.

Because of hypermetabolism and being in a high-stress state, burn victims need higher energy requirements (**Table 6**). The Harris–Benedict equation is an option to use

which takes into account stress factors and the percentage of burns. Use of the modified *Harris–Benedict equation* to estimate resting energy expenditure: BEE = (66.47 + 13.75 W + 5.0 H-6.76 A) × (Activity Factor) × (Injury and/or Burn Factor)

W = Weight in kg, H = Height in cm, A = Age in years.

WOUND CARE

In cases of TBSA < 10%, an outpatient criterion can be applied after the initial observation. The need for intravenous fluid resuscitation and ongoing complications must be dissolute. Early signs of sepsis should not be missed out. Maintenance of adequate oral nutrition and oral analgesics for pain relief must be taken into account. The wound should be rinsed with tap water or saline solution in order to get rid of debris or foreign body, except for neutral pH liquid. Adequate dressing with paraffin or ointment like nitrofurazone 0.2% should be carried out under sterile conditions. In cases of evident infection, eschar or larger TBSA, application of 1% silver sulfadiazine is done. However, in the presence of epithelialization, silver-containing agents should not be applied as these delay epithelialization.

Apart from face burns, 1% silver sulfadiazine is applied on burn wounds generously (**Table 7**).

TABLE 5: Choosing modes of nutritional therapy in a burn patient.

Oral	*Enteral*	*Parenteral*
Preserves GI function	Ryle's tube insertion	Total parenteral nutrition
Food has therapeutic qualities that tube feedings do not	Prevents bacterial translocation from the bowel	IV access required may predispose to infection

INDICATIONS OF HOSPITALIZATION FOR A BURN PATIENT

- *Second- and third-degree burns*: TBSA > 20% at all ages
- *Third-degree burns*: TBSA > 20% at all ages
- Second- and third-degree burns, with TBSA ≥ 10% in patients younger than 10 years or older than 50 years of age
- Burns over the face, ear, hand, and foot, including major joints, genitalia, and perineum
- Inhalation injuries, chemical burns
- Electrical burns, lightning strike
- *Polytrauma*: Associated orthopedic injuries, cardiac arrhythmias, traumatic brain injury
- *Pregnancy*: Monitor fetal heart rate and uterine activity
- Suspicion of child abuse
- *Long-standing co-morbid conditions*: Coronary artery disease, hypertension, diabetes mellitus, neurological ailments

The above mentioned are a spectrum of cases requiring immediate evaluation. However, if in any doubt, an emergency physician should consider the hospitalization of a patient based on the progression and prognosis of burns.

TABLE 6: Nutritional requirements in a burn patient.

Calories	*60% Carbohydrate*	*20–25% Protein*	*12–15% Lipids*	
Vitamins	*Vit C*: 1,000 mg/day orally	*Vit A*: 10,000 IU/day orally	• *Vitamin D*: 200–400 IU/day • Ca^{2+}: 1,000 mg daily orally	*Vitamin E*: 100 mg/day orally
Trace elements route—IV	*Copper*: 2.5–3.1 mg/day	*Selenium*: 315–380 µg/day	*Zinc*: 26.2–31.4 mg/day	• *1 week*: 20–40% TBSA • *2 weeks*: 40–60% TBSA • *4 weeks*: >60% TBSA

(TBSA: total body surface area)

TABLE 7: Wound care in burns.

First-degree burns	*Second-degree burns*	*Third- and fourth-degree burns*
• *Dressing/antibacterial agents*: Not required • Ointment/creams for local application are sufficient. These decrease local inflammation • Oral analgesics is prescribed for 5–7 days • Larger first-degree burns require hospitalization in order to administer fluid intravenously and pain relief	• *Superficial burns*: ○ Aseptic dressing with paraffin and woven fabrics ensure that the wound does not stick to the dressing ○ Use of polyurethane film sheets ± ○ In other cases, aseptic and clean wound dressing is done with paraffin or 0.2% nitrofurazone impregnated gauze • *Blister management*: Smaller blisters may be left intact whereas larger blisters need unroofing to be done, followed by serial dressings and follow-up: ○ *Deep burns*: Application of silver sulfadiazine, mupirocin, and nitrofurazone over the burns directly or underneath the gauze along with paraffin is mandatory • *Signs of delayed wound healing*: Increased risk of hypertrophic scar formation, keloid, discoloration, and contractures is present. Hence, the patient needs to be referred to a tertiary burn care center	• *Full-thickness burn*: Spontaneous eschar separation does not occur. Infection causes the eschar to separate spontaneously, due to the enzymatic products of bacterial growth • These types of burns require transfer to a burns unit for further surgical intervention

INHALATION INJURY: EARLY DIAGNOSIS AND TREATMENT

Inhalational injury comprises three different injuries caused by thermal and/or chemical irritants:

1. *Chemical injury*: Affects the whole respiratory system.
2. *Thermal injury*: Affects primarily the upper respiratory system.
3. Toxic inhalation of smoke; during indoor burn cases, inhalation of carbon monoxide or cyanide. These lead to spread of toxic irritants into systemic circulation. Extensive inhalational injuries can present even in the absence of skin burns.

Clinical Manifestations

- Decreased consciousness of patient, cyanosis, and burns over hair, face, ear, and nose is present.
- Voice hoarseness, mucosal edema, black sputum, and presence of carbon particles are present in mucosa.
- Neck burns present circumferentially along with perioral and facial burns.
- *Carbon monoxide intoxication*: Nausea, fatigue, dizziness, headache, chest pain, palpitations, visual disturbances, pain in abdomen, and disoriented mental status.

Management

- Remove the patient from the scene and decontaminate him/her.
- Maintenance of securing airway for position, insertion of airway, and prevention of tongue's backsliding.
- Support breathing with nasal cannulation/high-flow oxygen mask or endotracheal intubation in patients with apnea and/or obstructive breathing.
- Assessment of circulation by adequate fluid resuscitation, correction of electrolyte imbalance, warming, and support for the cardiopulmonary system are requirements.
- Oxygen support of 100% on high flow (7–8 L/min) via a nasal cannula or mask should be initiated.
- Mechanical ventilation/endotracheal intubation is indicated in patients with circumferential neck burns, perioral burns, facial burns, decreased level of consciousness, subglottic edema, or progressive hoarseness.

CRITERIA FOR REFERRAL TO A BURN UNIT/ SPECIALIST

There are two ways to transfer a patient: one is from the scene to a hospital and the other is from one hospital to a burns tertiary care hospital. *Red flags*: One must be aware of the likelihood of progression of the condition of the patient to a life-threatening situation during transport. With a potential to survive, there should be no delay in transport of the patient to the nearest healthcare facility within the vicinity. Patient referral depends on two golden rules: (1) Adequate communication and (2) fruitful teamwork. The following must be taken into consideration prior to transfer of the patient to another hospital: Initial stabilization of vital hemodynamic must be done. The referral hospital must be well informed about the condition of the patient. Adequate information should be communicated between healthcare physicians at the referral hospital and the current hospital. Adequate information of the patient includes age/gender of the patient, time of the accident, place of the accident, mode of injury, clear description of injuries (% of TBSA), weight/height of the patient, vital medical history of the patient along with laboratory results, neurological status, and medical attention provided to the patient immediately after the accident. Verbal as well as written documentation provides a representation of the overall condition and prognosis of the patient.

Checklist prior to transfer of patient: A—airway, B—breathing, C—circulation should be adequately secured and monitored. As mentioned above in management, transfer of the patient with unstable vitals is not a priority. Initial stabilization plays a higher hand at survival than transfer to a burns facility with a possibility of cardiac arrest en route. It is needless to say that during transfer and in view of a decreased neurological status, it is essential to secure the airway through intubation or to perform a tracheostomy and maintained over ventilator support:

- Two large venous catheters are established, preferably in the upper extremities.
- During transit, one must ensure that urinary catheterization is done prior to transfer. Maintain a urinary output for adults at 30 mL/h and children at 1 mL/kg/h.
- The patient should be discouraged of oral intake and a Ryle's tube is inserted in patients with burned TBSA >30%. Enteral nutrition should be initiated early in the stabilization of the patient and maintained at 10 mL/h infusion and may be increased as per patient tolerance.
- Lactated Ringer's solution is the fluid of choice in the initial 24 hours of burns prior to transfer. The amount of fluid to be administered is decided by the treating physician. In children, Ringer's lactate solution with dextrose is preferred.
- Cardiac monitoring (ECG) and respiratory status are to be monitored.
- Wet dressings should be avoided at all cost.
- The patient should be covered (even at unburned areas) in order to prevent hypothermia.
- Specialist referral is indicated as per **Table 8**.

MEDICOLEGAL INSIGHTS AND CHILD ABUSE

Burn patients need to be evaluated forensically. In patients with a high risk of mortality, injuries suspicious of nonaccidental purpose should be carefully investigated on the basis of the history of the accident and reported to respective authorities. In case of situations where the patient or relatives of the patient deny medical attention, medical care cannot be initiated. In the event of such a scenario, a detailed consent form should be duly signed by the patient as well as two witnesses against a probable risk of medical negligence. The patient and family members need to be acquainted of the possible risks of denying medical advice. They should provide a signed statement of agreeing to have read and understood the risks involved in denying medical attention. The consent of parents

TABLE 8: Referral of a burn patient to a specialist.

High index of suspicion	*Investigations to be acquired prior to the specialist's visit*	*Referral specialist*
Smoke inhalation injury	Chest X-ray	Pulmonologist
Facial burns, to rule out any corneal injury	Fluorescein stain	Ophthalmologist
Cardiac disease/ electrical burns	• ECG • 2D ECHO to be mobilized	Cardiologist
Diabetes mellitus	• Random blood sugar (RBS) • Estimated average glucose (eAG) • Glycosylated hemoglobin (HbA1c)	Endocrinologist
Associated skeletal injuries	X-ray trauma series	Orthopedic surgeon
Associated head injuries	Plain CT scan of the head	Neurosurgeon
Limb threatening, compartment syndrome, burn wounds on the chest, and a resultant decreased chest expansion	• Appropriate dressing materials based on the depth of the wounds and surface area of the burns • In an event of electrical burns, markers for rhabdomyolysis	Plastic and reconstructive surgeon

or legal guardian should be taken in view of medical care to be provided for children (**Fig. 4**). The legal guardian or parents have the legal right to deny any medical care to the patient. A written consent signed by the parents/legal custodian is taken. In case of a request for help, it should be availed. In the event of a nonaccidental injury (NAI), with a suspicious medical history, it becomes clearly evident of child abuse.

Possible Signs of Abuse in Burn Cases

- Delay in availing medical attention and seeking help from the nearest hospital
- Different scenarios of accident explained at the time of admission to a hospital
- Incongruity between clinical manifestations and history provided from family members
- Blaming the accident on another sibling or relative by the parents or legal guardian
- Parent/legal guardian expressing unruly behavior or violent actions
- Unpleasant or abnormal appearance of child
- Deranged relationship between the child and the parents
- Child should be taken into a secure environment and asked about the detailed events leading to the accident. This can be very helpful in finding out the cause and criminal of accident
- Past history provided in which the child has been treated at different hospitals at multiple situations
- Accusation by child directly on parents about the accident caused
- Highly irrelative/illogical expectation by the parents on the child.

FIG. 4: Scalds due to accidental outpour of hot milk over the lower half of the face, chest, and abdomen. ***(For color version, see plate 51)***

Possible Findings on Medical Examination

- *Indications of punishment*: Discoloration, ecchymosis on upper and lower limbs, genitals, back
- Injuries with varied stages of healing
- Blunt trauma causing liver/spleen rupture
- Cigarette burns or hot water burns (scalds) on the hands, feet, perineum
- Subdural hematoma (chronic signs) with or without damage to cranium
- Signs showing metaphysic decomposition, calcifications, periosteal bleed

Tell-tale Signs of Child Abuse

- Child is oversensitive or insensitive to painful stimulus.
- Manifestations of the clinical condition of the child are much before the proposed time of the accident.
- Varied degrees of burns and incisions are present closely.
- Covering up of lesions/injuries with clothing (scarf, jacket).
- Unusual locations of injuries such as tongue, lip, and frenulum.

PROGNOSTIGATION OF THE BURN PATIENT

Once the patient is stabilized, speak to the bystanders and prognosticate them of the resuscitative efforts being done and elicit more history on how the fire was doused, history of comorbidities, and past history of medications/surgeries and personal history. Build a rapport with the attenders. Get back to the patient to check if everything is going in accordance as planned. Check arterial blood gas (ABG). Check blood reports and urine reports. Prognosticate the patient by keeping the following points in mind:

- Natural history of the disease
- Complicating events
- Further treatment required

- Referral required or not
- Treatment cost
- The need for an intensive care unit (ICU) stay
- Surgical interventions required
- Morbidity and mortality
- High-risk consent documentation
- Guarded prognosis documentation
- The possibility of postburn contractures and the management required for its prevention and surgical management by a plastic and reconstructive surgeon.

SUMMARY

Burns are associated with significant morbidity and mortality. Burns affect the people of productive age groups and are the only form of trauma where the incidence is more in females. Most of the risk factors for burn injuries are preventable and the mortality and morbidity can be minimized with proper care. An emergency physician should be well aware of the structured plan for managing the burn patients in the emergency department (**Fig. 5**).

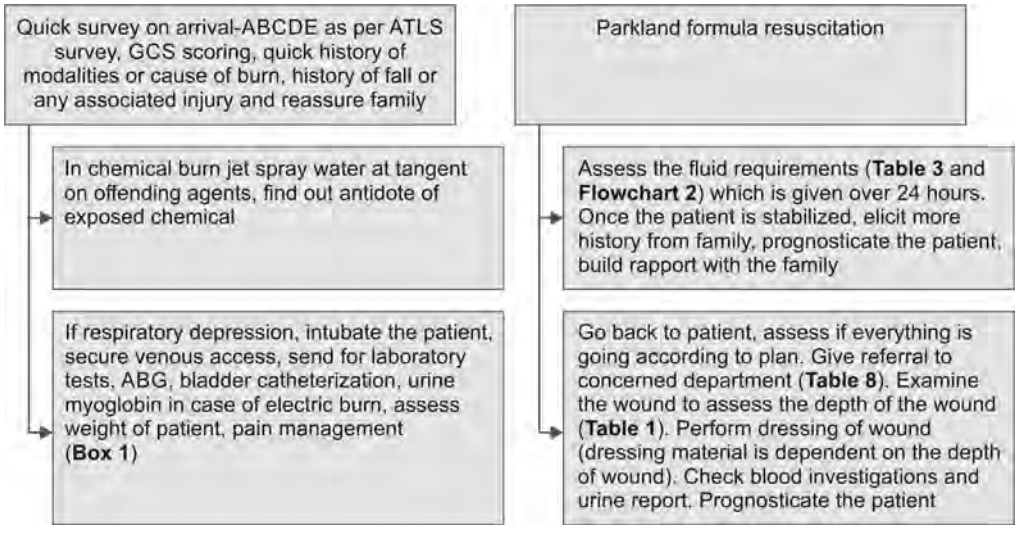

Quick survey on arrival-ABCDE as per ATLS survey, GCS scoring, quick history of modalities or cause of burn, history of fall or any associated injury and reassure family
Parkland formula resuscitation
In chemical burn jet spray water at tangent on offending agents, find out antidote of exposed chemical
Assess the fluid requirements (Table 3 and Flowchart 2) which is given over 24 hours. Once the patient is stabilized, elicit more history from family, prognosticate the patient, build rapport with the family
If respiratory depression, intubate the patient, secure venous access, send for laboratory tests, ABG, bladder catheterization, urine myoglobin in case of electric burn, assess weight of patient, pain management (Box 1)
Go back to patient, assess if everything is going according to plan. Give referral to concerned department (Table 8). Examine the wound to assess the depth of the wound (Table 1). Perform dressing of wound (dressing material is dependent on the depth of wound). Check blood investigations and urine report. Prognosticate the patient

FIG. 5: Summary—approach to a burn patient in the emergency department.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Accidental Hypothermia

Rahul Solanki

INTRODUCTION

Accidental hypothermia (HT) is an unintentional drop in core temperature to 35°C or below. It can be caused by environmental exposure or by decrease or conditions that decrease thermodynamic responses. Resuscitation in emergency can lead to iatrogenic accidental HT. Accidental HT can occur in people who were outdoor for recreational activities or in homeless people. It can occur in any climate (tropical or subtropical) or during any season. Trauma, sepsis, and diseases that decrease metabolic heat production or affect thermoregulation are presented in **Table 1**.

PATHOPHYSIOLOGY

Resting metabolism and neurological functions are decreased as a result of cooling. Even when the core temperature is normal, skin cooling induces shivering which directly increases metabolism by increased muscle activity and indirectly by increased ventilation and cardiac output. As core temperature decreases shivering increases and reaches at maximum level when core temperature is about 32°C and stops by about 30°C. With decreasing temperature metabolism generally decreases below 32°C.

CLINICAL FEATURES AND CLASSIFICATION

The clinical effects of HT are because of decreased function of brain and cardiorespiratory system (**Table 2**). Function of brain is impaired by cooling, which begins at about 34°C and worsens with further cooling. Clinical signs are confusion, irritability, apathy, poor decision making, somnolence, lethargy, coma, and death. Except death, most of the changes are reversible. Even patients in coma often recover neurologically intact. Cold brain has decreased metabolic requirements which can be neuroprotective, especially during anoxic conditions, e.g., drowning. Circulating blood volume is decreased because of cold-induced diuresis, plasma leak, and decreased fluid intake. There is bradycardia and decreased cardiac output because of cooling of heart. Atrial dysrhythmias and premature ventricular contractions and ventricular fibrillations (VFs) can occur as the heart cools to 30°C or below. Below 28°C, VF can be induced by hypocarbia, acidosis, and hypoxia. There is decreased ventilatory sensitivity to carbon dioxide which can result in hypoventilation and respiratory acidosis.

Swiss System Classification

This system of classification correlates clinical signs with the standard core temperature ranges of mild, moderate, and severe HT as well as two additional stages; profound HT and death due to HT. Stages of HT are:

- *HT I*: Clear consciousness with shivering: 35°C to 32°C
- *HT II*: Impaired consciousness without shivering 32°C to 24°C.
- *HT III*: Unconsciousness: 28°C to 24°C
- *HT IV*: Apparent death: 24°C to 13.7°C
- *HT V*: Death due to irreversible HT: <13.7°C

Patients having moderate HT (HT II) are likely to be shivering if the core temperature is above 30–31°C. Rescuers are advised to focus on the level of consciousness rather than the presence or absence of shivering. Trauma and other medical conditions that cause decreased level of consciousness or abnormal vital signs can lead to confusion while classifying the patients. As these conditions may also suppress or abolish shivering the rescuers may rewarm more aggressively at a given core temperature than would otherwise be necessary.

DIAGNOSIS

Hypothermia should be considered in patients if there is a history of cold exposure or diseases that predisposes them to HT, and if they have a cold trunk or a core temperature of <35°C.

Core Temperature Measurement

Mercury or alcohol-containing thermometers cannot measure temperature <35.6°C. When a nonelectronic thermometer device is used, it must be a low reading thermometer. Oral temperature is used only to rule out HT as the oral temperature is lower than core temperature by a variable amount. Rectal and bladder temperature can lag behind core temperature

TABLE 1: Conditions associated with secondary to hypothermia.

Impaired thermoregulation	*Central failure*: • Anorexia nervosa • Cerebrovascular accident • Central nervous system trauma • Hypothalamic dysfunction • Metabolic failure • Neoplasm • Parkinson's disease • Pharmacologic effects • Subarachnoid hemorrhage • Toxins
	Peripheral failure: • Acute spinal cord transection • Decreased heat production • Neuropathy
	Endocrinologic failure: • Alcoholic or diabetic ketoacidosis • Hypoadrenalism • Hypopituitarism • Lactic acidosis
	Insufficient energy: • Extreme physical exertion • Hypoglycemia • Malnutrition
	Neuromuscular compromise: • Recent birth and advanced age with inactivity • Impaired shivering
Increased heat loss	*Dermatologic disorder*: • Burns • Medications and toxins
	Iatrogenic cause: • Emergency childbirth • Cold infusions • Heat-stroke treatment
	Other associated clinical states: • Carcinomatosis • Cardiopulmonary disease • Major infection (bacterial, viral, and parasitic) • Multisystem trauma • Shock

changes by up to 1 hour. They can give false impression that the patient still cooling during rewarming. Until a patient is in a warm environment rectal or bladder temperature should not be performed as exposing a hypothermic patient causes further heat loss. Rectal probe should be inserted to a depth of 15 cm.

TABLE 2: Signs and symptoms of hypothermia.

System	***Features***		
	Mild (35°C to 32°C)	*Moderate (32°C to 28°C)*	*Severe (<28°C)*
CNS	Amnesia, dysarthria, and impaired judgment	Drowsiness, mydriasis, paradoxical undressing, and hallucinations	Coma and loss of ocular reflexes
CVS	Tachycardia progressing to bradycardia and raised BP	Atrial and ventricular arrhythmias, lowered BP, and J wave on ECG	Severe hypotension, bradycardia and asystole
Respiratory system	Tachypnea followed by decrease in minute volume and bronchospasm	Hypoventilation	Pulmonary edema and apnea
Renal and endocrine systems	Cold diuresis and shivering	Increased renal blood flow	Decreased renal blood flow, oliguria, and poikilothermic
Musculoskeletal system	Increased muscle tone followed by fatiguing and anoxia	Hyporeflexia and rigidity	No motion and peripheral areflexia

(BP: blood pressure; CNS: central nervous system; CVS: cyclic vomiting syndrome; ECG: electrocardiogram)

Esophageal Temperature

It is the most accurate and minimally invasive method of core temperature measurement. The probe should be inserted into the lower third of esophagus (approximately 24 cm below the larynx in adults). At this level of esophagus heated humidified oxygen does not affect esophageal temperature. It is usually preferable to protect airway with endotracheal intubation or supraglottic airway.

Epitympanic Temperature

Epitympanic probes are not accurate in the field settings as they are designed to be used in operating theaters. They can be useful when an esophageal probe is not available. Also used preferably over esophageal probe, if airway of the patient is not protected.

Heat Flux Thermometers

It is a noninvasive method of measuring core temperature in hypothermic patients in and out of hospital. The readings

accurately reflect the core temperature in operative and intensive care units.

MANAGEMENT

Out of Hospital Management

Before evaluating the patient and starting treatment, the patient should be moved to a safer place. Safety of the rescuers is the first priority during the rescue. Rescuers should not enter the scene if a hypothermic patient has an obvious fatal injury. After ensuring their safety, rescuers should determine whether the patient is in cardiac arrest. If there is an indication, rescuers should start resuscitation if the patient is in cardiac arrest. If vital signs are present in a patient but not alert then rescuers are advised to avoid causing cardiovascular collapse handling gently and by keeping the horizontal as much as possible. After removing the patient from the scene, encourage the victim to stay alert and focus on survival to minimize the chance of circumrescue collapse. Rewarming and movement of extremities should be avoided to prevent increased blood flow to cool peripheral tissue with resultant increase in return of cooled blood to central circulation. Carefully check signs of life and pulse for 60 seconds as it may be difficult to detect pulse in a hypothermic patient. All patients should be provided full body insulation and rewarming unless it does not impede cardiopulmonary resuscitation (CPR) or delay transport. Only electrical, chemical, or forced air heating packs or blankets should be used as they provide substantial amount of heat transfer.

Cold Stressed Patient who is not Hypothermic

A patient who is completely alert and shivering, well-nourished, and not hypothermic is not at risk for significant afterdrop and circumrescue collapse. Wet clothing of such patients can be removed. They may eat and drink and ambulate as there is no need to be horizontal. Core temperature afterdrop can contribute to cardiovascular instabilities in patients with moderate-to-severe HT during out of hospital care. In hypothermic patients, afterdrop as high as 5–6°C have been reported.

Circumrescue Collapse

It is syncope or sudden death that occurs in patients of cold-water immersion or after rescue and removal from water. It may be due to sudden hypotension or sudden onset of VF. *Prevent further heat loss*—core temperature should be maintained by providing vapor barrier and by adding insulation. Insulation can be added by extra clothing, blankets, quilts, insulated pads, and sleeping bags. Vapor barriers are bubble wraps, plastic sheets, reflective blankets, and garbage bags. They protect against heat loss from evaporation and convection. After these the patient should be rewarmed. Patients with decreased level of consciousness require active rewarming. Rewarming is not required for mild HT that is not complicated by other conditions. Active rewarming methods are preferred over shivering, because shivering is uncomfortable and can stress cardiovascular system. The patient should be insulated and given high carbohydrate drink and food if active rewarming is not possible. Shivering can increase core temperature by 1–3°C per hour in a well-insulated patient with adequate caloric reserves. Do not allow standing and walking in a hypothermic patient who is found sitting or lying down.

Active external rewarming is beneficial in alert, shivering patient and is mandatory in a patient who has decreased level of consciousness. Rewarming may be provided by using large chemical heat pads, large electrical heat pads or blankets, warm water bottle or Norwegian charcoal-burning HeatPac. Body-to-body rewarming of shivering person in a sleeping bag decreases shivering and does not increase the rate of rewarming.

A warm shower or bath should not be used for rewarming because it can lead to cardiovascular collapse. Vasodilation of skin causes increased afterdrop and decreased blood pressure. Cold skin is very susceptible to injuries from pressure and heat. A barrier should be used to protect the skin when using electrical or chemical heat pads and precautions should be taken against pressure injuries. Heated, humidified oxygen should be provided to prevent respiratory heat loss, but it should not be used alone as a rewarming method.

Cardiopulmonary Resuscitation in Hypothermic Patient

Hypothermia protects the brain from hypoxia by reducing brain activity. If core temperature is 20–28°C or not known, rescuers should perform CPR continuously for 5 or more minutes and limit interruptions to CPR to 5 minutes or less. If the core temperature is 20°C or below, CPR should be continued for 5 or more minutes with interruptions of 10 minutes or less. There is no known limit for duration of CPR in a severely hypothermic patient. If there are no contraindications to CPR, rescuers should attempt to resuscitate a patient with severe HT regardless of the measured core temperature. One must remember that low core temperature should not limit resuscitation.

Defibrillation in Hypothermic Patients

Rescuers should wait until a patient has been rewarmed at least 1–2°C before reattempting defibrillation. Above a core temperature of 30°C one should follow usual defibrillation protocol.

The guidelines of European Resuscitation Council recommend a modified approach to Advanced Life Support (ALS), consisting of up to three defibrillations with epinephrine withheld until the core temperature is higher than 30° (86°F) and with the interval between doses doubled until the core temperature is higher than 35°C (95°F). These recommendations conflict with the American Heart Association guidelines, which state, "It may be reasonable to consider administration of a vasopressor during cardiac arrest according to the standard ALS algorithm concurrently with the rewarming strategies." Hence, the administration of up to three doses of medication and defibrillation is likely to be a reasonable approach with further dosing guided by the clinical response.

Chest Compression

Rescuers should perform chest compression at the same rate as in a normothermic patient. During transport, use mechanical compression as manual compression is difficult to perform.

Ventilation in hypothermic patient is ineffective unless an advanced airway (endotracheal tube or supraglottic device)

is in place. If there is an advanced airway, ventilation should be at half the usual rate. If there is no advanced airway end-tidal CO_2 ($EtCO_2$) monitoring is not available, rescuers should administer ventilation to a hypothermic patient at the same rate as for a normothermic patient. Supplemental oxygen may be needed at altitudes above 2,500 m. At sea level, a hypothermic patient may not be hypoxemic. Management of airway is similar in hypothermic and normothermic patient. VF might occur during endotracheal intubation. The risk of VF should not preclude standard airway management with intubation, if indicated. Sometimes trismus prevents laryngoscopy, in that case use of supraglottic device is preferred than fiberoptic intubation or cricothyroidotomy. Cough of an endotracheal tube or supraglottic device should not be over inflated with cold air. Overinflation could cause kinking of the tube or rupture of the cuff if the patient rewarms and the air in the cuff expands. Neuromuscular blockers and anesthetic are likely to be ineffective below 30°C, but their metabolism is decreased and the effects are likely to be prolonged when the agents become effective as the patient rewarms. The dosage of these drugs should be lowered and dosing interval extended.

Fluid Management and Volume Replacement

In a hypothermic patient, intravenous access is difficult due to peripheral vasoconstriction. In such condition intraosseous (IO) access can be used. Central venous access can be used but if the catheter or guidewire comes into contact with the myocardium it may cause VF. In moderate and severe HT blood volume is decreased. Normal saline should be given for volume replacement to prevent hypotension and shock. Ringer lactate should not be used as they cannot metabolize lactate at cold temperature. Insulated tubing and fluid warmer should be used to avoid infusing cold fluid. Fluid should be warm to 40–42°C to avoid cooling or freezing of lines, fluids are best given rapidly as boluses.

Glucose and Insulin Use

In a hypothermic patient either hypoglycemia or hyperglycemia can occur. In a hypothermic patient with altered mental status, glucose is given by IO or intravenous routes. Treatment with insulin is not necessary if there is hyperglycemia in a hypothermic patient and it may not be effective below 30°C. Hyperglycemia has no known adverse effects in HT.

Cardiovascular Drugs

There are not sufficient data for the use of cardiovascular drugs in HT below 30°C. In HT, metabolism of drugs is decreased as protein binding is increased. It is better not to give vasoactive drugs in a patient with core temperature <30°C. Between 30 and 35°C drug should be given at the normal dose but with twice interval between doses. Atrial dysrhythmias often occur during rewarming and should not be treated if the patient is hemodynamically stable.

Pacing

Transcutaneous pacing may be used in a patient having bradycardia and hose blood pressure is too low to allow arteriovenous rewarming. Transvenous pacing is contraindicated in HT due to cardiac instability.

Transport and Triage

An alert patient with shivering can be treated in the field unless the patient has an injury or medical conditions requiring evacuation. Patient having asphyxia from drowning or avalanche burial are at risk of delayed complications and they should be shifted to a center capable of managing acute respiratory distress syndrome. Severely injured patients should be treated as soon as possible with active rewarming to prevent HT as they are unable to shiver and become hypothermic quickly, even during mild weather. A cold stressed or hypothermic patient with decreased level of consciousness should be treated with activity rewarming even if shivering. A patient with moderate/severe HT who is hemodynamically stable should be transported to nearest center with rewarming facilities. A hemodynamically unstable patient should be transferred to a center that can perform extracorporeal circulation (ECC) using extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass.

Importance of Serum Potassium

High-serum potassium is a marker of cell lysis and death. If hypothermic patient in cardiac arrest has serum potassium >12 mmol/L, CPR should be discontinued as patient can be declared dead without further warming.

Inhospital Management

In a patient with HT and stable circulation active external and minimally invasive rewarming is induced along with treatment of any condition causing secondary HT. Considering the risk of complications such as thrombosis and hemorrhage with rewarming methods (e.g., body cavity lavage, endovascular device, and extracorporeal heating system), the best approach may be the use of active external and minimally invasive rewarming. ECMO or cardiopulmonary bypass should be considered for patient with HT and cardiac instability who are not responding to medical management.

Treatment with ECMO and cardiopulmonary bypass is safe and efficient when signs of life and vital signs are absent (stage HT IV). After rewarming there are chances of developing severe pulmonary edema. It can be treated more efficiently with ECMO compared to traditional cardiopulmonary bypass.

If a patient with cardiac arrest due to HT is rewarmed to a core body temperature that is >32°C and asystole persists, irreversible cardiac arrest is very likely and termination of CPR should be considered. Staging-based management of accidental HT is summarized in **Table 3**.

HYPOTHERMIA OF EXTREMITIES

Frostnip and Chilblain (Erythema Pernio)

Frostnip is a temporary and mild form of cold-induced injury causing local paresthesia of the involved area that completely resolves with passive external rewarming. Chilblains (erythema pernio) are inflammatory skin changes caused by exposure to cold without actual freezing of the tissues. These skin lesion maybe purple or red papular lesions which are painful or pruritic with burning or paresthesia. They may be associated with edema or blistering and aggravated by warmth. If exposure

TABLE 3: Staging and management of accidental hypothermia (HT).

Stage	*Clinical symptoms*	*Typical core temperature*	*Treatment*
HT I	Conscious and shivering	35°C to 32°C	Warm environment and clothing, warm sweet drinks, and active movement (if possible)
HT II	Impaired consciousness and not shivering	<32°C to 28°C	Cardiac monitoring, minimal and cautious movements to avoid arrhythmias, horizontal position and immobilization, full-body insulation, active external and minimally invasive rewarming techniques (warm environment; chemical, electrical, or forced-air heating packs or blankets; warm parenteral fluids)
HT III	Unconscious, not shivering, and vital signs present	<28°C to 24°C	HT II management plus airway management as required; ECMO or CPB in cases with cardiac instability that is refractory to medical management
HT IV	No vital signs	<24°C	HT II and III management plus CPR and up to three doses of epinephrine (at an intravenous or intraosseous dose of 1 mg) and defibrillation, with further dosing guided by clinical response; rewarming with ECMO or CPB (if available) or CPR with active external and alternative internal rewarming

- Hypothermia may be determined clinically on the basis of vital signs with the use of the Swiss staging system. CPB denotes cardiopulmonary bypass, CPR denotes cardiopulmonary resuscitation, and ECMO denotes extracorporeal membrane oxygenation
- Measurement of body core temperature is helpful but not mandatory. The risk of cardiac arrest increases as the core temperature drops below 32°C and increases substantially if the temperature is <28°C. To convert values for temperature to degrees Fahrenheit, multiply by 9/5 and add 32

is continuous, ulcerative or hemorrhagic lesions may appear and progress to scaring, fibrosis, and atrophy.

Treatment

Affected part is kept elevated and passively external rewarming is used. Rubbing and massaging injured tissue is avoided. Applying ice and heat is also avoided. Protect the affected area from trauma secondary infection and further cold exposure.

Immersion Foot or Trench Foot

Immersion foot (or hand) is caused by prolonged immersion in cold water or mud usually below 10°C. It has three stages:

1. *Prehyperemic stage*: Characterized by symptoms of cold and anesthesia
2. *Hyperemic stage*: Hot sensation, severe burning, and shooting pain
3. *Posthyperemic stage*: With ongoing cold exposure the affected part becomes pale or cyanotic with diminished pulsation due to venospasms. This may result in blistering, swelling, redness, ecchymoses, hemorrhage, necrosis, peripheral nerve injury, and gangrene.

Treatment consists of air drying, protecting extremities from trauma and secondary infection, and gradual rewarming by exposure to room temperature. Avoid using ice or heat. Avoid massaging, moistening of the skin. Affected part can be elevated, cushions are used to protect the pressure sites.

Frostbite

Frostbite is injury from tissue freezing and formation of ice crystals in the tissue. With reperfusion of the frozen tissue, destruction occurs with damaged endothelial cell and progressive microvascular thrombosis causing further tissue damage. Only skin and subcutaneous tissue are involved in mild cases. Symptoms are prickling, numbness, itching, and pallor. Deeper structures are involved with increasing severity. The skin appear white or yellow, elasticity is lost and becomes immobile. Edema, hemorrhage blister, necrosis, gangrene, paresthesias, and stiffness may occur.

Treatment

Secondary exposure to cold is avoided. Associated systemic HT, concurrent condition, and injury are evaluated and treated. Fluid is given to avoid hypovolemia and to improve perfusion.

Rewarming

Rapid rewarming at temperatures slightly above normal body temperature may significantly decrease tissue necrosis and reverses tissue crystallization. If there is any possibility of refreezing, the frostbitten part must not be thawed. Ideally the frozen extremity must not be used. Rewarming is best achieved by warm bath emersion. The frozen external extremity is immersed for several minutes in a moving water bath heated to 40–42°C until the distal tip of the part being thawed flushes. If warm water is not available then passive thawing in a warm environment must be done. Dry heat is not recommended because it is more difficult to regulate and increases the chances of accidental burns. Once the frozen part is thawed and return to normal temperature (in about 30 minutes), external heat is discontinued. In the early stage, rewarming by exercise, rubbing, or friction is contraindicated. Application of casts, occlusive dressings, or bandages is avoided. Blisters must be left intact unless signs of infection supervene. Aseptic wound care may reduce the risk of infection. Nonadherent sterile gauge and fluffy dressings should be loosely applied to wounds. Tetanus prophylaxis status must be verified and dealt accordingly.

Medical and Surgical Treatment

Need for amputation have been decreased by the use of intravenous infusion of synthetic prostaglandins and tissue plasminogen activator and intra-arterial thrombolytic within 24 hours of exposure. Clinicians must watch for evidence of compartment syndrome and need for fasciotomy. Eschar formation without evidence of infection may be conservatively treated.

Debridement and amputation may be considered only after it is established that the tissue are necrotic. Prognosis of frostbite depends on the underlying comorbidities, the extent of initial tissue damage, the rewarming reperfusion injury, and the late sequelae. Neuropathic sequelae include numbness, tingling, pain, hyperhidrosis, and cold sensitivity of the extremities. Nerve conduction abnormalities may persist for many years after a cold injury.

AVALANCHE

The most common cause of death in avalanche burial is asphyxia. A victim who survives an avalanche initially may die from asphyxiation due to hypercapnia and hypoxemia, airway obstruction (constriction of the chest due to snow or other debris and trauma). A rapid decrease in survival occurs during the initial 35-minute asphyxia phase, an air pocket in front of the mouth or nose can slow asphyxiation and prolonging survival. Cooling of a victim of avalanche burial can be rapid, especially if the victim is asphyxiated. The average cooling rate after avalanche burial is about 3°C per hour. The current recommendation is to use standard resuscitation, if burial was 60 minutes or less or core temperature is 30°C or above. If there is return of spontaneous circulation (ROSC), the victim should be evacuated to the closest hospital that is able to manage associated injuries. A victim with vital signs who was buried longer than 60 minutes or with core temperature <30°C should be transferred to the nearest facility capable of providing active rewarming. CPR should be started if the victim is in cardiac arrest and has a patent airway. If the victim does not have a patent airway and is in cardiac arrest, decision to withhold CPR and resuscitation is reasonable. A victim of avalanche burial is most likely to be asphyxiated before becoming hypothermic. The highest serum potassium documented in an avalanche victim who was successfully resuscitated was 6.4 mmol/L. In 2015, the European Resuscitation Council proposed serum potassium of 8 mmol/L as the upper limit for attempting resuscitation of an avalanche victim. Resuscitation should be discontinued if serum potassium is 8 mmol/L or more.

SUMMARY

Hypothermia can be life-threatening. Rescuers should attempt to minimize further heat loss and begin rewarming of hypothermic patients in the field while minimizing after drop and preventing circumrescue collapse. Some patients are cold and dead, but other cold patients who are apparently dead can be resuscitated with full neurologic recovery. Unless there are definite contraindications, rescuers should do their best to resuscitate HT patients, even if they appear to be beyond hope.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Heat Illness

Omar Ghazanfar, Saleh Fares

INTRODUCTION

Heat illness is a common medical emergency in tropical areas, especially the heat stroke is cause of concern, clinically diagnosed as a core temperature >40°C with central nervous system dysfunction or multiorgan dysfunction (core temperature is at which blood perfusion of hypothalamus and vital organ of body like heart brain are maintained, normal core body temperature is 36–37.5°C and rectal temperature being the closest approximation).

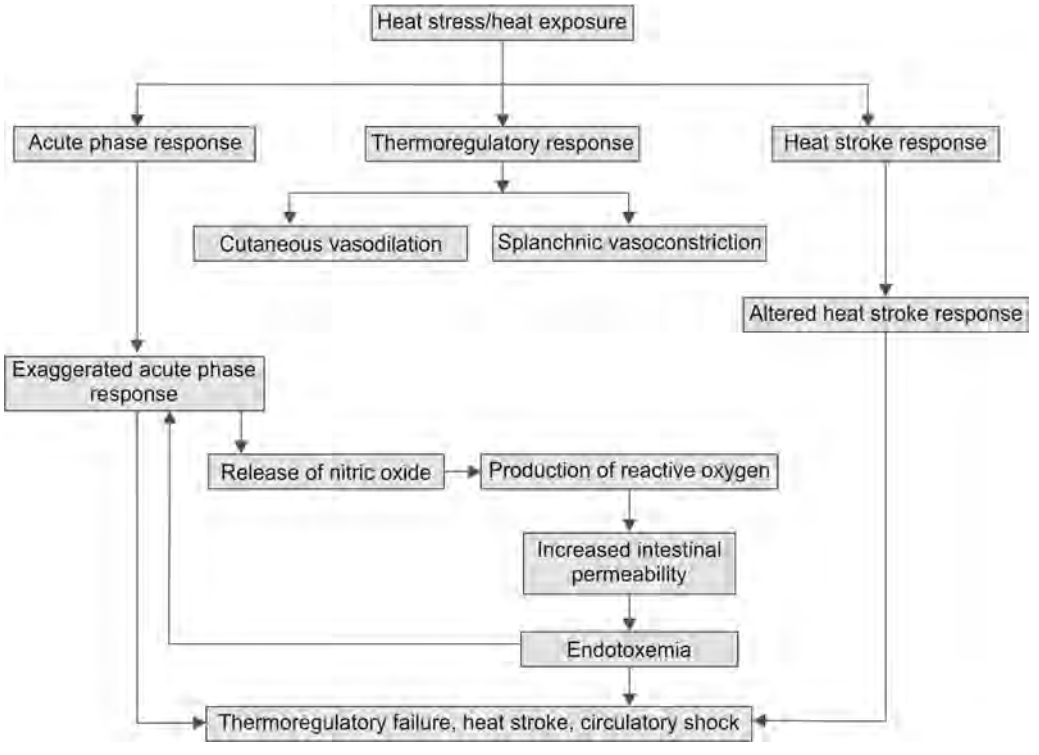
Heat stroke is one of the important treatable causes of multiple organ failure resulting from thermoregulatory failure. Heat stroke problem in tropics is increasing with rise of global warming. In India, Northern and Western India are worst affected due to heat stroke. Exertion-induced heat stroke is reported in military recruits. In spite of advances in the treatment, mortality due to heat stroke remains high. Pathophysiologic changes on exposure to heat are depicted in **Flowchart 1**.

CLASSIFICATION OF HEAT ILLNESS

Heat illness is a spectrum of disorders due to environmental exposure to heat. It ranges from minor conditions such as heat cramps, heat syncope, and heat exhaustion to the more severe condition known as heat stroke. A number of heat illnesses exist across a broad spectrum of presentations (**Table 1**).

HEAT CRAMP

Heat cramps are muscular spasms which result from a loss of salt and water due to excessive exercise. Heat cramps are



FLOWCHART 1: Pathophysiology of heat-related illness.

TABLE 1: Classification of heat illness.

Type	*Characteristic feature*
Heat cramps	Muscular pain which happens after exercise in hot conditions
Heat edema	Cutaneous condition characterized by dependent edema from vasodilatory pooling
Heat rash	Irritation of the skin that results from excessive sweating during hot and humid weather
Heat tetany	A result of short periods of stress in intense heat. Symptoms may include hyperventilation, respiratory problems, numbness or tingling, or muscle spasms
Heat syncope	Dizziness as a result of excess heat
Heat exhaustion	A precursor of a heatstroke; which include heavy sweating, rapid breathing, and a fast, weak pulse
Heat stroke	A core body temperature of >40°C (104°F) due to environmental heat exposure with either a lack or dysfunction of the central and peripheral thermoregulation centre. Symptoms include dry skin, rapid, strong pulse, and dizziness

associated with cramping in the abdomen and calves. This is caused by inadequate intake of fluid and electrolytes. Heavy sweating can also result in heat cramps, especially when the water is replaced without electrolyte replacement.

Heat cramps can be quite painful, but they do not result in permanent damage but can be an early symptom of heat exhaustion and heat stroke. Heat cramps can however indicate a more severe pathology in patients with heart disease or if it lasts for a prolonged period of time. Prevention includes oral rehydration during severe exercise or strenuous work and consumption of eat potassium-rich foods like bananas. After heat cramps occur, the affected patient should avoid strenuous work and exercise for several hours to allow adequate recovery.

HEAT EDEMA

Heat edema is a skin condition characterized by edema in dependant body areas as a result of vasodilatory pooling. Heat causes the blood vessels to dilate, resulting in gravitation of body fluids so body fluid moves into the hands or legs by gravity. The balance of salt in the body is also a risk factor for heat edema. If salt loss is less than normal, the increased salt level draws fluid into the hands and legs. Elderly patients have an increased risk of heat edema, especially if they have other medical conditions that affect their circulation. People visiting hot climates from colder climates may also have an increased risk of heat edema.

HEAT RASH

Heat rash occurs when the skin's sweat glands are blocked, and the sweat produced cannot get to the surface of the skin to evaporate. This causes inflammation that result in a rash. Common symptoms of heat rash include red bumps on the skin and a prickly or itchy feeling to the skin (also known as prickly heat). The rash appears as reddened skin with tiny blisters and is due to inflammation. It often occurs in skin creases or areas of tight clothing where air cannot circulate. Heat rash usually fades when the skin is allowed to cool. Medical treatment is necessary only if the area becomes infected. Heat rash can be prevented by avoiding hot, humid conditions, wearing lose fitting clothes, and using air conditioning or fans to allow air to circulate.

HEAT TETANY

Heat tetany (hyperventilation and heat stress) is usually related to short periods of stress in intense heat environments. Symptoms may include hyperventilation, respiratory problems, numbness or tingling, or muscle spasms. Treatment includes removing the affected person from the heat and slowing the breathing pattern.

HEAT SYNCOPE

Heat syncope occurs in a warm environment when the blood pressure drops due to dilatation of the arterioles in the skin to radiate heat. This condition usually occurs within 5 days of heat acclimatization, before the actual blood volume expands. This subsequently leads to reduction blood to the brain, causing light-headedness and near syncope during sudden postural movements or if the patient remains standing for a prolonged period of time. Individuals who perform strenuous work outside in warm climates are at particular risk.

Symptoms

Symptoms can include faintness, dizziness, headache, increased pulse, restlessness, nausea, vomiting, or brief loss of consciousness.

Diagnosis

The diagnosis of heat syncope is through a history and physical examination. During the physical examination, the healthcare provider should assess the vital signs including postural blood pressure and the pulse. If the patient experiences heat syncope, the patient is usually hypotensive and tachycardic. Excess sweating is also being a key sign. A detailed history is imperative. If the patient develops symptoms during physical activity in high temperatures, then the diagnosis of heat syncope can be made.

Treatment

The basic treatment for heat syncope is similar to other types of syncope. The patient is positioned in a seating or supine position with legs raised. If the patient can tolerate it, oral rehydration with salt or a drink containing electrolytes, can be administered slowly, and the patient is moved to a cooler area preferably under a shade. The affected person should be advised rest; as heat syncope can lead to heat exhaustion and subsequently heat strokes.

Prevention

Physical activity in extremely hot weather should be avoided. In the event of symptoms, the patient should be moved

to a shaded or cooler location. It is also recommended to avoid alcoholic beverages in hot weather as this can lead to dehydration which may exacerbate symptoms. Patients should also be encouraged to increase the intake of oral fluids during physical activity.

HEAT EXHAUSTION

Heat exhaustion is often a precursor of heat strokes if the patient is not treated appropriately and in a timely manner. Etiology and risk factors include hot, sunny, humid weather along with physical exertion in extremes of heat. Impaired thermoregulation in extremes of age results in geriatric and pediatric patients suffering from severe heat illness even at rest, if the weather outside is hot and humid with a lack of ventilation. Drugs including diuretics, antihistamines, and beta-blockers and agents of misuse such as alcohol, ecstasy, and amphetamines can also increase the incidence of heat exhaustion. During physical exertion, risk factors for heat exhaustion include wearing dark, padded, or insulated clothing; hats; and/or helmets in some professions, having a higher percentage of body fat, and lack of fluid intake leading to dehydration as well as pyrexia.

Symptoms

Symptoms include dizziness, nausea, headache, increased thirst, raised core body temperature, increased sweating, and reduced urine output. Heat exhaustion should be differentiated from heat stroke (**Table 2**).

Treatment

Basic management includes moving the person to a cool place with removal of extra layers of clothes. Passive cooling by fanning wet towels and increase intake of oral fluids, if the patient is conscious. Specific management includes following the usual Airway, Breathing and Circulation (ABC) approach. Supplemental oxygen may be required and if the patient is confused with impaired level of consciousness and/or vomiting, intravenous fluids and electrolyte replacement is needed.

TABLE 2: Differentiating heat exhaustion from heat stroke.

Heat exhaustion	• Heavy sweating • Heavy thirst • Rapid breathing • Headache blurred vision • Confusion • Dizziness • Cramps
Heat stroke	• No sweating • Red flushed hot dry skin • Symptoms of heat exhaustion are more severe • Difficult breathing • Confusion altered behavior • Convulsion collapse

HEAT STROKE

Heat stroke is a type of severe heat illness that results in a core body temperature of >40.0°C and associated with confusion. Other symptoms include red, dry or damp skin, headache, and dizziness which can be sudden or gradual. Complications can include seizures, rhabdomyolysis, and renal impairment.

Heat stroke results from extreme high environmental temperatures or severe physical exertion. There are certain *risk factors* (**Box 1**) including heat waves, humidity, and *medications* (**Box 2**) which include diuretics, beta-blockers, and alcohol as

BOX 1: Risk factors for heat stroke.

- Age >65 or <15
- Cognitive impairment
- Heart or pulmonary disease
- Poor access to ventilation
- Psychiatric illness
- Obesity
- Physical disability
- Poor fitness level
- Sickle cell trait
- Excess physical activity in high temperature
- Urban residence, especially on high floors
- Heat wave
- Drugs
- Current febrile illness
- Skin disease
- Lack of acclimatization
- Previous heat stroke
- Increased heat index
- Alcohol consumption
- Lack of sleep, food, and water

BOX 2: Medications and substances that contribute to heat-related illness.

- Alcohol
- Alpha-adrenergic agonists
- Amphetamines
- Anticholinergics
- Antihistamines
- Benzodiazepines
- Beta-blockers
- Calcium channel blockers
- Cocaine
- Diuretics
- Ephedra supplements
- Laxatives
- Neuroleptics
- Phenothiazines
- Stimulants

well as cardiac disease and skin pathology. Extremes of age and individuals with long-term chronic illness not associated with physical exertion typically occur in extremes of age or with chronic health problems. Heat stroke is a type of hyperthermia and is a pathological increase in the body's core temperature set point. Drinking sufficient fluids and avoiding excessive heat can be an effective preventative measure. Treatment includes rapid physical cooling of the body and supportive measures. Spraying the patient with water and using a fan, or placing the patient in an ice bath, or giving cooled intravenous fluids are some of the measures which can be taken. Adding ice packs is not routinely recommended. Heat stroke results in >600 deaths a year in the United States. Rates have increased in the last decade. The risk of death is over 5% in those with exercise-induced heat stroke and >65% in those with nonexercise-induced cases. Heat stroke can be classified as:

- Classical heat stroke
- Exertional heat stroke

Classical Heat Stroke

It is usually affected older age group with limited mobility and/or chronic diseases, and individual vulnerable to excessive environmental temperature and humidity. Laboratory feature like respiratory alkalosis is common.

Exertional Heat Stroke

It is usually seen in young healthy individual who overexert in the heat and humidity. Respiratory alkalosis with lactic acid, rhabdomyolysis, renal failure, disseminated intravascular coagulation (DIC), and hyperuricemia are frequently seen.

Symptoms

Heat stroke presents with a hyperthermia of >40.0°C in conjunction with disorientation and anhidrosis. Early signs include dizziness, mental confusion, headaches, and weakness. In exertional heat stroke, the affected person may sweat excessively. Pediatric patients may have seizures. Eventually there is impairment of consciousness, multiorgan failure, and death.

Etiology

Heat stroke occurs when the thermoregulation system is overwhelmed by a combination of excessive metabolic production of heat excessive environmental heat and insufficient or impaired heat loss. Alcohol, stimulants, medications as well as extremes of age can result in nonexertional heat strokes. Exertional heat stroke can occur in young individuals without existing health problems or medications and the spectrum of patients include athletes, outdoor workers, military personnel on outdoor maneuvers as well as emergency medical services (EMS) first responders wearing heavy personal protective equipment (PPE). In hot and humid environments, the humidity tends to reduce the degree to which the body can self-regulate the temperature by sweating and evaporation. Excessive body temperature can disrupt enzymes regulating biochemical reactions that are essential for cellular respiration and organ functions.

Young children, elderly adults, or disabled individuals left alone in a vehicle are at high risk of heat developing a stroke. In child deaths in hot cars, approximately 50% happened because parents forgot that the child was in the car, 18% happened after parents intentionally left the child in the car without understanding how hot it could get, and 30% happened after the child climbed into the car to play. This can have medical as well as legal consequences.

Prevention

The risk of heat stroke can be reduced by observing precautions to avoid overheating and dehydration. Light and loose-fitting clothes will allow perspiration to evaporate and cool the body. Wide-brimmed hats in light colors help to prevent the sun from warming the head and neck. Vents on a hat will help cool the head. Strenuous exercise should be avoided during daylight hours in hot weather. People working in confined spaces (such as automobiles) without air conditioning or ventilation, advised to maintain adequate hydration to prevent dehydration.

Treatment

Maintain ABC and cardiac monitoring. Important recommended investigations are summarized in **Box 3**. Treatment of heat stroke involves rapid mechanical cooling along with resuscitation measures. The body temperature must be lowered quickly. The patient should be moved to a cool area which is either indoor or in a shade and clothing may need to be removed to promote passive clothing. Active cooling methods include immersion in cold water, or a hyperthermia vest can be applied. Cold compresses to the torso, head, neck, and groin will help in bringing the body core temperature down. A fan or dehumidifying air conditioning unit may be used to aid in evaporation of the water (**Fig. 1**).

Immersion should be avoided for an unconscious person, but if there is no alternative, the patients' head must be held above water. Dantrolene, a direct-acting paralytic which abolishes shuddering and is effective in many other forms of hyperthermia has no individual or additive effects to cooling in the context of heat stroke, showing a lack of endogenous thermogenic response to cold water immersion. Aggressive ice-water immersion is the gold standard for life-threatening heat stroke.

BOX 3: Investigations in heat-related illness.

- Monitor core body temperature regularly
- CBC
- LFTs
- U&E
- Glucose
- Urate—may be a predictor of acute kidney injury
- Creatine kinase—may be a predictor of rhabdomyolysis
- Coagulation studies
- Arterial blood gases
- Urinalysis—may show myoglobinuria and impending acute kidney injury
- ECG
- CXR—to check for aspiration/pulmonary edema

(CBC: complete blood count; CXR: chest X-ray; ECG: electrocardiogram; LFTs: liver function tests; U&E: urea and electrolytes)

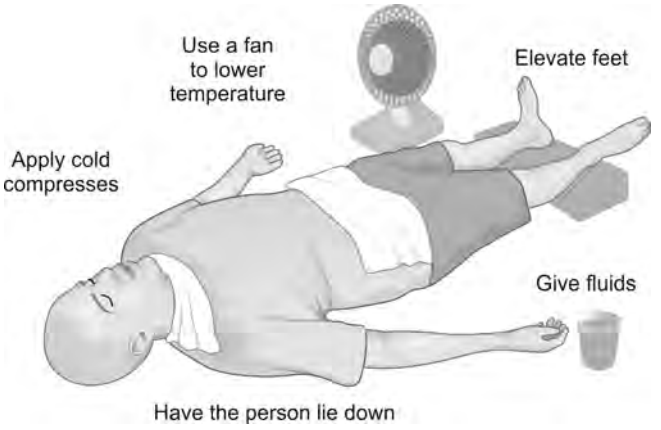


FIG. 1: Supportive measures for managing heat stroke.

Adequate hydration is essential adjunct to cool the temperature. In mild cases of dehydration, hydration can be achieved by drinking water or isotonic sport drinks. In exercise- or heat-induced dehydration, an imbalance of electrolytes can occur and is exacerbated by overconsumption of water. Hyponatremia can be corrected by intake of hypertonic fluids. Absorption is rapid and complete in most people, but in the event of confusion, impaired conscious level or if the patient is unable to tolerate oral fluid, then an intravenous rehydration and electrolyte replacement may be required. The person's condition should be reassessed at regular intervals including the vital signs to ensure stability.

Prognosis

It was believed that heat strokes rarely lead to permanent deficits and that the recovery is almost complete. However, research has showed that patients with heat stroke severe enough to require intensive care can leave to high percentage of morbidity and mortality. Some patients can have permanent loss of independent function or severe functional impairment at discharge which was persistent even 12 months after discharge from the healthcare facility.

SUMMARY

Heat illness is a wide spectrum of different symptomatology which can range of heat cramps to heat stroke with a multitude of pathologies within the spectrum. Extreme heat can affect any individual; however, the elderly and children are more susceptible to heat stress along with people with preexisting medical problems. Heat stress generally occurs when the body's thermoregulatory systems are unable to cope with extremes of temperatures and can lead to a wide spectrum of heat-related illnesses ranging from the simple heat cramps to the life-threatening heat stroke. Treatment revolves from instigating basic measures to remove the individual from the source as well as more advanced treatment strategies which include passive or active cooling as well as intravenous fluid and electrolyte replacement. The emphasis should however be on prevention strategies, especially in extremes of ages where heat stress can be life-threatening and result in significant morbidity and mortality.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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CHAPTER

Decompression Illness

Goma Bajaj, Devendra Richhariya

INTRODUCTION

Diving is a popular outdoor and pastime activity with numerous scientific benefits, though underwater environment is unforgiving and diving can be done safely. To avoid any problem during diving acquire sufficient medical or physical fitness and sound knowledge about use of equipment at high-pressure environment. Decompression illness (DCI) is a manifestation due to arterial gas embolism (AGE). AGE develops due to pulmonary barotrauma, alveolar wall damage, and gas enters into the systemic arterial circulation. Decompression sickness (DCS) develops due to large amount of gas release from tissue during or while coming to surface and less time for equilibration (decompression) of DCI incidence rates in the recreational community range from 2.0 to 4.0 per 10,000 person-dives. The DCS incidence rate in commercial decompression diving has been reported to be as high as 35.3 per 10,000 person-dives.

DIVING PHYSICS

Ambient pressure helps in dissolving inert gas within body tissues which is normally exist in equilibrium in a saturated state. When any pressure differences (gradients) develop, molecules move from higher to lower concentration until equilibrium is reestablished. The pressure of the diving environment is much greater than the pressure of the surface environment. The lungs when exposed to increased pressure underwater, the gas in the lungs is compressed and creates an inflow gradient from concentrated lung gas to the bloodstream and, subsequently, from the bloodstream into tissues as they are perfused. Lungs plays an important role in gas uptake and elimination and finally in decompression stress.

DEVELOPING DECOMPRESSION SICKNESS

Although DCS is commonly thought of as a bubble disease, bubbles are probably only the gateway to a complex array of consequences. Bubbles can develop within the tissues or reach to different and initiate biochemical cascades to produce secondary insults and effects. Vascular obstruction or interactions may stimulate platelet aggregation, leukocytes activation and aggregation, and fibrin deposition. Intravascular air may cause capillary endothelium damage, increased in endothelial permeability, and tissue edema exacerbating the ischemia process. Other possible contributing process is increased in release of cytokines complement activation and inflammatory cascade could play an important role in the pathophysiology of DCI. The in-activation variability of this inflammatory cascade might explain the differences between individuals in susceptibility to DCS. The inflammatory and coagulation cascades might also explain the failure of recompression treatment in some cases because, once activated, the resolution of bubbles will not immediately stop the response. A rapid ascent with full lungs and an obstructed airway from this very shallow depth could result in pulmonary barotrauma. Tissue rupture will allow gas from the alveolar space to enter the pleural space (pneumothorax), the pulmonary interstitium, the mediastinum (pneumomediastinum), and/or the pulmonary capillaries. Bubbles entering the pulmonary capillaries can be transported into the systemic arterial circulation and may reach critical tissues, such as the brain or the spinal cord, to produce serious symptoms. The symptoms of AGE can be very similar to those of DCS, sometimes making them difficult to separate.

SIGNS AND SYMPTOMS

Clinical manifestations of DCS categorized as type 1 and type 2. Type 1 DCS manifestations are mild and musculoskeletal pain and mild cutaneous symptoms and type 2 clinical manifestations are more serious. Itching and mild rashes (clear, mottled or marbled, and sometimes raised discoloration cutis marmorata) are common skin manifestations in type 1 category. Musculoskeletal manifestations of type 1 DCS are articular or periarticular pain and shoulders, elbows, wrists, hips, knees, and ankles joints are commonly involved. The joint pain (present at rest) may range from mild to severe, usually has a gradual onset and presents as a deep dull ache (**Table 1**).

Type 2 symptoms are divided into three categories: neurologic, inner ear, and cardiopulmonary. Neurologic symptoms include numbness; paresthesia or tingling; muscle

TABLE 1: Clinical manifestations of the decompression sickness.	
Skin	Itching, nonspecific skin rash, urticarial rash, and well-organized mottling (cutis marmorata)
Lymphatics	Localized pain in the region of lymph nodes, localized skin, and soft tissue swelling (lymphedema)
Musculoskeletal	Articular or periarticular pain, muscular pain, and usually no joint swelling and no redness
Respiratory	Dyspnea, cough, respiratory distress, retrosternal pain worsened on inspiration, tachypnea, tachycardia, hypotension, frothy bloody sputum, and low oxygen saturation
Central nervous system	Headache, unexplained fatigue, malaise, dizziness, impaired cognitive processes, paresthesia, limb weakness, speech difficulty, visual loss, ataxia, nausea, vomiting, convulsions, altered state of consciousness, confusion, visual field deficit, unusual distribution of sensory deficits, motor deficits, coordination deficit, gait and walking disturbance, ataxia, and positive Romberg sign
Spinal cord	Back pain, girdling abdominal pain, numbness, paresthesia, limb weakness, urinary or fecal dysfunction (with urinary issues being more common), motor and/or sensory deficits, anal sphincter weakness, urinary retention, loss of bulbocavernosus reflex, and loss of deep tendon reflexes
Peripheral nervous system	Numbness or paresthesia in a peripheral nerve distribution and patchy sensory deficits
Inner ear	Deafness, vertigo, nausea, vomiting, ataxia, tinnitus, acute sensorineural hearing loss, and nystagmus
High likelihood of decompression sickness if symptoms appear >10 min to 6 h duration (low likelihood if >12 h)	

weakness; impaired gait, physical coordination, or bladder control; paralysis; or change in mental status. Other neurologic features are headache, light-headedness, unexplained fatigue, malaise, nausea and/or vomiting, or anorexia. Inner ear symptoms include tinnitus, hearing loss, vertigo or dizziness, nausea, vomiting, and impaired balance. Cardiopulmonary symptoms occur when large bubble obstruct the large area of pulmonary vascular bed and may presents as the choking, dry cough sometime with pink frothy sputum, retrosternal pain, and dyspnea. Differentiate immersion pulmonary edema from cardiopulmonary DCS. Development of type 2 symptoms can be insidious or quick. Features such as walking difficulty, urinating problem, hearing problem, or vision problem can also occur. The following list ranks the initial manifestations of DCS, with frequency estimates for each: pain, particularly near the joints (68%), numbness or paresthesia (63%), constitutional symptoms (41%), dizziness or vertigo (19%), motor weakness (19%), cutaneous changes (10%), impaired mental status (8%), impaired coordination (8%), muscle discomfort (7%), pulmonary symptoms (6%), bladder or bowel dysfunction (3%), auditory symptoms (2%), impaired consciousness (2%), lymphatic involvement (2%), and compromised cardiovascular function (<1%).

Severe neurologic DCS symptoms usually appear within 10 minutes of surfacing and in 90% of cases symptoms will be present within the first 3 hours. In some cases, it can take up to 24 hours for symptoms to be noticed by the diver.

MEDICAL ASSESSMENT OF THE INJURED DIVER

The management of suspected DCS starts with history and physical examination. In addition to the usual medical questionnaire, the emergency physician should seek the following information: Time of onset and evolution of symptoms and signs: Onset of symptoms <10 minutes after surfacing could indicate AGE while >10 minutes after surfacing is more likely associated with DCS.

Profiles of the Recent Dives

Depth-time exposure, ascent rate, ascent stops (obligatory decompression stops or nonobligatory safety stops), and patterns of repetitive dives should be noted. Greater depth and duration imply a larger inert gas burden, but using maximum depth alone to assess severity can be misleading given the common use of multilevel dive profiles. The use of oxygen-enriched mixtures (nitrox) and helium-oxygen and helium-oxygen-nitrogen mixtures (trimix) is increasingly common by divers. Decompression stress is reduced by using nitrox.

Thermal Stress

Decompression stress also increases with being warm during the descent and/or bottom phase of a dive. Being cold during the ascent and/or stop phase inhibits inert gas elimination, increasing the decompression stress.

Exercise Stress

Decompression stress increases subsequently with exercise during the descent and/or bottom phase of a dive as increase in inert gas uptake. Light exercise during the ascent and/or stop phase promotes inert gas elimination, reducing the decompression stress. Vigorous exercise during the ascent and/or stop phase can promote bubble formation and increase risk. After-dive exercise, particularly with high joint forces, can promote bubble formation and increase risk.

Altitude Exposure and Diving

Flying to a destination near sea level before diving creates no risk (outside the possibility of mild dehydration or impairment due to long periods of relative immobility). Flying soon after diving increases decompression stress because the pressure in an aircraft cabin is below ground-level atmospheric pressure.

State of Hydration

Dehydration is often considered as a risk factor and can elevate the decompression stress of a given exposure.

Contributing Factors

Assessment of physical and medical fitness (present or chronic) including history of DCS and medication use should be done. The physical evaluation should focus on:

- *Vital signs*: Any changes in vital signs should be evaluated rapidly and managed urgently. Vital signs should include rectal temperature to detect hypothermia or heat exhaustion. Causes of shock may be cardiopulmonary DCS, tension pneumothorax, hypovolemia due to physical trauma, or from a neurogenic shock due to spinal cord DCS. Blood glucose level should be measured to rule out hypoglycemia in any patient presenting with altered state of consciousness or neurologic symptoms.
- *Cardiac and lung auscultation*: Evaluate for breath sounds on each side, subcutaneous emphysema, displaced trachea, and Hamman's sign (potentially indicating pneumothorax or mediastinal emphysema from a pulmonary barotrauma).
- *Ear examination*: Evaluate for signs of middle ear barotrauma that could be associated with inner ear damage.
- *Neurologic examination*: Evaluate mental status, cognitive function, gait and walking, cranial nerves, sensory function, limbs strength, cerebellar function, and reflexes. Anal sphincter tone and bulbocavernosus reflex are essential to verify in patients with suspected spinal cord DCS and possible spinal shock. Neurologic examination can show very unusual distribution of deficits because bubbles can cause vascular occlusions at many different locations in the nervous system and can be confusing for the physician so unusual neurologic complaints or findings should not be dismissed as imaginary.
- *Skin examination*: Any rash or swelling should be noted.
- *Joint examination*: Joint examination is often inconclusive; pain may be the only presentation in DCS because there are usually no signs of joint inflammation and joint movement rarely alters the pain.
- *Abdominal examination*: Evaluate for bladder distension that can be present with spinal cord DCS. If present, urinary catheterization will be mandatory.

DIAGNOSTIC WORKUP

For establishing the diagnosis of DCS there are no specific diagnostic investigations available. Useful laboratory investigations are hemoglobin-hematocrit, (severe DCS associated with hemoconcentration due to increased vascular permeability mediated by endothelial damage and kinin release). In the evaluation of the injured divers, chest radiographs are essential to exclude pneumothorax and pneumomediastinum. A pneumothorax should be treated first before recompression in a hyperbaric chamber. It may also be crucial to recognize and treat a pneumothorax before any medical evacuation to the hyperbaric center. Patient with tension pneumothorax should be resolved before air transportation of the DCS patient. Secondarily, chest radiographs may be helpful in differentiating drowning and immersion pulmonary edema. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful to rule out cerebral and spinal cord lesions in patients suffering from neurologic DCS. MRI may also be helpful in predicting clinical outcome in divers with spinal cord DCS. CT scanning may be helpful in excluding other causes of neurologic symptoms, such as subarachnoid hemorrhage or cerebrovascular accident. Emergency physician must understand that in clear cut cases of neurologic DCS, first priority is recompression therapy and CT/MRI is not the priority. Limb radiographs may show evidence of gas in the soft tissue and periarticular spaces, but the absence of such finding does not exclude DCS. Limb radiographs are not recommended as part of the routine evaluation for DCS. It has been demonstrated in the research that coagulation activation can be present in DCI and relationship has been found between the plasma D-dimers level and the presence of sequelae in neurologic DCS.

DIFFERENTIAL DIAGNOSIS OF DECOMPRESSION ILLNESS

Decompression illness should be differentiated from the other conditions with similar symptoms including inner ear barotrauma; middle ear or maxillary sinus barotrauma; contaminated breathing gas; oxygen toxicity; musculoskeletal strains or trauma sustained before, during, or after a dive; seafood toxin ingestion; immersion pulmonary edema; water aspiration; and coincidental neurologic disorders, such as stroke. Hypoglycemia, thermal stress, and age-related conditions should also be considered. Medical or event history can provide important insights.

TREATING DECOMPRESSION ILLNESS

There are several steps in DCI management: on-the-scene evaluation and first aid, transport, and definitive medical evaluation and treatment. Providing high partial pressure oxygen is the primary first aid measure for DCI. Inert gases from the lung will be eliminated by providing high oxygen concentration to the patient. Ischemic insults produced by bubble blockages can also be minimized by high oxygen partial pressure in the bloodstream. Sustained oxygen delivery can reduce or even eliminate symptoms. Various oxygen delivery systems are available at diving site such as continuous flow oxygen systems and nonrebreather or pocket masks; however, such equipment delivers modest oxygen fractions. With the help of demand valve oxygen therapy (DVOT), higher fraction of oxygen can be achieved for spontaneously breathing patient. Oxygen rebreather systems can also provide the highest fractions with minimal gas use. Chemical oxygen generating systems may be the only option available in some remote locations, but these systems provide only limited flow rates and volumes. Even if a diver's symptoms improve or disappear with the administration of oxygen, detail medical evaluation is advised because subtle issues can be missed or signs and symptoms can return once oxygen delivery is stopped.

HYPERBARIC OXYGEN THERAPY

The definitive treatment of DCI is hyperbaric oxygen therapy (HBOT), the delivery of oxygen at a partial pressure substantially higher than that achievable at normal atmospheric pressure. Recompression therapy in a hyperbaric chamber reduces the volume of bubbles. Both bubbles and dissolved gas are eliminated by HBOT. HBOT improves delivery of oxygen to ischemic tissues, blood vessel permeability and tissue edema is

reduced. The initial pressurization is to 2.8 ATA, equivalent to the pressure found at 18 m (60 ft) of seawater. Patients breathe pure oxygen, with scheduled air breathing breaks to reduce the risk of central nervous system oxygen toxicity. The usual duration of the treatment is just under 5 hours, but duration can be extended pressures depending on patient's response. HBOT can be conducted in monoplace chambers (can accommodate only one patient) or multiplace chambers (can accommodate more than one patient).

Treatment Efficacy

In view of limited definitive data and research, rapid HBOT is the best available option for achieving the good prognosis. Delay in starting the treatment associated with incomplete resolution of symptoms. But researchers are not able to establish a maximum time after which recompression is ineffective. Many anecdotal reports describe clinical improvement in DCS cases treated many days after the onset, even with neurologic involvement. So, HBOT therapy can be initiated even several days after the first symptoms. The course of HBOT therapy and duration will vary according to the particulars of each case. Full resolution of DCS symptoms can often be achieved with one or sometimes multiple HBOT treatments. The normal clinical approach is to continue treatments until no further improvement is seen in the patient's symptoms. Sometimes residual symptoms resolve slowly, over a period of times after the HBOT therapy is ended. Full resolution of symptoms can sometimes take months.

ADJUNCTIVE THERAPIES

Fluid Administration

Fluid resuscitation is recommended for the treatment of divers with DCS. Isotonic fluids are preferred choice over hypotonic fluids to prevent an osmolar gradient that may contribute to tissue edema and to prevent electrolyte imbalance. The goal is to maintain a good urinary output (1–2 mL/kg/h).

Anticoagulants and Antiplatelet

Inert gas bubbles cause platelet accumulation, adherence, and thrombus formation so antiplatelet and anticoagulants are included in the therapy, but fail to show any benefit. Aspirin is commonly administered to divers suffering from DCI but has no benefits. Heparin has no beneficial therapeutic effect and may also pose a significant risk of hemorrhage in both spinal cord DCS and inner ear DCS. Administration of subcutaneous low-molecular-weight heparin for thromboembolic prophylaxis is recommended for bedridden patients.

Corticosteroids

Corticosteroids were the important components for the treatment of neurologic DCS. According to various studies, use of high-dose corticosteroids in acute traumatic spinal cord injuries may have limited benefit and can cause invasive infections and avascular necrosis. Currently, the efficacy of corticosteroids in DCI treatment remains unproven.

Nonsteroidal Anti-inflammatory Drugs

Studies do not show any benefits of adding nonsteroidal anti-inflammatory drug (NSAID), tenoxicam, in the treatment of DCS. NSAIDs are not recommended in the initial first-line treatment of DCS because they can confound the clinical evaluation by masking the pain.

ALTERNATIVE TREATMENT TECHNIQUE: IN-WATER RECOMPRESSION

In the remote locations where HBOT and recompression chambers are not available or no facility available for quick transfer of the patient, in-water recompression may be an alternative to chamber recompression. This technique involves bringing the diver underwater again, to make gas bubbles back into solution, elimination of the excess gas to reduce symptoms. The concept of in-water recompression looks simple, but it is practical only with great amount of planning, manpower support, equipment, appropriate water conditions, and suitable patient status.

Patient's consciousness, oxygen toxicity, gas supply, and even thermal stress poses critical challenges during this procedure. An unsuccessful in-water recompression may deteriorate the condition of the patient. The medical and research communities do not have consensus over utility of in-water recompression. As a general rule, a diver who develops symptoms of DCS should be removed from the water and receive oxygen first aid on the surface without delay and transfer to advanced medical center for definitive medical care.

SUMMARY

Decompression illness though rare but is a major concern for divers as well as for emergency physician because of its potential severity and risk of sequelae. Signs and symptoms of DCS depend on multisystem involvement. They frequently involve much more than the classic description of joint pain, with neurologic symptoms increasingly recognized. Neurologic examination findings can be confusing. History and physical examination are important for evaluation. Symptoms will not develop during the bottom phase of a dive, before decompression. Symptoms of AGE develop within 10 minutes of surfacing. Symptoms of DCS normally appear within 6 hours after surfacing, but they may not become apparent for >24 hours. DCS should be differentiated from various other conditions. High-concentration oxygen is the best first aid for both DCS and AGE. HBOT is the normal definitive medical treatment. The search for adjunctive therapies continues but none have been convincingly supported. Early consultation with diving medicine specialists is recommended.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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242 CHAPTER

Drowning

Pratika Agarwal, Devendra Richhariya

INTRODUCTION

Drowning is a leading cause of accidental death around the world, especially in children (among 5–14 years of boys) and young adults. World Health Organization (WHO) estimates about 0.7% (>500,000) of all death worldwide are due to drowning. There are an estimated 8 million nonfatal drownings worldwide each year, many of which may lead to severe morbidity.

More important, it is a disease that can be prevented through improved public education and treated appropriately through a simple understanding of the underlying pathophysiology. The primary cause of systemic injury in drowning patients is hypoxemia, and its correction should be the focus of prehospital and ED resuscitation and treatment. Once the condition is stabilized, the disposition of a patient can be determined by physical examination findings and response to treatment, with patients displaying mild symptoms are able to be safely discharged after a short period of observation. Overview of the drowning is shown in **Figure 1**.

DEFINITION AND TERMINOLOGY

According to WHO, drowning is defined by "drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid." Immersion is when upper

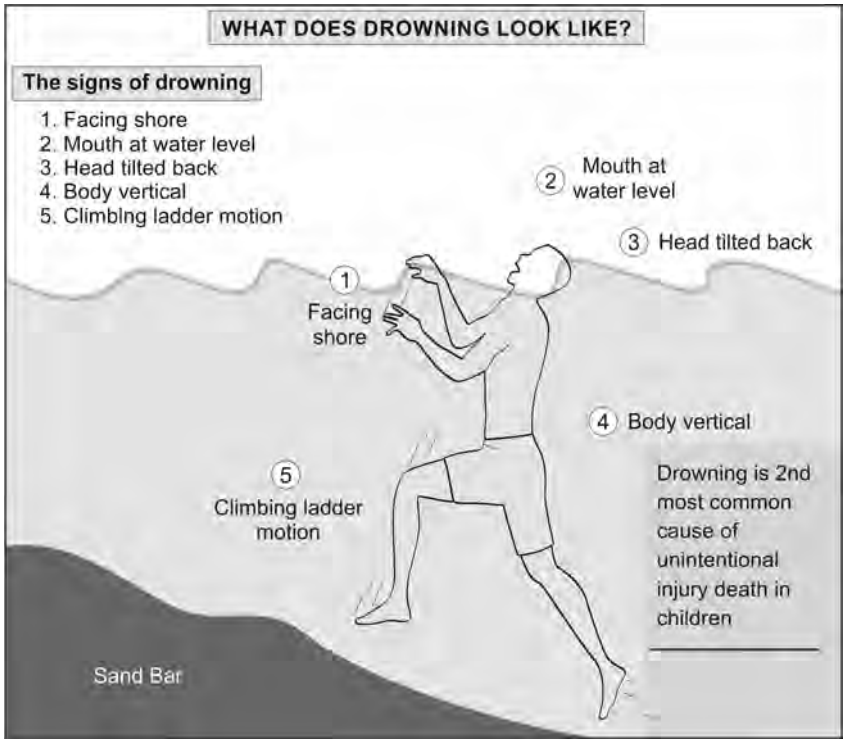

WHAT DOES DROWNING LOOK LIKE?
The signs of drowning
1. Facing shore
2. Mouth at water level
3. Head tilted back
4. Body vertical
5. Climbing ladder motion
2 Mouth at water level
3 Head tilted back
1 Facing shore
4 Body vertical
5 Climbing ladder motion
Drowning is 2nd most common cause of unintentional injury death in children
Sand Bar

FIG. 1: *Overview of drowning*: Drowning person not able to clear his/her airway and water enter the mouth. Some amount of water swallowed and spat out. Person cannot hold the breath >1 minutes and water is aspirated into the lungs if the person is not rescued, water aspiration continues, hypoxia leads to apnea and loss of consciousness and finally asystole.

airway above water (water splash over the face) and exhibits cardiorespiratory response to skin and deep body temperature. Submersion is when upper airway under the water. Submersion is associated with upper airway reflexes, water aspiration, swallowing emesis, and electrolyte disorders. Extent of cardiac pulmonary and neurological injury determines the submersion outcome. If no evidence of respiratory impairment during immersion and submersion is not considered as a drowning and considered as water rescue. If person is rescued any time, interruption of drowning process is nonfatal drowning. While fatal drowning is when death occurs at any time as a result of drowning. The terms like "near drowning", "dry/wet drowning", "active/passive drowning", and "secondary drowning" should not be used now.

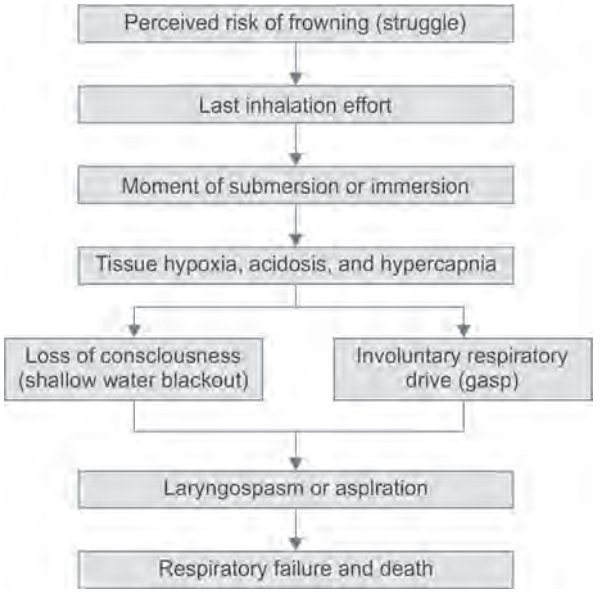
RISK FACTORS FOR DROWNING

Main risk factors for drowning are male with age <14 years, alcohol and other substance abuse, along with risky behavior, and patient with epilepsy cardiac problems (arrhythmias) are also at high risk. Age-wise distribution of risk factors is shown in **Table 1**.

PATHOPHYSIOLOGY AND STAGING OF DROWNING

In the first event, in the sequence of drowning person who is not able to clear the airway, water starts entering the oral cavity and water spats out or is swallowed. Person starts holding the breath but not able to hold it more than a minutes and water aspirated to airway. Reflex response occurs as coughing or laryngospasm (onset of brain hypoxia). At this point, if person is not rescued then aspiration of water and hypoxia leads to apnea, loss of consciousness, cardiac dysrhythmias and asystole. Whole sequence of events from immersion, submersion, aspiration of water, laryngospasm, hypoxia, apnea, loss of consciousness, tachycardia, bradycardia, pulseless electrical activity (PEA), and finally asystole completes in few minutes. Process can take hours in conditions such as hypothermia and ice water drowning. Pathophysiology and staging of drowning are summarized in **Flowchart 1**.

If person is rescued alive then clinical presentation depends on how much water is aspirated to the lung. Aspirated water causes dysfunction of surfactant which is present in alveoli. A very delicate alveolar-capillary membrane is also disrupted due to osmotic gradient differences, increase in permeability of the membrane, and shift of fluid, plasma, and electrolytes, this leads to blood-stained pulmonary edema and finally decreases in exchange of oxygen and carbon dioxide. Finally in decreased lung compliance, larger areas in the lung are evolved where ventilation perfusion ratio is either very low or zero, atelectasis bronchospasm also persists. Though the hypothermia (drowning in cold water) provides protective mechanism by delaying cellular anoxia, adenosine triphosphate (ATP) depletion decreases oxygen consumption by the brain (5% with each reduction of 1°C between 36°C and 20°C).


Perceived risk of frowning (struggle)
Last inhalation effort
Moment of submersion or immersion
Tissue hypoxia, acidosis, and hypercapnia
Loss of consciousness (shallow water blackout)
Involuntary respiratory drive (gasp)
Laryngospasm or aspiration
Respiratory failure and death

FLOWCHART 1: Pathophysiology and stages of drowning.

TABLE 1: Risk factors for drowning as per age group.

Infants	*Children and adolescents*	*Adults*	*All ages*
• Unsupervised bath • Bath tub • Residential pools • Low- and middle-income families	• Underlying medical conditions • Unsupervised swimming • Unsupervised • Autism disease	• Underlying medical conditions • Intoxication • Trauma • Tourism • Swimming alone	• Inability to swim • Seizure disorder • Cardiovascular disease • Substance abuse • Trauma (diving in shallow water, boating)

RESCUE FROM WATER AND RESUSCITATION IN DROWNING VICTIM

Prehospital Care of Drowning

Drowning Chain of Survival

There are five critical links, which are described in drowning chain of survival in **Figure 2** in which first link is measures for prevention of drowning and make sure scene safety in and around the water, second link is identification of distress person from the water and also ask someone to call for more help, third link is throw the floatation toward distress person, fourth link is remove the victim if it is safe to do, and provide medical help as per requirement in fifth link.

Water Rescue and in Water Resuscitation

Bystander and Trained Rescuer response: Bystander plays important role in rescue and resuscitation. But death of the bystander is reported if they try to attempt rescue in fast running water. So, it is advisable to bystander to avoid entering the water, or help victim with throwing rope or rescue aid and floatation device toward them. Two bystander rescuers can enter the water instead of one and never jump with head first into the water because of risk of spinal injury. *Trained rescuers* are professional and work with team and special

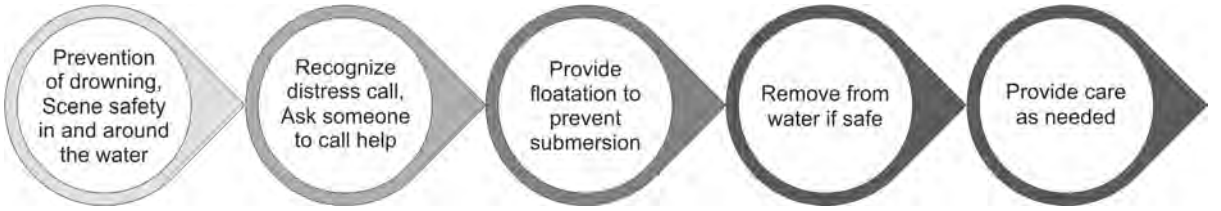
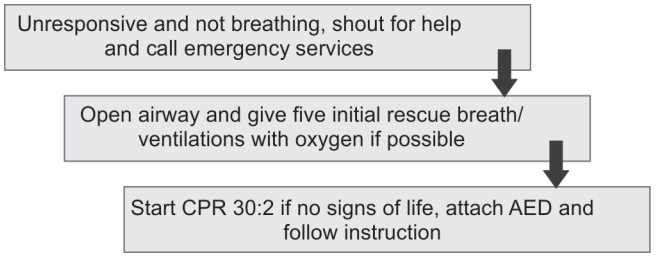

Prevention of drowning, Scene safety in and around the water
Recognize distress call, Ask someone to call help
Provide floatation to prevent submersion
Remove from water if safe
Provide care as needed

FIG. 2: Drowning chain of survival.

equipment. If rescue takes <10 minute of time, favorable outcome is expected. >25 minutes of submersion is associated with poor outcome. *In water resuscitation* can be given by the trained rescuer/surf lifeguard as they take water breathing apparatus inside and start giving the ventilation alone to the victim, attempting chest compression is not helpful. Further action can be decided on the basis of other situation such as distance to land and availability of rescue boat. Victim should be removed promptly from water, chances of spinal injury are very rare in drowning victim unless there is history of shallow water diving and use of water slide. Rescuer should try to keep the victim in vertical position with airway open to avoid vomiting and aspiration.


Unresponsive and not breathing, shout for help and call emergency services
Open airway and give five initial rescue breath/ ventilations with oxygen if possible
Start CPR 30:2 if no signs of life, attach AED and follow instruction

(AED: automated external defibrillator; CPR: cardiopulmonary resuscitation)

FLOWCHART 2: Cardiopulmonary resuscitation in drowning.

Initial Resuscitation on Land

Once the drowned person is taken to the land, he/she should be in supine position and standard protocol should be followed like check for responsiveness and respiration. Person should be kept in recovery position (lateral decubitus), if unconscious but breathing. Person needs only ventilation if gasping pattern or apnea and heart is still beating. Cardiac arrest in drowning is due to hypoxia so follow traditional cardiopulmonary resuscitation (CPR) airway, breathing, and circulation (ABC) sequence rather than circulation-breathing-airway (CAB) sequence. Initially, five rescue breaths are given followed by 30 chest compressions, and continue till signs of life reappear or rescuer becomes exhausted. European Resuscitation council recommends five initial rescue breaths instead of two initial rescue breaths. Drowning cardiopulmonary resuscitation algorithm is shown in **Flowchart 2**. During the resuscitation in drowning person, lots of foam (admixing moving air and water) will keep coming, do not try to remove until it prevents ventilation completely. In this situation, turn the victim on their side and direct suctioning to remove regurgitated material. Regurgitation of gastric content and aspiration is most frequent complications during CPR in drowning which further cases difficulty in initiation of ventilation. Dry the victim chest, attach the pads and turn on the automated external defibrillator (AED), and follow the instructions of AED.

Advanced Prehospital Care

After initiating the basic life support to drowning person, start advanced life support as soon as possible as drowning presents with wide variety of clinical symptoms. Person with drowning and pulmonary damage should be given oxygen by mask at the rate of 15 L/min. If any signs of deterioration or respiratory fatigue, early intubation and mechanical ventilation are recommended. Maintain oxygenation saturation 92–96% and set positive end-expiratory pressure (PEEP) to at least 5–10 cmH_2O. If patient is severely hypoxic, higher PPEP 15–20 cmH_2O is required. Gastric tube is placed to for gastric decompression. In prehospital setting, peripheral venous access is the preferred route for drug administration. Rapid crystalloid infusion can be considered in case of hypotension if not corrected by adequate ventilation and oxygenation and continued if transfer time is prolonged. Use of norepinephrine and epinephrine dose of 1 mg can be used but higher dose can be used (though controversial), if usual recommended dose is not effective due to mechanism of cardiac arrest due to hypoxia and hypothermia. Monitoring device such as electrocardiograph, $ETCO_2$, and echocardiography is used to confirm the vital parameters. Follow standard advance life support protocol, if patient is in cardiac arrest.

At any point of time, it is very difficult to decide when to stop resuscitation, no factor/factors predict good or poor outcome. It is advised to continue basic life support till signs of life reappear, rescuers are exhausted, or advanced-cardiac life support team is available to take over. Continue advanced life support till patient rewarmed, asystole persists >20 minute, or rigor mortis, and putrefaction. The primary cause of morbidity and mortality in drowning is hypoxia. In addition, the actual volumes of water commonly aspirated are much smaller than originally postulated. Therefore, a resuscitative strategy focused on expelling water from the lungs, instead of reversing hypoxia, will do more harm than good.

In general, all drowning patients should receive initial resuscitative efforts. In general, a submersion time >10 minutes or resuscitation time >25 minutes has been shown to correlate with death or survival with poor neurologic outcome. If there is high suspicion for cervical spine injury (witnessed diving or fall from height, known ethanol ingestion, facial trauma), appropriate precautions should be taken with in-line stabilization, application of cervical collar as long as it does not delay intubation.

Emergency Department Care

The patient of drowning may present with wide range of symptoms. Patient may be completely asymptomatic, or may present with mild cough dyspnea or pulmonary. Patient may

be confused or present with coma. Patient may present in emergency department in cardiac arrest state.

Majority of the person aspirates only small amount of the water and they recover in short period of time. And small section of the drowning person 5–7%% who are rescued by the lifeguards needs hospitalization. Thermal protection should be provided to the drowning person once the measures described in resuscitation section (secure airway, improve oxygenation, and gastric tube) are in place.

In emergency department physical examination, chest X-ray arterial blood gases analysis should be performed. Detail history along with precipitating risk factors such as trauma, seizure, or cardiac arrhythmia should be noted. Measurement of hematocrit, urea nitrogen, and electrolytes is usually inconclusive. Electrolyte disturbance is of no clinical relevance in either salt or fresh water drowning and needs no treatment. In majority of patient, metabolic acidosis (routine use of bicarbonate not recommended) is corrected spontaneously by patient effort to increase his minute ventilation or set the increased minute ventilation or higher peak inspiratory pressure in mechanical ventilation. Toxicological evaluation and computed tomography of head and neck can be considered in specific situation.

Rescued patient can be safely discharged if maintaining good arterial oxygenation without any adjuvant therapy. Patient with grade 2–6 and multisystem involvement need hospitalization and management in intensive care as described in **Table 2**.

Treatment in Intensive Care Unit

Respiratory System

As discussed in pathophysiology section, the predominant changes in the lungs are surfactant dysfunction, alveolar collapse, atelectasis, and intrapulmonary shunting. Severity of illness is ranging from mild self-limiting illness to severe hypoxia and severe acute respiratory syndrome (ARDS). Lung protective ventilation strategies as used in ARDS are beneficial. Even if drowning person is maintaining adequate gas exchange, it is advisable not to wean patient from

TABLE 2: Grading for drowning patient - disposition and management plan.

Grade	***Rescue/Grade 1***	***Grade 2***	***Grade 3***	***Grade 4***	***Grade 5***	***Grade 6***
Prehospital evaluation	*Responsive*	*Responsive*	*Responsive*	*Responsive*	*Nonresponsive but pulse present*	*Nonresponsive but pulse absent*
Clinical presentation	Without cough/ cough	Crepitations/ rales in few lung fields	Crepitations/rales in all lung fields (acute pulmonary edema) with normal blood pressure	Crepitations/rales in all lung fields (acute pulmonary edema) with hypotension/ shock	Unconscious Usually post-CPR revival (ROSC)	If submersion time >1 h (evidence of death →Death → follow forensic procedure If submersion time less than 1-hour CPR if ROSC follow as mentioned below
Interventions	None/oxygenation or monitoring may not be required	Vital monitoring chest X-ray	Vital monitoring electrolytes hemogram, coagulation profile, chest X-ray, high-flow oxygen by face mask/NIPPV	Vital monitoring electrolytes hemogram, coagulation profile, chest X-ray, high-flow oxygen by face mask/NIPPV	Vital monitoring electrolytes hemogram, coagulation profile, chest X-ray	Vital monitoring electrolytes hemogram, coagulation profile, chest X-ray
Further management	None	Low-flow oxygen	Orotracheal intubation and mechanical ventilation	Orotracheal intubation and mechanical ventilation + PEEP, crystalloid and vasopressors infusion	Orotracheal intubation and mechanical ventilation+ PEEP, crystalloid and vasopressors infusion	Orotracheal intubation and mechanical ventilation+ PEEP, crystalloid and vasopressors infusion
Disposition	If no significant history or risk factors can be discharged from incident site	• Observe in ED for 4–6 h • Discharge with pre-caution	Admission and treatment in intensive care unit	Admission and treatment in intensive care unit	Admission and treatment in intensive care unit	Admission and treatment in intensive care unit
Survival	100%	99%	95–96%	75–85%	55–75%	5–10%

(CPR: cardiopulmonary resuscitation; ED: emergency department; NIPPV: noninvasive positive pressure ventilation; PEEP: positive end-expiratory pressure; ROSC: return of spontaneous circulation)

mechanical ventilation at least for 24 hours. In early weaning situation, local pulmonary injury may not resolve adequately pulmonary edema recur and reintubation needed and patient needs hospitalization for longer period of time. Corticosteroid is not much beneficial in reducing lung injury but is helpful in bronchospasm along with bronchodilators.

Early radiographic appearance of opacities is usually misdiagnosed as pneumonia and prophylactic antibiotics are not useful as this adds more resistant and aggressive organism. Early-onset pneumonia can be due to drowning in polluted water and aspiration of gastric contents, so better to monitor the patient on daily basis with patient's temperature pattern, total leukocyte count, culture and sensitivity, response of sputum, and tracheal aspirates, if any new pulmonary infiltrates on serial chest X-rays. Bronchoscopy may be used to clear the mucus plug and also monitoring the lung infections.

Prolonged mechanical ventilation also increases the risk of nosocomial pneumonia and is usually diagnosed on third or fourth day of hospitalization. Once the diagnosis of pneumonia is confirmed, empiric broad spectrum antibiotics, covering both gram-negative and gram-positive organism, should be started and definitive antibiotic after confirmation of organism by culture and sensitivity test.

In few patient (refractory cardiac arrest, submersion in ice cold water), pulmonary function deteriorates and refractory hypoxemia develops, in these patients, extracorporeal membrane oxygenation (ECMO) is helpful in maintaining the oxygenation.

Treatments under investigations for critically ill patients and not recommended now are artificial surfactant, inhaled nitric oxide, and partial liquid ventilation with perfluorocarbons.

Circulatory System

Rescued drowning person can present as cardiac dysfunction and hemodynamically instability, which is usually become normal after correcting hypoxia, rapid crystalloid infusion. Echocardiography can be performed, if these measures do not restore hemodynamic stability and decision can be taken to start inotropic vasopressors or both.

Neurologic System

One of the most worrisome outcomes after drowning resuscitation is permanent neurologic damage which is primary determined by duration of hypoxia. Immediate neurologic assessment and care should be started, if patient is comatose after rescue. Maintain normal level of blood glucose, adequate oxygenation. Maintain neuroprotective hypothermia between 32°C and 34°C for 24 hours. Therapeutic hypothermia has been shown to be of benefit in cardiac arrest, and case reports have suggested similar outcomes for victims of submersion. This should be initiated only after proper resuscitation, with a focus on ventilation, and only in facilities with the proper policies, equipment, and training to initiate and maintain the hypothermia for 24–48 hours.

COMPLICATIONS

Drowning patient may present with multisystem involvement as shown in **Table 3** and should not be misinterpreted as infection. After first 72 hours of resuscitation, features of sepsis and disseminated intravascular coagulation are possible. Renal insufficiency or failure is reported due to hypoxia shock myoglobinuria or hemoglobinuria.

TABLE 3: Multisystem involvement in drowning.

Organ system	*Effects*
Pulmonary	Pulmonary edema ventilation perfusion (V/Q) mismatch and acute respiratory distress syndrome (ARDS)
Neurological	Hypoxic encephalopathy, traumatic brain injury, and spinal injury
Acid-base	Metabolic acidosis
Cardiac	Decrease cardiac output, dysrhythmias, and infarction
Renal	Azotemia

PROGNOSIS

The most consistent prognostic indicator found in the literature is duration of submersion, and this highlights the pivotal role that hypoxia plays in the injury process. Other factors that have been found to have some prognostic value are–delay in initiation of CPR, delay in arrival of emergency medical services (EMS), need for prolonged resuscitation, low Glasgow coma scale score (≤5), pH <7, and asystole on arrival to the ED.

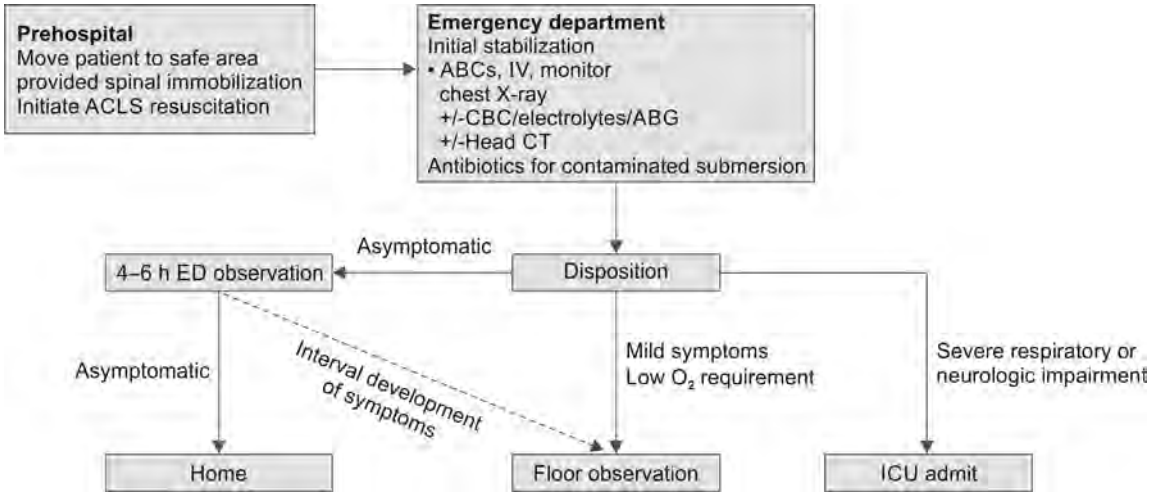
PREVENTION

Expert and research studies suggest following measure to prevent the drowning:

- Unnecessary accumulated water should be drained from bucket pond.
- Apply flood control measures in flood prone area
- Mandatory fencing and rules for swimming pools
- Apply safety signs and warning flags
- Encourage to learn swimming and water safety skills
- Swim in area with life guards and swim with others
- Do not swim after taking alcohol
- Use of grills over water well
- Constant and closely supervise children who are near water
- Learn about use of life jacket and about first aid CPR

SUMMARY

According to WHO, drowning is the second most common cause of unintentional death after road traffic accident. Estimated problem is even bigger as data are not available or unreliable from most of the countries. Drowning problem is more common in children aged 1–14 years and male persons. Alcohol and epilepsy are important risk factors for drowning. Drowning associated with multiple complications such as ARDS, renal failure, and hypoxic encephalopathy. Management (summarizes in **Flowchart 3**) includes CPR, and intensive care unit management including therapeutic hypothermia and ECMO. Prevention is important aspect to decrease the morbidity, mortality, and economic burden on the society.



(ABC: airway, breathing, and circulation; ABG: arterial blood gas; ACLS: Advanced Cardiovascular Life Support; CBC: complete blood count; CT: computed tomography; ED: emergency department)

FLOWCHART 3: Approach to drowning.

MULTIPLE CHOICE QUESTIONS

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CHAPTER

High-altitude Emergencies

Eric Revue, Anthony Chauvin

INTRODUCTION

In the realm of high-altitude medicine, the term high altitude refers to terrestrial elevations over 1,500 m (4,921 ft), and is commonly divided into three categories—(1) High altitude, (2) Very high altitude, and (3) Extreme altitude. High-altitude emergencies refer to pathologies related to hypoxia increasing with altitude. These pathologies, of which there are three types—(1) Acute mountain sickness (AMS), (2) High-altitude cerebral edema (HACE), and (3) High-altitude pulmonary edema (HAPE). They are of varying degrees of severity but require rapid treatment, otherwise they can become fatal. Around one-quarter of people suffer to AMS at moderate altitude and this proportion up to 50/85% at >4,000 m. The incidence of HACE and HAPE estimates at 0.1–0.4%. This chapter focuses on recent advances in the prevention and treatment of these conditions.

PATHOPHYSIOLOGY AND ACCLIMATIZATION

Acute high-altitude illness is arbitrary classified as high above 1,500 m but symptoms are more common above 2,500 m. Risk factors for developing high altitude are:

- *Individual*: Women, people younger than mid adulthood, history of migraine, obesity, coronary heart disease, and permanent resident <900 m
- *Altitude*: Poor acclimatization, rate of ascent, absolute change in altitude, and altitude >4,000 m

To minimize hypoxemia due to altitude and maintain a normal cellular despite decreased the partial pressure of oxygen (PO_2), an elevation by step is required. The process of acclimatization is complex and incompletely understood. Recommendations stats that people need to stop ascension as soon as he feels symptoms of AMS and stay several days at this altitude. Preacclimatization affords some protection against high-altitude illness. A graded ascent (rest day every 600–1,200 m) and a slow ascent rate (maximum 600 m/day) should allow adequate time for acclimatization and are associated with a lower incidence and severity of illness on ascend.

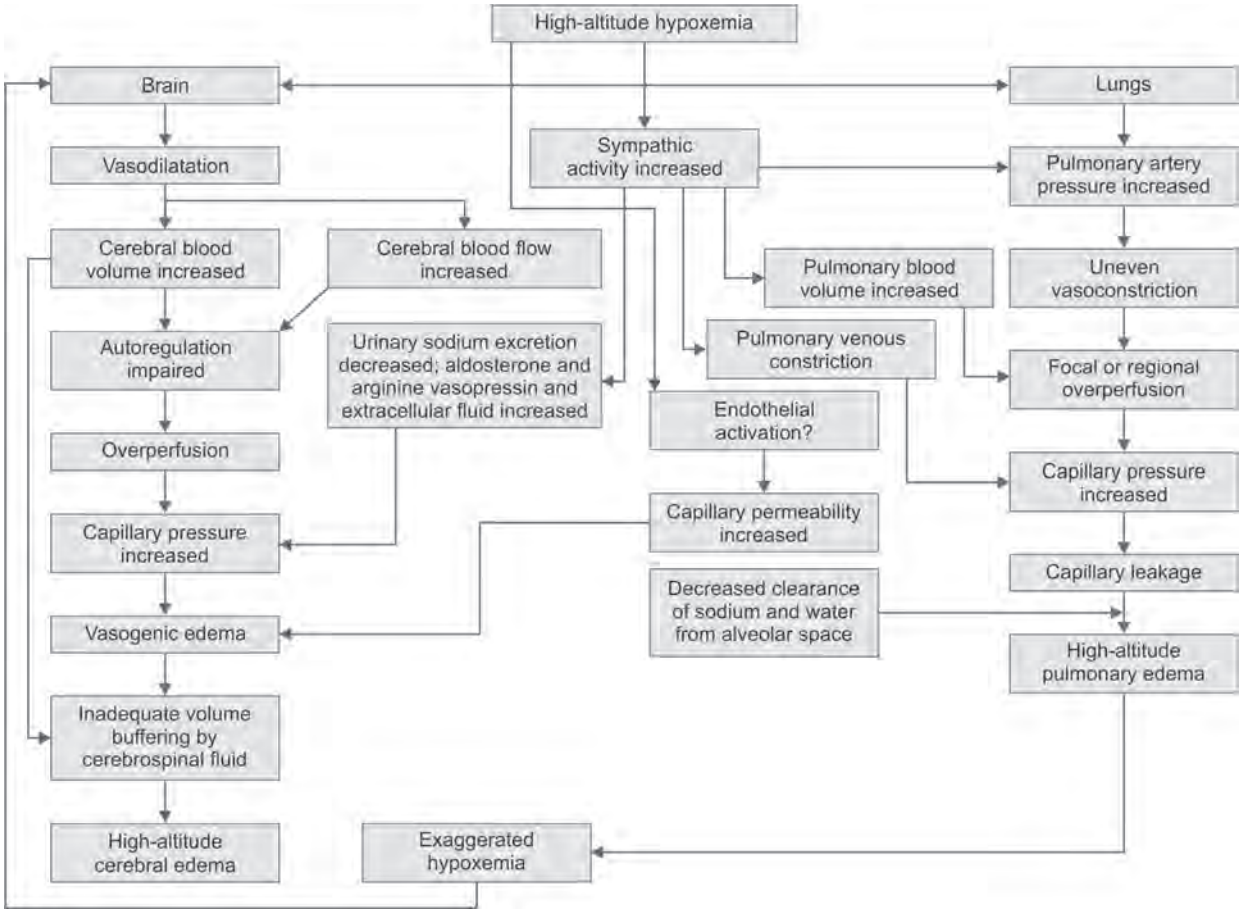
Acute mountain sickness is the clinical manifestation of inadequate acclimatization and hypoxemia induced by the reduction of partial pressure if oxygen, inspired O_2, alveolar O_2, arterial blood oxygen, and so arterial oxygen saturation. Pathophysiologic changes of high altitude which leads to HACE and HAPE are depicted in **Flowchart 1**.

ACUTE MOUNTAIN SICKNESS

Acute mountain sickness is a multisystem disorder with prominent neurological features characterized by headache, and fatigue, anorexia, nausea, or vomiting; fatigue or weakness; dizziness or lightheadedness; or insomnia. Headache is the more common symptom. The diagnosis of AMS is clinical; no diagnostic modalities or physical findings can reliably confirm the diagnosis. Symptoms generally occur at elevations above 2,500 m (8,202 ft) but sometimes occur at as low as 2,000 m (6,562 ft). These nonspecific symptoms may easily be mistaken for a variety of other conditions, particularly in the setting of comorbid illness or the extremes of age. Symptoms of AMS typically develop 6–10 hours after ascent but could appear as earlier (i.e., 1 h). Onset beyond 3 days at a given altitude, the absence of headache, or the lack of rapid response to oxygen or descent suggests other diagnoses. Subarachnoid hemorrhage, intracranial mass, migraine, dehydration, exhaustion, carbon monoxide exposure, substance abuse, and alcohol hangover, among others, are diagnoses that must be considered in the early evaluation of possible AMS. The severity of AMS can be graded using the Lake Louise Questionnaire (**Table 1**).

Treatment

- *Nonpharmacologic*: First of all, the prevention is important—avoid alcohol and sleeping medications. In case of mild AMS, avoid further ascent until symptoms resolved. Acclimatization for 1–2 days at the same altitude is recommended. Hydration by water and reducing activity level could help the patient. In case of moderate or severe AMS, the patient must descend at less altitude.
- *Pharmacologic*: In case of mild AMS, consider classical analgesics and antiemetics. In case of moderate or severe



FLOWCHART 1: Pathophysiologic changes in high-altitude illness.

TABLE 1: Severity of acute mountain sickness.

Symptoms		*Points*
Headache	• No headache	0
	• Mild headache	1
	• Moderate headache	2
	• Severe headache incapacitating	3
Gastrointestinal symptoms	• No gastrointestinal symptoms	0
	• Poor appetite or nausea	1
	• Moderate nausea or vomiting	2
	• Severe fatigue/weakness, incapacitating	3
Fatigue and/or weakness	• Not tired or weak	0
	• Mild fatigue/weakness	1
	• Moderate fatigue/weakness	2
	• Severe fatigue/weakness, incapacitating	3
Dizziness/ lightheadedness	• Not dizzy	0
	• Mild dizziness	1
	• Moderate dizziness	2
	• Severe dizziness, incapacitating	3
Difficulty of sleeping	• Slept as well as usual	0
	• Did not sleep as well as usual	1
	• Woke up many times, poor night's sleep	2
	• Unable to sleep	3
• Mild AMS—A Lake Louise score of 5 or less • Moderate-to-severe AMS – A make Louise Score of 6 or more		

AMS, consider dexamethasone (4 mg every 6 h); and/or acetazolamide (250–500 mg/day/os); if unable to descend, vigilant observation for deterioration; oxygen (1–2 L/min) and/or portable hyperbaric therapy (2–4 psi) for a few hours if available. The hospital care is based on the same recommendations.

HIGH-ALTITUDE CEREBRAL EDEMA

Diagnosis

High-altitude cerebral edema is preceded in major case by symptoms of AMS and is considered the end stage of AMS. HACE can present 3–5 days after arrival to elevations as low as 2,750 m (9,022 ft) but is most commonly seen in remote environments well above this altitude, where the onset of symptoms may be much more abrupt over a period of hours. The diagnosis is clinical and based on altered sensorium and ataxia. Mental status changes may include irrational behavior that rapidly progress to lethargy, obtundation, and coma. If untreated, death results from brain herniation.

Treatment

Treatments are immediate descent or evacuation at 1,000 m (3,281 ft), oxygen to maintain SaO_2 >90%, and dexamethasone (8 mg IV/IM/PO initially, then 4 mg per 6 h). If descent is not an option, one may use a portable hyperbaric chamber and/or supplemental oxygen to temporize illness, but this should never replace or delay evaluation/descent when possible.

HIGH-ALTITUDE PULMONARY EDEMA

Leakage of the pulmonary blood gas barrier leads to accumulation of fluid in the lungs. In high-altitude, pulmonary vasoconstriction occurs and pulmonary hypertension occurs in all individual. HAPE should be differentiated from asthma, bronchitis, heart failure mucus plugging, myocardial infarction, pneumonia, and pulmonary embolus.

Diagnosis

Manifestations of HAPE include decreased exercise tolerance and a prolonged recovery period after exertion at altitude. Dyspnea, chest discomfort, and dry cough are frequent. In severe cases, the physical examination reveals tachycardia and tachypnea. Auscultation reveals rales, often asymmetrical in distribution, and usually found in the right mid-lung initially. Cyanosis and orthopnea may become prominent in severe cases. The electrocardiogram could report sinus tachycardia and may suggest acute pulmonary hypertension (i.e., right axis deviation, right bundle branch block, right ventricular hypertrophy by voltage, and right atrial enlargement). Hemodynamic measurements reveal high-pulmonary artery pressure and pulmonary vascular resistance, as well as low to normal pulmonary wedge pressures, cardiac output, and systemic arterial blood pressure.

Treatment

The treatment is based on oxygen (4–6 L/min until improved, then 2–4 L/min to conserve supplies and maintain SaO_2 >90%); minimize exertion and keep patient warm; descend or evacuate at 500/1,000 m (1,640–3,281 ft) as soon as possible; if descent/O_2 unavailable, portable hyperbaric therapy may be lifesaving; consider nifedipine (10 mg PO, then 30 mg extended-release PO q 12–24 h) if no HACE; consider inhaled beta-agonists (salmeterol, 125 lg inhaled per 12 h, or albuterol); consider EPAP mask; dexamethasone only if HACE develops.

PREVENTION OF HIGH-ALTITUDE ILLNESS

Optimize acclimatization is the primary goal to prevent the illness. Recognize the illness early stage and treat correctly. Avoid ascend to higher altitudes if symptoms persist. Start treatment measures, if symptoms do not improve despite pharmacologic therapy, descend to lower altitude. In the presence of confusion, ataxia, or dyspnea at rest with relative hypoxemia, descend and/or treat immediately with definitive therapy. For all forms of altitude illness, descent is the definitive treatment. But due weather and logistic constraint descend is not always possible. Although prevention and treatment strategies are organized into pharmacologic and nonpharmacologic approaches, in clinical practice these strategies are often combined for best results. **Table 2** summarizes the pharmacologic approach for prevention and treatment of high-altitude illness (HAI), including newer strategies.

SUMMARY

Acetazolamide remains the best choice for prevention of AMS. The best treatment for all HAI is descent or oxygen, or both. Dexamethasone is excellent for treating moderate to severe AMS, and for HACE. First-line therapy for HAPE supplemental oxygen; if oxygen is not available descent is primary therapy. Combined measures, e.g., oxygen and descent are more effective than drug therapy. Definitive treatment for HACE is descent and should not be delayed. Important adjunctive treatments for HACE are dexamethasone and supplemental oxygen until descent can be facilitated.

TABLE 2: Drug therapy for high-altitude illness.

Drug	*Indications*	*Doses*	*Adverse effect*	*Comments*
Acetazolamide	Prevention of acute mountain sickness	125 mg every 12 h. Begin 24 h before ascent. Continue for at least 48 h after arrival at highest altitude	*Common*: Paresthesiae, polyuria, altered taste of carbonated beverages *Less common*: Nausea, fatigue, and headache *Rare*: Stevens-Johnson or anaphylaxis	Enhances acclimatization; pregnancy category C; avoid if breastfeeding
	Treatment of acute mountain sickness	250 mg PO every 12 h		
Dexamethasone	Treatment of acute mountain sickness	4 mg every 6 h PO, IM, or IV	*Common*: Mood changes, insomnia, and dyspepsia *Rare*: Adrenal suppression, psychosis, and hyperglycemia	Rapidly improves AMS symptoms, beware minor rebound symptoms; lifesaving in cases of HACE; pregnancy category C
	High-altitude cerebral edema	8 mg initially, then 4 mg every 6 h PO, IM, or IV		
Ibuprofen	Prevention of acute mountain sickness?	600 mg every 8 h during ascent	Dyspepsia; exercise-induced kidney injury	Risk of gastrointestinal bleed
Budesonide	Prevention of acute mountain sickness	200 µg every 12 h, beginning 3 d before ascent	Sore throat, myalgias, headache, and oral candidiasis	Vastly more expensive than acetazolamide or dexamethasone; optimal regimen needs validation

Continued

Continued

Drug	*Indications*	*Doses*	*Adverse effect*	*Comments*
Tadalafil	Prevention of high-altitude pulmonary edema	10 mg PO every 12 h starting 24 h before ascent. Continue for 2–4 d at max sleeping altitude	*Common*: Headache, facial swelling *Rare*: priapism	BID dosing, compared with TID dosing with sildenafil; fewer side effects, less hypotension when compared with nifedipine; pregnancy category B
Nifedipine	Prevention of high-altitude pulmonary edema	30 mg extended release, PO every 12 h, starting 24 h before ascent	Reflex tachycardia, hypotension (uncommon)	Pregnancy category C; Not necessary, if oxygen available
	Treatment of high-altitude pulmonary edema	30 mg extended-release PO every 12 h		

MULTIPLE CHOICE QUESTIONS

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CHAPTER

Electrical and Lightning Injuries

Neeraj Mangla, Sahanya Ramesh Shetty

INTRODUCTION

Electrical injuries are caused due to contact of human body with electric current. This produces heat energy disseminated onto the skin surface superficially and transmitted internally throughout the body. Though, they account for a lower incidence, there is a high risk and fatality associated with it. The injury sustained affects multisystem increasing risks of morbidity and mortality. Factors determining the magnitude of injury include:

- Resistance offered by the victim
- Voltage source
- Course traversed by the electric current
- Time frame of contact

ETIOLOGY

Majority of the cases include contact with household appliances or occupational hazards. Predisposing risk factors can be distributed among the infants in contact with household cables, adolescent boys playing near or around exposed high-voltage current sources and adults handling heavy duty wires and cables daily at their workplace.

- *Low-voltage injuries (<600 V)*: It is usually caused by alternating current, where the victim is unable to let go easily. This causes prolonged contact with the source and greater degree of superficial burns and cutaneous injuries (**Figs. 1A** to **C**). *Note: Rhabdomyolysis and secondary trauma are uncommon.*
- *High-voltage injuries (>600 V)*: These are predisposed by either alternating or direct current. Injuries involve deep second-degree burns. Trauma occurs due to tetany and fall from height. Contact is usually brief with rhabdomyolysis.

PATHOPHYSIOLOGY

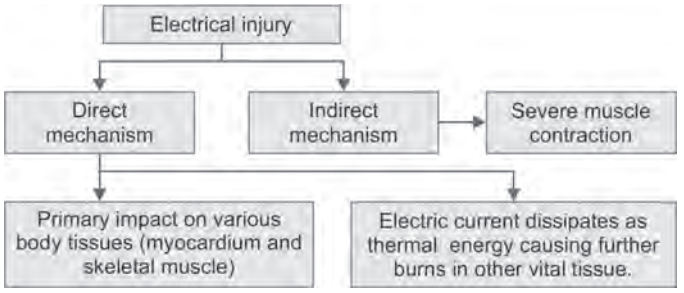
Degree of electric burns depends on the strength of the electric current passed into the patient.
According to Ohm's law,

$$\text{Electric current } \alpha \frac{\text{Voltage of the source}}{\text{Resistance}}$$

FIGS. 1A TO C: (A) "Flashover effect" over the posterior aspect of arm and forearm; (B) Superficial burns sustained after an electrical injury over lateral aspect of chest and abdomen; (C) Hyperpigmented skin with superficial burns. ***(For color version, see plate 51)***
Courtesy: Dr Gaurav B Shetty.

The extent of injury caused will be different in different parts of the body even with the same voltage, since resistance across tissues is varied. Resistance across tissues is as follows:

Highest resistance is seen in fat, tendon, and bone, followed by skin. Least resistance: Nerves, blood vessels, and muscles. Tissues with moisture (like muscles) have decreased amount of resistance than tissues with no moisture (like skin). Higher resistance by the skin offers to more diffuse burns, while lower resistance by skin can cause deeper burns, affecting vital visceral organs (**Flowchart 1**). Be it dry or moist, electrical energy passes through highly resistant skin and disperses through tissues with lesser resistance easily. As a result, burns appearing mild on the surface may have deranged underlying


Electrical injury
Direct mechanism
Indirect mechanism
Severe muscle contraction
Primary impact on various body tissues (myocardium and skeletal muscle)
Electric current dissipates as thermal energy causing further burns in other vital tissue.

FLOWCHART 1: Algorithm portraying electrical current pathophysiology.

TABLE-1: Physiological changes corresponding to varied intensity of currents.

Intensity of current (IN mA)	*Physiological changes*
1	Not perceptible—mostly tingling
7–9	"Let-go" for an average man
6–8	"Let-go" current for an average woman
3–5	"Let-go" current for an average child
16–20	Tetany of skeletal muscles
20–50	Paralysis of respiratory muscles; respiratory arrest
50–100	Threshold for ventricular fibrillation
>2	Asystole

tissues. The electric current at which removal of the electrical source is barred due to tetany (muscle contraction) is the let-go threshold (**Table 1**).

Direct Contact

The mechanism of electrical injuries involves heating up of tissues from skin at the superficial layers to deeper tissues causing electrothermal burns. Primarily affected areas will be those in contact to the source point with the ground. The extent of organs involved during the transitory course of current (entry to exit) helps in estimation of the magnitude of the injury and prognosis of patient. Any trail of current in line with the vertical axis of the body is risky as it indirectly affects the myocardium, muscles for respiration, central nervous system (CNS), in cases of gestational mothers—uterus, and viable fetus. Horizontal course of current: It affects the cardiopulmonary system and musculoskeletal system and spares the CNS. *Mechanism of injury in cardiac tissue involves in either of the two pathways:*

1. *Tissue damage of myocardium leading to necrosis*: Majority of the cases show presence of widespread, patchy band like necrosis including the coronaries, myocardium, right and left conduction pathways, and the nodal tissue. In high-voltage injuries, the smaller vessels are likely to be more damaged due to coagulation necrosis. This may further develop into compartment syndrome in cases of injuries to vascular territories in extremities that dampen the overall circulation.

FIGS. 2A TO C: Deep burns over posterior aspect of thigh and posterior gluteal region. ***(For color version, see plate 51)***

Courtesy: Dr Gaurav B Shetty.

2. *Cardiac arrhythmias*:
   - *Current coursing through lower limbs*: It might involve soft tissues around the point of contact, hence may not be life threatening but definitely limb threatening.
   - *Electrical arcs*: An electrical arc can produce temperature up to 2,500–5,000°C that results in deep thermal burns (**Figs. 2A** to **C**) at the surface of the skin. Arcing current causes direct tissue damage by exposure to ionized superheated air, which are typically skin burns. High-voltage injuries can cause thermal as well as flame burns, along with effects of direct electric current along the arc pathway.
   - *Flame*: Incineration of clothing can cause direct burns through flames. Electrothermal and arcing current result in incineration of clothing.

CLINICAL MANIFESTATIONS

Cardiovascular System

- Ventricular fibrillation and cardiac standstill (PEA—pulse less electrical activity/asystole) are the most fatal and dreaded complications in early management.
- Most common changes in cardiac activity include sinus tachycardia (>150 bpm) and ventricular arrhythmias.
- *Other defects in conduction pathways*: Bundle branch blocks, atrioventricular blocks, and QT interval prolongation are also common.
- Supraventricular tachycardias and atrial fibrillation
- Necrosis and thermal burns of myocardium may cause infarction, pericardial injury, and heart failure.

Respiratory System

Clinical presentation involves either direct impact on respiratory center leading to respiratory arrest or due to suffocation

attributed to the contraction of respiratory muscles involved in the pathway of electric current. Respiratory failure initially presents due to underlying cardiac arrest.

- Toxic inhalation of carbon monoxide or other substances can cause thermal burns of passages within the airway. Chemical toxins (ozone) can cause mucous membrane irritation, decreased pulmonary function, and alveolar hemorrhage.
- *Complications*: Pneumonitis, pulmonary effusion, hypoxia due to direct CNS dysfunction, fluid shifts causing edema, pain, ventilator-associated pneumonia, acute respiratory dysfunction syndrome secondary to excessive fluid resuscitation, and/ or ischemia
- *Late findings*: Pulmonary embolus may develop from underlying deep venous thrombosis (DVT) due to immobilization of limbs, or due to fractures of long bones.

Renal System

Due to vascular damage, kidneys are at high risk for ischemic injury. Resultant effect may cause thrombosis and vasoconstriction of blood vessels. In addition, excessive myoglobin released may lead to myoglobinuria. This leads to a progression toward acute kidney injury and renal failure.

Skeletal System

Muscular contraction is caused by tetany, producing rhabdomyolysis, orthopedic injuries, and necrosis of muscles. Prolonged time of contact with source causes deeper tissue damage. Patients may have multiple sequelae such as burns, fractures which may be masked and missed out during initial assessment. Limited range of motion and deformities respective to joints are signs of possible underlying fractures (**Figs. 3A** to **C**).

- *Compartment syndrome*: Patient with high-voltage injuries is more prone to compartment syndrome even with a contact <1 second. Patients typically present with ongoing muscle pain and pain on muscle movement (**Figs. 4A** to **C**).
- *Vascular injury*: Electric current passing through extremities may cause spasm in peripheral arteries, thrombosis, and/ or aneurysm formation. Extensive injury to vascular system may lead to rhabdomyolysis or compartment syndrome. High-voltage injuries (>600 V) associated with multiple crush injuries, extensive burns, and cardiopulmonary arrest lead to myoglobinuria, elevated creatine phosphokinase (CPK) level, elevated serum myoglobin level, and urine dipstick positive for blood. Acute limb ischemia may present due to thrombosis. Risks of DVT are increased in patients, since they are immobilized due to morbid injuries or possible surgeries.

Central Nervous System

- Transient loss of consciousness, coma, convulsions, agitation, quadriplegia, hemiplegia, and visual disturbances are most common symptoms seen in high-voltage injuries. Head computed tomography (CT) is indicative of any intracranial injury.
    - Spinal cord injuries are primarily due to vertebral fractures occurring at multiple levels. Magnetic resonance imaging (MRI) study may not completely correlate with clinical picture of patient in electrical injury. Mortality increases in cases of extension of the cord dysfunction to the brain stem.
- Signs of a basilar skull fracture (postauricular ecchymosis, hemotympanum, and clear nasal drainage), cervical injury
- Peripheral nerve damage or permanent weakness in extremities may present with transient paresthesia or delayed onset of the same. Peripheral nerve damage may occur in trivial electrical burns. Contact with the electric current may cause median or ulnar neuropathy more often than radial neuropathy.
- High-voltage injuries produce cutaneous burns as entry and exit wounds (**Fig. 5**). Severely injured patients may present with burns on the palms, feet, and on the skull.

Other Clinical Features

- *Fixed and dilated pupils*: Due to traumatic brain injury as a result of fall also cerebral tissue damage due to direct pathway of electric current, or as a result of death in some cases.

FIGS. 3A TO C: Comminuted fracture over the distal metacarpal bone.

Courtesy: Dr Gaurav B Shetty.

FIGS. 4A TO C: S/p wound debridement of anterior aspect of forearm and posterior aspect of forearm. ***(For color version, see plate 51)***

Courtesy: Dr Gaurav B Shetty.

FIG. 5: "Entry" site of an electrical burn, sustained from an electrical pole. ***(For color version, see plate 51)***

Courtesy: Dr Gaurav B Shetty.

- Low-grade intravascular coagulation supervenes due to hypoxia, rhabdomyolysis, and release of procoagulants from tissue damage.
- If the patient has come in contact with a DC source, there will be burns visible at the sites of entry and exit. However, when in contact with AC source, due to its cyclic movement there may be no distinct or evident entry and exit point.
- In 50% cases, tympanic membrane may rupture causing temporary sensorineural hearing loss. Complications with a delayed onset include mastoiditis, sinus venous thrombosis, meningitis, and brain abscess. Hearing should be briefly checked in the ED with regular follow-up of a patient with hearing deficits.
- Injuries to visceral organs include bowel perforation and intra-abdominal hemorrhage, whaich areseen in high-voltage injuries.
- Cataracts usually present as a common complication after lightning injuries (rarely acutely). Retinal detachment, corneal burns, intraocular hemorrhage, and intraocular thrombosis are also present in high-voltage injury.

EVALUATION OF ELECTRICAL INJURIES

Initial assessment and resuscitation include securing airway, breathing, and adequate circulation along with acute management of multiple traumas. Treatment module should generally follow along the same guidelines of pediatric and adult resuscitation as for any other traumatic injury.

History

Acquire details of events leading to accident, time span of contact, type of current, sustained fall from height, physical environment, and underlying medical conditions.

Investigations

Complete analysis of magnitude of injury is essential for better prognosis. Complete blood count, serum electrolytes, sequential evaluation of liver, and pancreatic and renal function are essential to rule out ischemic vascular changes and possible renal or liver failure electrocardiogram (ECG) with routine cardiac monitoring, and troponin levels. Elevated Serum myoglobin, blood urea nitrogen, creatinine level, and creatine kinase (CK) give an early indicator of rhabdomyolysis. Early analysis of urine for myoglobinuria may indicate rhabdomyolysis.

Creatine kinase-muscle/brain (MB) and troponin might be elevated in electrical burns, especially when pathway of current is through thoracic trunk. Brain natriuretic peptide (BNP) may also be raised in some cases.

Metabolic changes can be estimated with arterial blood gas values. Ophthalmic and otoscopic assessment is done for signs of tympanic membrane rupture, ocular nerve damage, mastoiditis, sinus thrombosis, retinal detachment, corneal burns, or intraocular thrombosis. Precautionary treatment is done for stress ulcers in stomach. A pregnancy test is mandatory in all women of childbearing years. Psychiatry consultation is necessary immediately after patient regains consciousness and is stable.

Imaging

Evaluation of the chest, abdomen, thoracic, head, spinal, and pelvis for trauma should be performed according to trauma guidelines.

- CT scan/MRI brain—in cases of severe traumatic brain injury following fall from a height and abnormal neurological findings
- Evaluation with a FAST (focused assessment with sonography in trauma) examination to screen for intra-abdominal injuries/hemorrhage
- Radiological studies—in order to rule out possible fractures and/or dislocations, X-ray can be done.

Special Considerations

It is of no doubt that care should be availed immediately, however, one must assure that the patient has been completely separated from the point source of electric current prior to any treatment and/or being moved away safely with the help of insulated equipment. In contrast to electrical injury, rescuer is not susceptible to any harm or danger when in contact with a patient of lightning injury; hence treatment can be started immediately.

- *Pregnant patients (20–24-week gestation):* Additional measures have to be taken to monitor fetal heart rate and uterine activity for up to 4 hours due to mechanical injuries caused by electrical trauma. Patient should be asked about use of seatbelt during a motor vehicle accident, along with episodes of fainting, pain, last menstrual pain, gestational age of fetus, any p/v bleed or discharge and/or presence of fetal movements. Monitoring of viable fetus with no signs of distress is essential with the use of fetal Doppler ultrasound and an external transducer to detect uterine contractions. Physical examination should include abdominal tenderness and evaluation for any orthopedic injuries. In cases of premature labor induced, tocolytic therapy should be started. In cases with fetal distress, cesarean delivery is performed by the obstetrician.
- *Children*: Children (aged <5 years) who inadvertently place end of a power cord in the mouth produce oral and lip burns. The electric current passed between the cords produces significant tissue damage due to elevated local temperature. Most common sites involve the tongue, lateral commissure, and/or alveolar ridge. In up to 10% cases, bleeding of labial artery occurs when the eschar begins to separate after a few days of the burn. Children with this kind of injury are admitted in the hospital for observation. In some cases, outpatient home care and review is adequate. Proper counseling for parents about possible bleed is essential for up to 2 weeks of incident. Home care involves the use of normal saline for rinsing and gentle wound debridement of necrotic tissue. Specialty consulting is needed for the prevention of deformities and dysfunction. Follow-up and review to maintain local wound care and preventing any infection. Older children have a higher incidence of high-voltage injuries and upper extremity injuries, often requiring fasciotomy or skin grafting.

TREATMENT

Intervention should initiate with securing airway, maintaining breathing, and adequate circulation at the earliest. Administration of oxygen and ventilation should be started immediately in a patient with signs of apnea. Alternative airway such as bougie assistance, video-assisted laryngoscope, and fiber optic equipment should be ready. In adverse cases, cricothyrotomy can be performed under sterile conditions. Stabilization of cervical spine should be maintained in unconscious and/or those that require intubation. It is safe to assume that any patient of electrical or lightning injury may have sustained a spinal cord injury. Hence in all cases, proper head and neck immobilization is essential.

Fluid Management

In cases of severe high-voltage electrical injury, presenting symptoms generally include an amalgamation of considerable visceral injury along with extensive burns. This leads to loss of fluid into third space compartment. An extensive degree of breakdown of muscle causes myoglobinuria, CK, and CK-MB testing can be helpful. CK helps to assess for rhabdomyolysis. A CK-MB >80 ng/mL is predictive of limb amputation. In significant cases, progression to renal failure is noted. Establish intravenous (IV) access and give isotonic fluids to maintain urine output at 1–1.5 mL/kg/h. Obtain an ECG and place the patient on cardiac monitoring. *According to Parkland formula, it is ideal to raise fluid requirement by two times on the basis of burnt surface area***.** Fluid requirement should be calculated from the time of burn. Establishment of an isotonic balanced crystalloid like Ringer's lactate solution for fluid resuscitation is necessary. Keep a note of the urine output on an hourly basis and maintain an output between 0.5 and 1 mL/kg/h in the initial 24 hours.

For correction in serum electrolyte imbalances, start sodium bicarbonate at 1–2 mEq/kg. In cases of high-voltage injuries and larger extent of burns, one is likely to develop severe acidosis and myoglobinuria. Hence an initial bolus of fluids should be administered following a correction by sodium bicarbonate.

In order to increase osmotic dieresis, patient should be started on mannitol at 1 g/kg of body weight. Maintain a urine output at 2–3 mL/kg/h, at a urinary pH above 6.5. Sodium bicarbonate alkalizes the urine; therefore it causes myoglogin to be more soluble. The recognized drug of choice for dieresis is acetazolamide, as it causes alkalization of urine. One of the red flags includes the progression to hyperosmotic hypoalbuminemia. Careful caution in administration of acetazolamide is essential to prevent this.

Initial IV rate in adult is up to 1.5 L/h with close monitoring of urine output in order to decrease the level of serum CK in serum less than five times normal or urine myoglobin level return to normal. It is comprehensible that a urinary catheterization is compulsory for the constant monitoring or urine output. One must also look out for hematuria or dark-colored urine, indicating a possible myoglobin-induced tubular necrosis. This can be treated with an initial bolus of fluids in order to promote dieresis and sodium bicarbonate.

Pain Management

For better pain control, it is advisable to start a short-acting opioid such as fentanyl (1 μg/kg IV), as a continuous infusion and is more easily titratable. In case airway is not secured, it is vital to intubate the patient. Superficial and deep burns need cleaning and dressing under aseptic conditions, along with antibiotic coverage. Update tetanus immunization as indicated. It is evident that in higher percentage of burns, risks of containment of infections are much higher. Use of sterile gowns, gloves, and face masks/shield is important in prevention of nosocomial infections.

In order to prevent acute limb ischemia and compartment syndrome, fasciotomy is indicated in patients with >20% burn surface area, myoglobinuria, and/or full thickness burn over 12% body surface area. Checkerboard escharotomy is required on a patient sustained >50% electrical burns (**Fig. 6**). According to the condition of patient, involvement of general surgeon/orthopedic, neurosurgeon can be helpful in early surgical intervention, if required.

TASER INJURIES

Taser is a device that produces two-barbed projectiles in to the victim's body. There may be an initial 50,000 V shock followed by multiple subsequent shocks. Most injuries are caused due to direct effects of Taser and/or mechanical injuries due to subsequent fall or physical interactions after the act.

FIG. 6: Checkerboard escharotomy done on a patient sustained more than 50% electrical burns. ***(For color version, see plate 52)***
Courtesy: Dr Gaurav B Shetty.

Clinical features: Usually minor
- Fractures and traumatic brain injury
- Injury to eye/testicles
- Pneumothorax
- *Injury to gravid patients*: Monitor fetal heart rate and uterine activity
- Ventricular fibrillation and Taser-induced arrhythmias
- Cognitive abnormalities
- Traumatic injuries from metallic barbs

Approach to such patients should follow the standard guidelines of Advanced Cardiovascular Life Support/Advanced Trauma Life Support (ACLS/ATLS). Chest pain along with shortness of breath is indicative of increase in sympathetic tone. ECG is to study underlying arrhythmia due to stressful event. The main point to be assessed is if the patient is under the influence of alcohol and/or recreational drugs or the patient is suffering from any mental illness. At any event of cardiac arrest, standard ACLS protocol is to be followed.

INJURIES CAUSED BY LIGHTNING STRIKES

In contrast to electrical injury, exposure time to victim is in milliseconds with voltage in millions, ampere in thousands. Hence the total energy transferred is limited. Due to excessive rain accompanying lightning strike, water acts as a conductor of current over the skin producing *"the flashover effect"*. The rapid expansion of air causes concussive blast. These cause a unique pattern of injury over the skin surface. Patients are usually thrown over the ground due to the lightning strike. Types of lightning injuries:
- *Direct strike:* The greater part of the lightning passes directly into the person.
- *Side flash:* It includes a direct strike of lightning to a person and a resultant discharge to a second person in close proximity.
- *Stride potential:* Initially, the lightning strikes the ground then enters the body from one foot and exits from the other.
- *Flashover phenomena*: Lightning current moves along the body, resulting in blast effect on the clothing.

Clinical Features
- Burns can be arc burns, flash burns, superficial, or deeper burns.
- *Lichtenberg figures*: A fine branching rash that resembles branches of tree is unique for lightning injuries. These changes in skin are temporary and superficial, and fade within weeks.
- *Ophthalmic changes*: Retinal detachment and cataracts
- Tympanic membrane rupture
- Sudden death, cardiac arrest, and coronary vasospasm
- *Central nervous system dysfunction*: Immediate or delayed symptoms may present. Ischemic stroke, spinal cord injury, and keraunoparalysis (mimics spinal cord injury) may occur. These patients may develop cerebral salt wasting syndrome, transient or permanent stroke, and/or peripheral nerve lesions.
- *Traumatic injuries*: Spinal cord injury/fractures and skull fractures
- Pinpoint cerebral hemorrhage, ischemia, and infarction
- Myoglobinuria and rhabdomyolysis
- Vasospasm may mimic stroke, myocardial infarction, and bowel ischemia, or cause signs of compartment syndrome.

Management
- *Low-voltage injuries*: Patients with normal ECG, no syncope or arrhythmias and/or minimal superficial burns can be discharged without cardiac monitoring. However, proper counseling about risks of chest pain, agitations, syncope, palpitations, and compartment syndrome should be done. Written follow-up for the same should be provided and arranged with the regional burn center or primary healthcare provider.
- *High-voltage injuries*: Patients with high-voltage injuries should be admitted/referred to a tertiary burn center. Depending upon the type of injuries sustained, orthopedic, ENT, neurologist/neurosurgeon, cardiologist, vascular surgeon, plastic surgeon, and ophthalmologist should be consulted. Prior to transfer to a burn center, initial stabilization is a must, keeping in mind the possible complications after the initial treatment. Therefore, airway, breathing, and circulation should be in control before shifting the patient to the burn unit. This may include fasciotomy or escharotomy, if necessary. The transport of patient should be accompanied by ACLS/Advanced Life Support (ALS) certified paramedics, who are aware of treatment guidelines such as fluid resuscitation, neurological status, and analgesia. Trauma takes precedence over burn patients with severe traumatic injuries will require transfer to a trauma center first.

Management Summary
- Primary and secondary survey as per ACLS/ATLS guidelines
- Airway secured to maintain adequate ventilation
- Intravenous fluid resuscitation
- Electrocardiogram/arterial blood gas/complete blood count (CBC)/CK-MB/serum electrolytes
- Gastrointestinal injury can be assessed better with CT abdomen.
- Repeat neurological examination
- *Magnetic resonance imaging brain*: In order to confirm cerebral hemorrhage, ischemia, and infarction

- Admission to specialized burns intensive care unit
- Consult with plastic surgeons/orthopedics/ENT/ophthalmologist

DISPOSITION

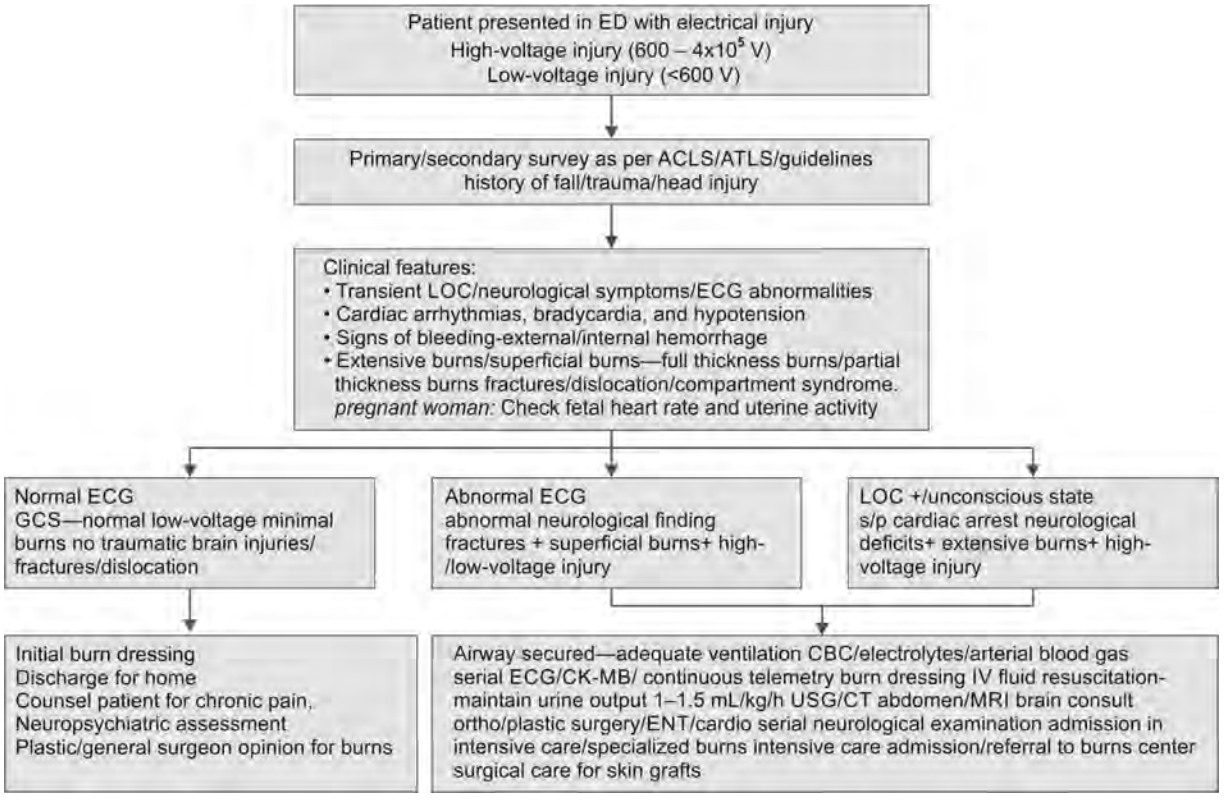
- *Patients suffering low-voltage electrical injuries*: Asymptomatic with no cardiopulmonary arrest, no loss of consciousness, no extensive or superficial burns, and whose neurological examination as well as ECG is normal and can be safely discharged after initial observation. They have to be counseled regarding possible neurological symptoms that may present hours after this accident and to review weekly otherwise.
- *Patients presenting with higher voltage* injuries and/or experienced cardiopulmonary arrest, abnormal neurological findings suggestive of CNS injury and/or spinal cord injury, extensive burns, or vascular damage in extremities, visceral injuries should be transferred in to intensive care unit or to a specialized burns intensive care unit. Indications of admission in electrical and lightning injury are shown in **Box 1**.

SUMMARY

Electrical burns related hospitalization and fatalities in burn centers are mostly occupationally related. Children have a predisposition to injuries from low-voltage sources, such as electric cords, because of their limited mobility within a relatively confined environment. During adolescence, however, a more active exposure to the environment is possible and may lead to more severe high-voltage injuries or death. At the time of presentation, documentation of injuries is important not only for the immediate resuscitation of the victim but also medicolegally. Nearly all cases of electrical injuries eventually involve litigation for negligence, product liability, or worker compensation (**Box 1**). Lightning incidents often include more than one victim when the current "splashes" to other individuals or as ground current spreads the electrical power throughout the area where a large group may be sheltered in a storm. It is not possible to predict the amount of underlying tissue damage or severity, based on the cutaneous involvement. Management approach for electrical injuries is shown in **Flowchart 2**.

BOX 1: Indication for admission in "Electrical" and "Lightning" injury.

- Cardiac arrest
- Documented loss of consciousness
- Abnormal ECG dysrhythmia observed in prehospital or ED setting
- History of cardiac disease
- Presence of significant risk factors for cardiac disease
- Concomitant injury severe enough to warrant admission
- Suspicion of conductive injury
- Hypoxia
- Chest pain


Patient presented in ED with electrical injury
High-voltage injury (600 – 4x10^5 V)
Low-voltage injury (<600 V)
Primary/secondary survey as per ACLS/ATLS/guidelines
history of fall/trauma/head injury
Clinical features:
• Transient LOC/neurological symptoms/ECG abnormalities
• Cardiac arrhythmias, bradycardia, and hypotension
• Signs of bleeding-external/internal hemorrhage
• Extensive burns/superficial burns—full thickness burns/partial thickness burns fractures/dislocation/compartment syndrome.
pregnant woman: Check fetal heart rate and uterine activity
Normal ECG
GCS—normal low-voltage minimal burns no traumatic brain injuries/ fractures/dislocation
Abnormal ECG
abnormal neurological finding fractures + superficial burns+ high-/low-voltage injury
LOC +/unconscious state
s/p cardiac arrest neurological deficits+ extensive burns+ high-voltage injury
Initial burn dressing
Discharge for home
Counsel patient for chronic pain,
Neuropsychiatric assessment
Plastic/general surgeon opinion for burns
Airway secured—adequate ventilation CBC/electrolytes/arterial blood gas serial ECG/CK-MB/ continuous telemetry burn dressing IV fluid resuscitation-maintain urine output 1–1.5 mL/kg/h USG/CT abdomen/MRI brain consult ortho/plastic surgery/ENT/cardio serial neurological examination admission in intensive care/specialized burns intensive care admission/referral to burns center surgical care for skin grafts

(ACLS: Advanced Cardiovascular Life Support; ATLS: Advanced Trauma Life Support; CBC: complete blood count; CT: computed tomography; CK-MB: creatine kinase muscle/brain; ECG: electrocardiogram; GCS: Glasgow coma scale; LOC: loss of consciousness; MRI: magnetic resonance imaging; USG: ultrasonography)

FLOWCHART 2: Summarizing management of electrical injury.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

To access the Short Answer Questions of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

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CHAPTER

Snake Bite

Jaideep C Menon, Joseph K Joseph

INTRODUCTION

Snakes are one of the most successful predator species partly because of their tremendous adaptability. Snakes survive on land, in the seas and certain species are arboreal. Snakes are amongst the most adaptive and resilient predators with certain species having adapting to the cold of the arctic, certain to the altitude of the Himalayas, some others to the depths of the oceans, and some others to the harshness of deserts. But most snakes thrive in the tropical rain forests. Snakes have long captured the imagination of humans and have been deified in many of the older civilizations.

EPIDEMIOLOGY

Human beings are not the natural prey of snakes but get bitten accidentally in most cases. Worldwide, there are about 4.5–5.4 million bites estimated every year, half of them leading to envenomation. The largest number of bites occurs in the South-East Asia with about 50,000 people dying of snakebite annually in India alone.

SNAKES

There >3,400 species of snakes of which about 300 are venomous out of which half of them are capable of producing toxicity from their bite. Venomous snakes are broadly classified as elapid, viperids, and some of the colubrid. Snakes have been subclassified as venomous, mildly venomous, and nonvenomous, depending on the presence of venom glands and their delivery apparatus or its absence. Snakes kill their prey either by constricting them to death (e.g., pythons, anacondas, and boa constrictors) or by immobilizing them through the action of venom when injected.

Snakes possess most of the organs that mammals do like the lungs, kidneys, heart, brain, spleen, liver, intestines, etc. The difference being in that all the organs are stretched out usually placed in an anteroposterior position and not side-to-side, the right-side organ generally is larger than the left and in many species the left lung may actually be absent. Snakes have poor visual and auditory function with the absence of an external ear. Snakes compensate for this through it bifid tongue which is capable of picking chemicals from the environment which it then places in the receptacles of an organ at the base of the skull called the Jacobsen´s organ. The Jacobsen's organ is able to analyze the chemical and helps the snake decide if the chemical is that of a possible prey. It is to say that it is nature's ultimate chemical autoanalyzer. The belly scales (ventral scales) of a snake sense vibration which helps them in both avoiding danger as also in the capture of prey. Constrictors generally release their coils once they sense that the heartbeat has stopped which they sense through their ventral scales.

Certain species called the "pit-vipers" have a small circular pit between their eyes and nostrils (**Fig. 1**) which is a heat-sensitive organ able to pick up temperature differences of a fraction of a degree Celsius, thereby helping it spot warm-blooded mammals even in the dark. Arguably it is the presence of venom glands with their delivery system which have given venomous snakes an evolutionary advantage. Venom glands are modified salivary glands whose secretions help the snake both in the capture of prey, by immobilizing it and also in the process of digestion of the prey. Snake venom enzymes and proteins have a strong corollary to human pancreatic ones.

Elapids include species of cobra, king cobra, krait, coral snakes, taipans, mambas, and sea snakes. Terrestrial elapids

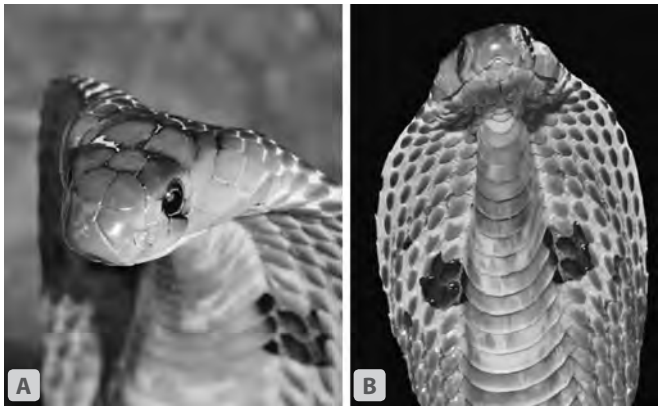
FIG. 1: Pit Viper showing pit between the nostril and eyes. ***(For color version, see plate 52)***

have long, slender bodies with smooth scales (**Fig. 2A**), a head covered with large shields (**Fig. 2B**) and not always distinct from the neck, and eyes with round pupils. These snakes have grooved fangs that are short, fixed, and covered by mucous membrane. In addition, their behavior is usually quite active, and most are oviparous (lay eggs).

Viperids have keeled scales (**Fig. 3**), a stocky build with a short tail, and due to the location of the venom glands, a triangle-shaped head distinct from the neck. The great majority have vertically elliptical or slit-shaped, pupils that can open wide to cover most of the eye or close almost completely, which helps them to see in a wide range of light levels. Their fangs are long, movable, and canalized like hypodermic needles. Typically, vipers are nocturnal and ambush their prey. There are two subfamilies, typical vipers (Viperidae) and pit vipers (Crotalinae).

Sea snakes (Hydrophilidae), an elapid often considered as a separate family, have adapted to a marine way of life in different ways and to various degrees. All have evolved paddle-like tails for swimming and the ability to excrete salt. Most also have laterally compressed bodies, their ventral scales are much reduced in size, their nostrils are located dorsally, and they give birth to live young (viviparity). This reduction in ventral scaling has greatly diminished their land mobility, but aids in swimming. All sea snakes are venomous.

Differentiating features of poisonous and non-poisonous snake: Snake can be differentiated on the basis of anatomy of head pupil fangs and tail. Venomous snake has triangular head, elliptical pupil, venom apparatus, and single row tail. Nonvenomous snake has rounded head and pupil, double row tail, and no venom apparatus. Differentiating features are shown in **Figure 4**.



FIGS. 2A AND B: (A) Common Indian cobra—*Naja naja*—head showing scales; (B) common Indian cobra—*Naja naja*—head showing hood and scales. ***(For color version, see plate 52)***

Courtesy: Gerard Martin.

FIG. 3: *Russell viper—Daboia russelii* head showing scales. ***(For color version, see plate 52)***

Courtesy: Gerard Martin.

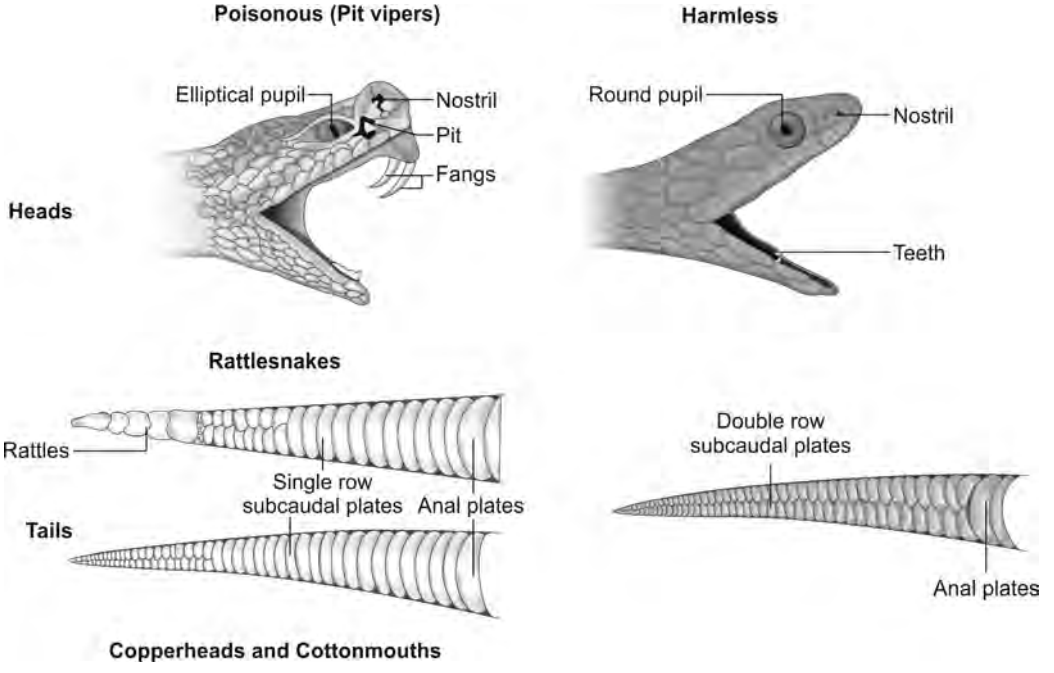


FIG. 4: Differentiating features of poisonous and nonpoisonous snake.

VENOM

Venom is mostly composed of proteins (96–98%) by weight, comprising both enzymatic and nonenzymatic ones, peptides, and glycoproteins. Venom composition is variable between the different species and also within the snake species from different geographical locations. The amount of venom also varies depending on how big the snake is, whether fed or not, season, age, sex, etc. About 80–90% of viperids and 25–70% of elapids, venom consists of enzymes of which 26 have been identified with 12 being common to most species. The enzyme/protein constituents (**Table 1**) of snake venom are described below.

TABLE 1: Components of snake venom.

Enzymes	*Nonenzymatic proteins*
Proteases—metalloproteinases and serine proteases	3-finger toxin
Phospholipases	Lectins
Nucleases (nucleotidases, DNAse, and RNAse)	CRISP (cysteine rich secretory proteins)
Arginine ester hydrolases	Cobra venom factors
Hyaluronidases	Nerve growth factor
L-amino oxidase	Natriuretic peptides
Acetylcholinesterases	Vascular endothelial growth factors (VEGFs)

Mechanism of Action-snake Venom

Krait and Russell's viper has presynaptic neurotoxin that means acetylcholine release is inhibited from the presynaptic membrane so recovery is slow and delayed and depends on regeneration of terminal axons. While cobra venom has postsynaptic neurotoxin that means cobra toxins bind to acetylcholine receptors and produce neuromuscular blockade. Anticholinesterases reverse the neuromuscular blockade thus neostigmine is useful in cobra but not in krait/viper.

CLINICAL FEATURES OF SNAKE ENVENOMATION

Signs of local toxicity at the bite site would suggest envenomation. Signs of systemic toxicity of viperid and elapid species are as listed in **Tables 2** and **3**.

MANAGEMENT OF VENOMOUS SNAKEBITE

The management of snakebite includes firstly ascertaining whether it was a snakebite at all, if yes as whether venomous or not as also looking for signs and symptoms suggestive of both local and systemic envenomation. Evidence of venomous snakebite per se does not establish envenomation as a good number of bites especially with Cobra species could be dry (bite without injection of venom). Onset of symptoms is variable and would depend on a number of factors including amount of venom injected, bite site, body mass, level of activity immediately after bite, use of pressure bandage, etc. Absorption tends to be

TABLE 2: Signs and symptoms suggestive of viperid bite (hematotoxic).

Clinical signs	*Symptoms (biochemical parameters suggesting envenomation)*
Presence of fang marks with significant local signs at the bite site such as swelling, pain, erythema, and cyanosis	Nausea, recurrent vomiting, and abdominal pain
Tender lymphadenopathy of the nodes draining the bite site	
Hemoptysis, epistaxis, hematuria, hematemesis and melena, chemosis, macular bleed, excessive menstrual bleed, bleeding from the bite site or cannula, bleeding into the muscles, gingival sulci bleed, bleeding into the skin, and mucous membranes showing as purpura or petechiae (Devaraj, 1979; Menon, 2014)	• Deranged hemostatic profile evidenced by either of or all of an abnormal • WBCT—whole blood clotting test • PT (prothrombin time) >1.5 times control • Activated plasma thromboplastin time (APTT), 1.5 times above normal
Abdominal tenderness	Low back ache or loin tenderness
Hypotension resulting from hypovolemia or direct vasodilatory effect of venom	Muscle pain indicating rhabdomyolysis
Lateralizing signs suggestive of an intracerebral bleed	• Low platelet count <100,000/cmm • Crenated RBC's in peripheral smear
Bilateral parotid enlargement (viper head appearance)	Rise in serum urea and creatinine, 30% over that of baseline
Conjunctival edema and subconjunctival hemorrhage	Proteinuria
Confusional state	Raised D dimer
Jaundice	Raised liver enzymes—AST and ALT
Ptosis (*Russell viper* bite)	Decreased fibrinogen
	Dysgeusia with a metallic taste in the mouth
	Passage of reddish or dark-colored urine or a reduction in the amount of urine

(AST: aspartate transaminase; ALT: alanine transaminase; RBC: red blood cell)

TABLE 3: Signs and symptoms suggestive of elapid bite—cobra and krait (neurotoxic).	
Clinical signs	***Symptoms biochemical parameters suggesting envenomation***
Fang marks, swelling, necrosis, blistering and local reaction at the bite site, and lymphangitis	Pain, swelling, and inflammation of the bitten part
Descending paralysis, initially of muscles innervated by cranial nerves, commencing as a ptosis, diplopia, or an ophthalmoplegia (the eyelid feels heavy with a difficulty in focusing)	Diplopia, dysphagia, dysgeusia (tingling sensation in the tongue with a loss of taste), dysphonia, and dyspnea (5D's)
"Broken neck" sign due to paralysis of neck muscles	Descending paralysis
Diaphoresis, circumoral pallor, and paresthesia	Abdominal pain and vomiting
Miosis (pupillary constriction)	Profound thirst
Painful lymphadenopathy	Palpitation, breathlessness, and chest pain
Paralysis of jaw and tongue may lead to upper airway obstruction and aspiration of pooled secretions as the victim is unable to swallow	Confusional state usually due to cerebral hypoxia
Bulbar paralysis and respiratory failure can cause cyanosis, altered sensorium, and coma	Fall in tidal volume/respiratory volumes
Krait bite often presents in the early morning with paralysis that can often be mistaken for a stroke	

more when bitten proximally as there is much less distance for venom to traverse to reach the central circulation as also when bitten in areas which are highly vascularized and with less of subcutaneous fat absorption tends to be rapid, e.g., scalp. Increased physical activity involving movement of the bitten limb tends to increase absorption of venom especially so in children with less of subcutaneous tissue and a low body mass. Lower blood volume in children leads to more concentration of venom in the circulation.

Brief History and Physical Examination

The questions to be asked are, time of bite and place where bitten (inside the house, near a water body, fields, plantation, etc.), activity at the time of bite, activity immediately after the bite and first aid given, previous bite or antisnake venom (ASV) administration, alcohol intake, and other diseases especially diabetes, hypertension, and cardiac or neurological conditions. A pictorial chart showing the common venomous snakes of the area is shown for identification. The fang marks are searched for and marked as also signs of inflammation including tender enlargement of the draining lymph nodes examined for and immediate first aid should be provided.

First Aid

Symptoms of anxiety related to snakebite may mimic some of the neurological symptoms and should be allayed. Sedatives should not be given as it would mask the symptoms of neurotoxicity in an elapid bite. Rings, wristwatch, bracelets, bangles, anklets, etc., on the bitten limb are removed and the bite site should be washed in cold water. Tight ligatures and tourniquets should not be applied as that can lead to gangrene of the affected limb and increased local reaction at the bite site. A pressure bandage is advocated similar to one which would be applied for immobilizing a limb in case of a fracture. The pressure bandage could be tied such as to be able to insinuate one finger between the bandage and limb. Venom is absorbed through the lymphatics (large molecular weight fractions) and small venules (small molecular weight fraction), pressure adequate to compress the lymphatics and venules would be enough to retard entry of venom into the central circulation.

In case of signs envenomation, the pressure bandage/tourniquet is to be only removed after the ASV has been started, preferably half an hour after starting ASV. Sudden release of venom on removal of a tourniquet has led to respiratory arrest in cases of elapid bites. Injection tetanus toxoid is given 0.5 mL IM irrespective of whether venomous or nonvenomous, for pain management oral paracetamol and tramadol are recommended but aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are not recommended.

Triaging

Patient should be assessed immediately in triage. Airway assessment should be priority. Tracheal intubation and initiation of mechanical ventilation are helpful in patient with respiratory distress and bulbar palsy. Early critical care support is given for multiorgan failure to the patient and after resuscitation, antitetanus toxoid antibiotics are given for preventing wound sepsis.

Whole Blood Clotting Test

The victim is triaged by way of observation for ptosis to rule out neurotoxicity and signs of bleeding at any site. The most common bleed is observed in the gingival sulci. This is complemented by a WBCT (whole blood clotting test) (**Fig. 5**), which is considered the most reliable test of coagulation in hemotoxic bites which can be carried out at the bed side:

- *Procedure*: A 2–5 mL of fresh venous blood is placed in a new, clean, and dry glass test tube and left at ambient temperature for 20 minutes. It is important that the tube be clean glass and dry as the mechanism under review is the contact clotting mechanism. The use of plastic bottles, tubes, or syringes will give false readings and should not

be used. The glass vessel should be left undisturbed for 20 minutes and then gently tilted not shaken. If the blood is still liquid then the patient has uncoagulable blood. The test tube must not have been washed with detergents as this will inhibit the contact element of clotting mechanism. The test should be carried out every 30 minutes from admission for the first 3 hours. If everything is normal, it is repeated at 1 hour interval until 6 hours and twice more at 3 hours intervals and then at 6 hourly intervals till 24 hours.

- *Interpretation*: If all the tests are normal no further triage would be needed. A normal 20 WBCT and clot lysis would exclude a viperid envenomation. But it occasionally so happens that the bleeding parameters turn abnormal only 24 hours after the bite, especially in pit viper bites.

Differentiating Hematotoxic (Viperid) and Neurotoxic (Elapid) Bites

Hemostatic abnormalities are prima facie evidence of viperid bite given a history of snakebite. All viperid bites can potentially cause renal failure. Rarely ptosis can also be seen with viperid bites (*Daboia russelii*). Presence of signs and symptoms (***see*** **Table 2**) with hemostatic abnormalities as evidenced from an abnormal WBCT or a Prothrombin time and activated plasma thromboplastin time (PT/APTT) >1.5 times normal suggests viperid envenomation. Signs of neuroparalysis, typically starting with ptosis and proceeding on to a descending paralysis are suggestive of an elapid bite (***see*** **Table 3**). Muscles innervated by cranial nerves are involved first, descending downward.

Apart from the bleeding, clotting abnormalities, *Russell viper* envenomation (south India and Sri Lanka) can also present with dark brown-colored urine acute renal insufficiency, ptosis, ophthalmoplegia, and facial paralysis. While *Russell viper* (Myanmar) can produce conjunctival edema (chemosis), and acute pituitary insufficiency. Syndromic approach of snake bite is described in **Figure 6**.

Laboratory Investigations

Recommended laboratory test are described below:

- *Hematology*—total Leukocyte count, differential count, erythrocyte sedimentation rate (ESR), platelet count, and blood grouping. Blood grouping should be done immediately as venom fractions are known to interfere

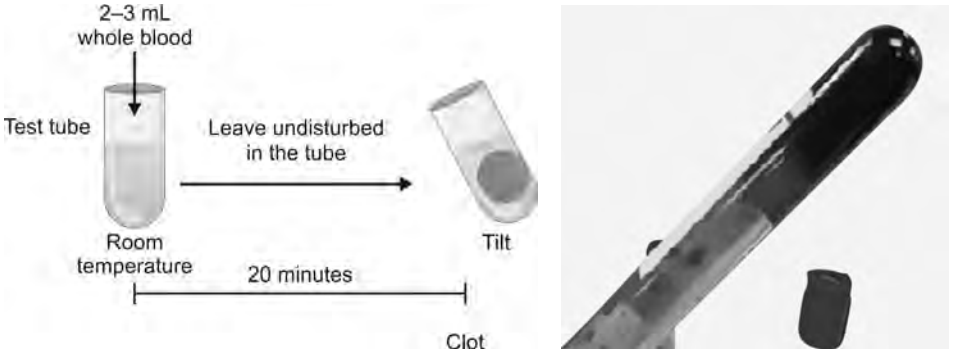


FIG. 5: Showing procedure of 20 whole blood clotting test (WBCT) to check coagulopathy in snake bite. ***(For color version, see plate 52)***

Syndrome 1	• Local swelling with bleeding and clotting abnormalities—all species of Viperidae • Local swelling with bleeding, clotting abnormalities with shock or acute kidney injury dark brown urine, facial paralysis, ptosis ophthalmoplegia—*Russel viper* (India and Sri Lanka) • With conjunctival edema (chemosis and acute pituitary insufficiency *(Russel viper Myanmar)*
Syndrome 2	• Local swelling with paralysis—*Cobra/King cobra* • Minimum or no local swelling with paralysis, bitten on ground while sleeping—*Krait*
Syndrome 3	• Bitten on land—*Russel viper* • Bitten on land while sleeping indoor—*Krait* • Bitten in water—*Sea Snake*

FIG. 6: Syndromic approach to snake bite.

with grouping test. Peripheral smear (to look for crenated RBCs, an early sign of envenomation) is done.
- Prothrombin time and activated plasma thromboplastin time, serum fibrinogen, and serum D dimer.
- *Biochemical*—aspartate transaminase/alanine transaminase/alkaline phosphatase (AST/ALT/ALP)/serum bilirubin.
- Urea/creatinine/Na^+, K^+, creatinine phosphokinase, and blood sugars.
- *Urinalysis*—urine routine and microscopy.
- Myoglobin/hemoglobin.
- Platelets, urinalysis, Hb, and blood urea nitrogen (BUN) to be repeated at 12 hourly intervals the first 2 days and daily in case of viperid bites.

SPECIFIC TREATMENT FOR SNAKE BITE

Antisnake Venom

The only treatment available for venomous snakebite is ASV. Types of ASV available are polyvalent-liquid/ dry lyophilized. Dose in victim is same in all age group, child, pregnancy, and elderly. Regarding ASV Anaphylaxis, there are no recommendations of test dose. Premedication with antihistamine (pheniramine 25 mg IV) and hydrocortisone (100 mg IV) can be given but no evidence that this regimen is effective in preventing the ASV reaction. Keep Injection adrenaline 0.5 mg 1:1,000 ready. Physician should be ready to handle this situation. Shelf life of liquid ASV—2 yearsat 4°C.

Indications of Antisnake Venom

If following features develop in patient with suspected or proven snake-bite—rapid developing swelling in more than half of the affected limb, enlarged and tender lymph node. Coagulation abnormalities are epistaxis, hemoptysis, hematuria, and gum bleeding. Neurotoxic features are ptosis, ophthalmoplegia, regurgitation, and nasal voice bulbar palsy. Cardiotoxic features are hypotension, shock, and arrhythmia. Acute kidney injury (AKI) (renal failure)—features of rhabdomyolysis hyperkalemia dark brown urine oliguria or anuria, raised urea creatinine.

Doses of Antisnake Venom

Start with 10 vials of ASV diluted in 100 mL of normal saline. Start ASV at 10–15 drops/min for the first 15 minutes, watch for allergic reactions. If there is no evidence of reaction to the ASV, continue with the ASV at a constant speed such as to finish in 1 hour. Continue to monitor the vital signs at 5 minutes intervals for the first 30 minutes and then at 15 minutes intervals for 2 hours.

Further Requirement of Doses

Repeat doses of ASV are given as 10 vials, 6 hours after the first dose in case of viperid bites as the liver takes up to 6 hours to replenish the coagulation factors. Doses >30 vials are rarely required, if symptoms do not settle with 20 vials other causes to be looked for like a species not covered by the polyvalent ASV, geographical variation of venom of the same species, etc. In cases of elapid bites, 10 vials of ASV could be repeated after 2 hours, if symptoms of neuroparalysis have not improved. Very rarely does one require doses of >20 vials in elapid bites. Mechanical ventilation would be required in patients with respiratory failure. Signs of recovery are spontaneous bleeding from various sites which usually stops, blood starts clotting (20 WBCT), urine color become normal, recovery in shock, and rise in blood pressure. Feature of postsynaptic neurotoxic (cobra bite) improves within hours but presynaptic neurotoxic feature (krait bite) takes longer time to improve.

Neostigmine and Cobra Envenomation

Cobra venom is alpha-bungarotoxin, which reversibly blocks postsynaptic acetylcholine receptors. Neostigmine is an anticholinesterase that prolongs the half-life of acetylcholine and can therefore reverse respiratory paralysis and neurotoxic symptoms. It is particularly effective for postsynaptic neurotoxins such as that of *Naja naja* venom. Despite the fact that the neostigmine test (neostigmine 0.5 mg IM with atropine 0.6 mg IV) was actually an Indian discovery, it is still poorly used in India. There is doubt over its efficacy against presynaptic neurotoxins such as those of the *Bungarus caeruleus* and the *Daboia russelii*.

In case of neuroparalysis, *neostigmine*—0.5—2.5 mg in adults and 0.025 mg/kg in children IV infused over 5 minutes. Give concurrent administration of atropine 0.6—1.2 mg IV in adults and 0.01 mg/kg of atropine IM or SC in children. If the neostigmine test is positive, same is repeated at half hourly intervals to a total of five doses. This is followed up by repeat injections at increasing intervals of 2–12 hours. If there is no improvement in symptoms after one hour, neostigmine should be stopped.

Observation for Antivenom Response

If an adequate dose of appropriate antivenom has been administered, the following responses may be observed:
- *General*: The patient feels better. Nausea, headache, and generalized aches and pains may disappear very quickly. This may be partly attributable to a placebo effect.
- *Spontaneous systemic bleeding (e.g., from the gums)*: This usually stops within 15–30 minutes.
- *Blood coagulability (as measured by 20WBCT)*: This is usually restored in 3–9 hours. Bleeding from new and partly healed wounds usually stops much sooner than this.
- *In shocked patients*: Blood pressure may increase within the first 30–60 minutes and arrhythmias such as sinus bradycardia may resolve.
- Neurotoxic envenoming of the postsynaptic type (cobra bites) may begin to improve as early as 30 minutes after antivenom, but usually takes several hours. Envenoming with presynaptic toxins (kraits and sea snakes) will not respond in this way.
- Active hemolysis and rhabdomyolysis may cease within a few hours and the urine returns to its normal color.

Supportive Care

In victims presenting with hematemesis, a Ryle's tube is passed into the stomach and in patients with a likelihood of progression to renal failure, it is prudent to have an indwelling Foley's catheter. Both this be done early in the course of hospitalization as the likelihood of traumatic bleed is considerable in case of viperid bites.

Pain Management

Nonsteroidal anti-inflammatory drugs are avoided in venomous snakebite especially viperid. Paracetamol could be given orally; in case of severe pain one could use tramadol hydrochloride.

Antibiotics

A wide range of antibiotics has been used as prophylaxis against secondary infection especially in cases of significant necrosis at the bite site. Combination of amoxicillin with clavulanic acid can be used for the same.

SPECIAL SITUATIONS

- *Late presentation of snake bite victims*: Sometimes snake bite patient presents late in emergency department after several days. ASV only neutralizes unbound venom so perform the 20WBCT test if coagulopathy presents then give 8–10 vials of ASV.
- *Children*: Children should receive the same dose as adults.
- *Pregnant women*: There is no dose modification and the same dose of ASV should be given as would be given to a nonpregnant lady. There is a significant likelihood of fetal loss in victims of snakebite treated with ASV. Envenomation is not an indication for a cesarean section in term pregnancy and the mode of delivery is decided on by the obstetric status. Lactating mothers can continue to breast feed their infants if their physical condition so allows.
- *Locked in syndrome*: Locked-in syndrome (LIS) is a condition in which a patient is aware but cannot move or communicate verbally due to complete paralysis of nearly all voluntary muscles in the body except for the eyes. Total LIS is a version of LIS wherein the eyes are paralyzed as well. This is not an uncommon presentation of elapid especially krait bite. It is mandatory that this diagnosis should be kept in mind in individuals presenting with flaccid quadriparesis without any other apparent cause. It has to be kept in mind that often the victim of a krait bite is unaware that he has been bitten and the local signs tend to be minimal.
- *Maximum dose of ASV*: There is no such maximum dose but doses above 30 vials do not benefit.
- *Use of fresh frozen plasma*: FFP or platelet concentrates in case of low platelet count or bleeding manifestation can be given.

COMPLICATIONS

- *Skin necrosis/amputations*—necrosis or debridement of the bitten part especially with a compartment syndrome. Rarely amputation of a toe, foot, or extremity.
- *Acute respiratory distress syndrome (ARDS)*—one of the most dreaded complications of venomous snakebite, especially viperids with a very high-mortality rate. Mechanisms postulated include direct action of venom fractions, aspiration and lung injury secondary to an inflammatory storm triggered by venom fractions. Mechanical ventilation is the treatment of choice with ancillary support.
- *Acute kidney injury*—a dreaded complications which can potentially be caused by all viperids. The causes of AKI in snakebite envenomation are multifactorial and include acute tubular necrosis (ATN), disseminated intravascular coagulation (DIC), hemoglobinuria, myoglobinuria, and direct nephrotoxicity of venom fractions being implicated. Pericapsular bleeding could also be causative. AKI is almost always reversible and is treated with renal replacement therapy following standard guidelines. Very unusually patients develop cortical necrosis in which case they proceed to develop chronic kidney injury (CKI). Typically patients who complain of flank pain within 12–24 hours of the bite are the ones who progress on to develop AKI.
- *Capillary leak syndrome (CLS)*: It is characterized by hypotension with hemoconcentration, hypoalbuminemia without albuminuria, and generalized edema. This syndrome is due to a capillary hyperpermeability with massive extravasation of plasma containing macromolecules <200 kD and at times up to 900 kD. This complication is also seen with viperid bites with a significant mortality. Zinc containing snake venom metalloproteinases has been implicated which act by degrading the compact proteins of basement membrane underlying the endothelial cells.
- *Cerebrovascular accident (CVA)*: Most venom fractions of both viperids and elapids do not cross the blood brain barrier. Other than for symptoms of neuroparalysis following an elapid bite, involvement of the CNS could be by way of a CVA secondary to either thrombosis or hemorrhage seen in viperid bites especially *Daboia Russelii* (*Russell viper*). Thrombotic CVA could be due to the direct thrombotic effect of viperid venom fractions or secondary to DIC. Thrombotic CVAs usually occur 2–3 days after the bite, whereas hemorrhagic CVAs generally occur earlier.
- *Cardiac complications* could range from myocarditis seen in elapid bites (cobra, sea snakes, etc.), hemopericardium in viperid bites, stress cardiomyopathy, acute coronary syndromes (ACS), and tachyarrhythmias. ACS is more seen in viperid bites, especially with *Russell viper*, thrombosis secondary to venom action or DIC being implicated just as with thrombotic CVA.
- *Hypopituitarism* one of the long-term complications reported with a viperid bite, especially *Russell viper* resulting from a Sheehan like syndrome secondary to bleeding in the pituitary fossa.
- *Eczema/squamous cell carcinoma*: Severe eczema at the bite site has been reported with snakebite envenomation. Very rarely squamous cell carcinoma has been reported at the bite site.
- *Psychological trauma*: There is a significant psychological trauma attributed to snakebite and hospitalization for the same especially in children and in women.

DISPOSITION

Snake bite patient should be admitted in intensive care unit because they may require management for various complications such as respiratory failure, and acute renal failure due to rhabdomyolysis needs hemodialysis, intracranial bleed, DIC, encephalopathy, paralysis and coma, hypotension and shock, tetanus and cellulitis, and compartment syndrome and gangrene.

SUMMARY

Venomous snakebite is a medical condition with a far-reaching impact on the family of the victim. Snakebite which has been relisted as a NTD (neglected tropical disease) is a common disease condition that one encounters anywhere in the tropics and is eminently amenable to treatment. If diagnosed early and treated well the victim goes back to a normal productive life which cannot be said of most of the other catastrophic diseases that one encounters during daily practice.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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246 CHAPTER

Arthropodes: Insect Bites and Stings

Au Kin Heng Constantine

INTRODUCTION

An arthropod is an invertebrate animal with a segmented body and paired, is jointed appendages and an exoskeleton. The name *arthropod* is based on the Greek *arthr*, meaning joint, and *pod*, meaning foot. Arthropods comprise 84% of all animal species on Earth. Entomologists classify arthropods into classes, orders, families, genera, and species. Common orders include Blattaria (cockroaches), Coleoptera (beetles), Diptera (flies and mosquitos), Ephemeroptera (mayflies), Hemiptera (wasps, ants, and bees), Isoptera (termites), Lepidoptera (butterflies and moths), Odonata (dragonflies and damselflies), Orthoptera (grasshoppers and crickets), Phthiraptera (lice), and Siphonaptera (fleas). As healthcare professionals, it is often not necessary be aware of this detailed classification. A description of the morphology of arthropods may be good enough for clinical practice. The following are some arthropods that have medical significance. Adult insects consist of six legs and three body regions (head, thorax, and abdomen), and some insects have wings. Adult spiders have eight legs and two body regions (cephalothorax and abdomen). Adult mites and adult ticks have eight legs and one body region but no true mouth (with mouthparts only). Adult scorpions have eight legs with a broad flat body region and a tail with a stinger. Adult centipedes have a pair of legs in each body segment. The number of body segments is numerous and the shape is usually flat. Adult millipedes have two pairs of legs in each body segment and the number of body segments is numerous and the shape is usually cylindrical. Because millions of arthropod species exist on Earth, this chapter can only include common ones that have medical significance. Stress is put on the general principles. Travel has become very popular and many exotic regions have become accessible. In managing a patient who has a recent travel history, clinicians should think about the possibility of arthropod-related diseases of the destinations. Delusion of parasitosis and other psychiatric diagnoses like amphetamine bugs must be excluded.

Etiology

Because millions if not billions of different arthropod species exist on Earth (**Fig. 1**), the following discussion only includes those ones that people commonly encounter. Adult arthropods may look very different from larval/developmental stages. Please consult a biologist, entomologist, veterinary surgeon, or poison center if needed.

PATHOPHYSIOLOGY

Exposure to arthropods can be experienced via bites, stings, local irritation causing local infection, systemic hypersensitivity, anemia, ingestion, and arthropod-borne diseases and ingestion. Venom and irritating chemicals complicate the condition. The proceeding section is a brief summary of the common contacts (**Table 1**).

Locally

- *Blockages of orifices and skin attachment*: Small arthropods may enter and block any orifices of our body. Sometimes arthropod body parts remain lodged. A tick may stick strongly on the skin.
- *Local wounds*: Bites, stings, and even scratching by arthropod feet might result in local wounds. The wounds are usually small. Some wounds may carry foreign bodies. Bees leave their stings behind. Mouthparts may be broken. Soil or other dirt may be present. Local inflammation with increased blood flow, increased capillary permeability, and increased white cell count are common. The severity of a rash can range from local pain, itchiness, and swelling that lasts for a few hours to extensive swelling that lasts for days. As with every wound, local infection by superimposed bacteria can happen. Cellulitis, necrosis, and sepsis may follow.
- *Invasion of human tissues—myiasis*: Myiasis means infestation of larvae of flies in the organs or tissues of humans or other animals. Myiasis can be classified into intentional therapeutic myiasis, accidental myiasis, facultative myiasis, and obligate myiasis. Therapeutic myiasis is to use larvae for wound debridement. The use was very common before the antibiotics era. Accidental myiasis occurs when eggs are ingested accidentally. The larvae may survive for a short while, which is considered a relatively benign condition. The patient may complain of stomach pain, nausea, and vomiting, which is also known as pseudomyiasis because of the lack of full development of a fly. In facultative

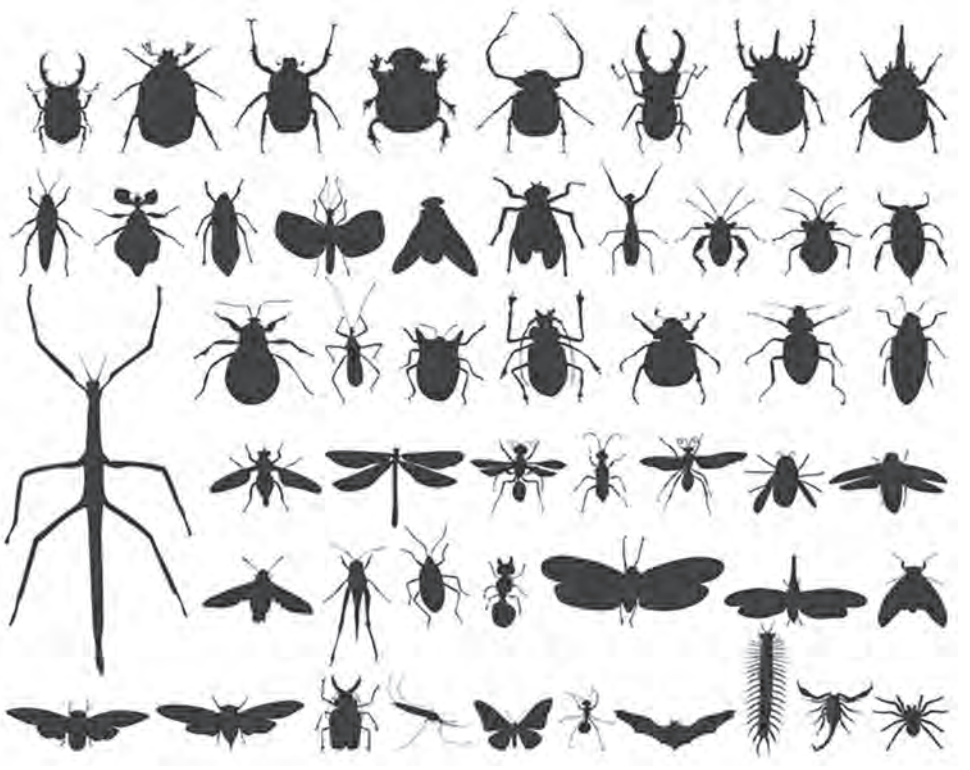

FIG. 1: Different types of arthropod.

TABLE 1: Common arthropods that have contact with humans.

Arthropod	*Nature of contact/Wounds and harm*	*Transmission of diseases*	*Remark*
Ants			
Ants (worldwide)	• Bite and sting • Skin lesion is erythematous with a central wheal. Later, pustules may develop	Not known	
Fire ants (worldwide), harvester ants (USA), and velvet ants (USA)	• Painful sting • Skin lesion is erythematous with a central wheal. Later, pustules may develop • Reexposure can lead to serious systemic reactions	Not known	
Bees			
Bees (worldwide)	• Sting • The wound shows local swelling with a central white spot with erythematous halos • Reexposure can lead to serious systemic reactions	Not known	
Honey bees (worldwide), bumble bees (worldwide), and Africanized honey bees (in Central and South America, Mexico, and USA)	• Painful stings • The wound shows local swelling with a central white spot with erythematous halos • Reexposure can lead to serious systemic reactions	Not known	
Beetles			
Beetles (worldwide)	• Most are benign (except blister beetles)	Not known	
Blister beetles (worldwide)	• Secrete irritating chemicals causing kidney failure, cardiovascular collapse, coma, and even death	Not known	Cantharidin penetrates the skin and pederin causes blisters

Continued

Continued

Arthropod	*Nature of contact/Wounds and harm*	*Transmission of diseases*	*Remark*
Bugs			
Bed bugs (worldwide)	• Bite and suck blood from humans • Red blotches grouped in linear pattern with urticarial wheals and sometimes bullous	Suspected	
Conenose bugs (in the Americas)	• Bite at night • Feed on human blood • Variable lesions	Vectors for *Trypanosoma cruzi* that causes Chagas disease via fecal contamination of the bite	
Wheel bugs (USA)	• Painful bite • Lesion shows swelling, inflammation, and induration	Not known	
Caterpillars			
Urticating caterpillars (worldwide)	• Venomous hairs or spines that can sting or irritate the skin with immediate burning sensation • Variable lesions • Burning sensation	Not known	The venom of *Lonomia* in South America contains anticoagulants
Centipedes			
Centipedes (worldwide)	• Painful bite • Typical lesions show two hemorrhagic punctures	Not known	Cytolysin-based venom
Cockroaches			
Cockroaches (worldwide)	• Food contamination and possibly allergy • Bite occasionally • Blocking orifices	Many bacteria, fungi or viruses mechanically	
Earwigs			
Earwigs (worldwide)	• Relatively harmless • Abdominal cerci of larger ones may pinch human skin • Trivial lesion	Not known	Some live in water wells
Fleas			
Adult fleas (worldwide)	• Bite and feed on blood • The lesions vary from one species to another	• Plague (*Yersinia pestis*), rickettsial diseases (murine typhus, *Rickettsia typhi*) • An intermediate host of dog tapeworm (*Dipylidium caninum*)	
Flies (biting)			
Black flies (worldwide)	• The lesion has variable patterns with systemic reactions	Onchocerciasis	
Congo floor maggot (sub-Sahara Africa and Cape Verde Islands)	• Myiasis • Nocturnal bite blood-feeding larvae • The lesion is usually a pinprick	Not known	
Deer flies (worldwide)	• Painful bites • The lesion is deep and singular; cellulitis	Tularemia (deer fly fever/rabbit fever) and loiasis (Loa Loa)	
Horse flies (worldwide)	• Painful bites • The lesion is deep and singular; cellulitis	Not known	
Biting midges (worldwide)	• Bite • The lesion is minute popular in pattern with erythematous halo • Wheals may occur	Oropouche fever (a virus in the Simbu group of *Bunyaviridae*)	

Continued

Continued

Arthropod	*Nature of contact/Wounds and harm*	*Transmission of diseases*	*Remark*
Sand flies (worldwide)	• Bite and suck blood • Lesions may be red papules or wheals	Leishmaniasis (*Leishmania donovani*), bartonellosis (*Bartonella bacilliformis*), and sandfly fever	
Stable flies (worldwide)	• Bites • The lesions are small evanescent vesicles	Not known	
Tsetse flies (tropical Africa)	• Bites • The lesions are small punctures with hemorrhaging	African trypanosomiasis (*Trypanosoma brucei*)	
Flies (nonbiting)			
House flies/filth flies (worldwide)	Do not bite. They may contaminate food and water and may cause myiasis	Transmission of disease is mainly carried out mechanically. More serious examples include typhoid, cholera, and dysentery	
Eye gnats (almost worldwide)	Do not bite but may scratch the eyes	Yaws (*Treponema pertenue*) and pinkeye are transmitted by eye gnats	
Nonbiting midges (worldwide)	Hypersensitivity reactions in the eyes or respiratory tract	Not known	Mass emergence of nonbiting midges may cause traffic accident and other nuisances
Flies (nonbiting) and myiasis			
Human bot flies (Central and South America and Mexico)	• Do not bite but may cause myiasis • Superficial, painful, swollen with a central opening	Not known	
The larvae of screwworm flies (Central and South America, South Pacific region, and tropical Africa)	• Extensive damage to human tissues and cause pocket-like sinuses • Fatal myiasis	Not known	
Tumbu flies (tropical Africa)	• Red or shiny nodules and furuncular myiasis	Not known	
Wohlfahrtia flies consist of *W. magnifica* (Arabian Peninsula, Asia, North Africa and southern Europe)	• Myiasis • Causes deep lesions	Not known	
W. vigil (Canada and northern USA)	• Myiasis • Causes papules or pustules	Not known	
Lice			
Body lice (worldwide)	• Bites and feeds on human blood • The lesion is red papules, 3–4 mm in diameter, with purpuric halo	Epidemic typhus (*Rickettsia prowazekii*), trench fever (*Bartonella quintana*), and louse-born relapsing fever (*Borrelia recurrentis*)	Not the bite but crushing the lice and their feces into skin transmits these diseases
Head lice (worldwide)	• Irritate the skin and may cause secondary infection • Itchy scalp is the common presentation	Not known	
Pubic lice (worldwide)	• Irritates the skin and may cause secondary infection • The lesion is variable and may present as blue spots	Not known	
Millipedes (worldwide)	• May burn the skin • The lesions range from yellow to brown. Blisters may be present	Not known	

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Arthropod	*Nature of contact/Wounds and harm*	*Transmission of diseases*	*Remark*
Mites			
Chigger mite (worldwide)	• Irritation and itchiness on the skin • The lesion is variable and may present as a red, dome-shaped papule	Scrub typhus in Asia	
House dust mites (worldwide)	• Do not bite but cause allergies, especially in the respiratory tract	Not known	
Biting mites (worldwide)	• Painful bites • The lesions vary	May possibly transmit rickttesial pox	
Scabies mites (worldwide)	• Intense itchiness and secondary infection • Burrows and papules are formed on the skin	Not known	
Follicle mites (worldwide)	• Live on human skin and are usually harmless	Not known	
Mosquitoes (worldwide)			
Mosquitoes (worldwide)	Bite and cause puncture, hemorrhages, popular lesions, or wheals with edema	Malaria (*Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* and *Plasmodium falciparum*), yellow fever (flavivirus), dengue fever (DEN-1, DEN-2, DEN-3, and DEN-4), Rift Valley fever, Ross River virus disease, and Chikungunya fever. Mosquitoes transmit lymphatic filariasis (*Brugia malayi*), and many other filarial worms. Encephalitis transmitted by mosquitoes include Eastern equine encephalomyelitis, Western equine encephalitis, Venezuelan equine encephalitis, Japanese encephalitis, St. Louis encephalitis, West Nile encephalitis (West Nile virus), and La Crosse encephalitis	
Moths			
Moths (worldwide)	• Stinging hairs or spines cause skin irritation • Some body parts may detach and cause irritation in the respiratory system • Skin lesions vary	Not known	
Pentastomes/Tongue worms			
Pentastomes/tongue worms (worldwide)	• Reside in human liver, spleen, lungs, throat, and eustachian tubes • They are benign and may cause irritation in the throat	Not known	
Scorpions			
Scorpions (worldwide)	Sting painfully and some species give fatal venomous sting to humans. Lesions vary	Not known	
Spiders			
Violin spider (Africa, Australia, South America and USA)	Bites cause variable lesions plus necrotic wounds and possible hemolytic anemia	Not known	

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Arthropod	*Nature of contact/Wounds and harm*	*Transmission of diseases*	*Remark*
Widow spiders (worldwide)	• Bite causes two small puncture wounds, and neurotoxic venom may be fatal • Myocarditis and dyspnea can occur as well	Not known	
Hobo spiders (Europe and USA)	• Bite is usually painless at first. Induration followed by expanding erythema and blister • Necrosis may develop with eschar formation	Not known	
Sydney funnel web spiders (Australia)	• Bite site may be extremely painful • Death within 1 h	Not known	The venom acts on the somatic and autonomic nerves, quickly causing hypotension and apnea
Tarantula spiders (USA)	Painful bites. The urticating hair may cause much irritation on the skin and mucosal surfaces	Not known	
Ticks			
Ticks (worldwide)	• Bite and feed on human blood. The lesion is a red papule with erythema. Hypersensitivity to tick saliva causes erythematous ring • Tick-paralysis is caused by the neurotoxin in tick saliva	Babesiosis (protozoan; Europe and USA), Colorado tick fever (virus; Canada and USA), Crimean-Congo hemorrhagic fever (virus; Africa, Asia and Europe), Kyasanur Forest disease (virus; India), Lyme disease (spirochetes; Australia, China, Europe, Japan, and USA), relapsing fever (spirochetes worldwide), *Rickettsiae* (many diseases, e.g., African tick bite fever in sub-Saharan Africa; American boutonneuse fever/maculatum fever in the Americas; boutonneuse fever/ Mediterranean fever in Africa; ehrlichiosis and anaplasmosis in the USA; Japanese spotted fever in East Asia, Japan, Mediterranean, and the Middle East; North Asian tick typhus/Siberian tick typhus in Central Asia, Mongolia, and Siberia; Queensland tick typhus in Australia; Rocky Mountain spotted fever in the western hemisphere; tickborne lymphadenopathy in Europe), tick-borne encephalitis (virus in Europe), and tularemia (bacterium in Canada, Europe, Japan, Mexico, Russia, USA)	
Wasps			
Yellow jackets (worldwide), hornets (worldwide), and paper wasps (worldwide)	• Give painful stings and may cause allergic reactions • The lesion is central white spot with erythematous halo • The degree of local swelling varies • Reexposure can lead to serious systemic reactions	Not known	

myiasis, a larva leaves the necrotic tissue and invades the healthy tissue, causing pain and damage. Screwworm flies and human bot flies may develop in human tissue. Tissue damage and occasional death may occur.

Systemic

Allergic reaction or hypersensitivity: Allergic reaction or hypersensitivity is usually classified into type I (IgE-mediated), type II (cytotoxic reaction), type III (antibody-antigen complex), and type IV (T-lymphocytes and macrophages). Type I, II, and III are usually immediate in onset, whereas type IV usually has a delayed onset of a few hours to days. The venom, protein substances, and foreign bodies infiltrated by stings and bites can certainly cause allergic reaction. Beware that a simple contact by an arthropod on the skin or mucous area can cause allergy. Local allergic reaction is usually irritating and may subside in a few hours. However, if the site involved is the throat or head and neck region, a severe local reaction can compromise the airway. Severe systemic allergic reaction can occur, if the allergens reach the blood or lymphatic circulation and different organs are involved. Anaphylaxis is one of the worst forms of systemic presentation of hypersensitivity. It is usually quick in onset, with obstruction in the upper airway and the lower airway. Swelling in the lips and tongue, dyspnea, and wheezing may be found. Pruritus, urticaria, erythema, and angioedema are found on the skin. Cardiovascular collapse may occur due to peripheral vasodilation, increased vascular permeability, and possibly arrhythmia.

- *Anemia*: Anemia, ranging from mild to severe, may occur depending on the number of bites and duration of bites.
- *Ingestion and food contamination*: For some readers, eating arthropods may be an alien idea. However, people do eat arthropods. For example, scorpions are roasted or cooked in other ways in China. It is believed that the venom of scorpions is heat liable. Some may consume scorpions raw with the tail and stinger removed. If the preparation is not perfect, the venom may enter the body via the gastrointestinal tract. Gastric acid and other enzymes may denature the venom though. Some players of survival games eat scorpions and black widow spiders. Ingestion of the arthropods, their body parts, or chemicals may be accidental as well. Cockroaches, flies, and other arthropods may contaminate food by their body parts, fluids, feces, etc.

Venom and other Irritating Chemicals

Arthropods have many venoms and irritating chemicals. Here are some common examples.

- *Necrotic venom*: The venom in bees and wasps has phospholipase A. The venom in violin spiders has lipase and hyaluronidase. Possibly, the lipase induces neutrophil chemotaxis, causing tissue necrosis.
- *Neurotoxic venom*: Tick paralysis is caused by a neurotoxin and the presentation resembles Guillain-Barré syndrome. The venom in widow spiders is a kind of neuromuscular-damaging protein. It affects ion transport, leading to sweating, muscular spasm, weakness, paralysis, and convulsions. Scorpion venom contains multiple low-molecular-weight proteins, salts, mucus, and some other organic compounds. The low-molecular-weight proteins increase the permeability of the sodium channel in the neuromuscular junction and the autonomic nervous system. Presentation includes blurred vision, paralysis, abnormal eye movement, excessive salivation, convulsion, respiratory paralysis, myocarditis, and death.
- *Other venoms*: In the bites of blister beetles, cantharidin penetrates the skin and pederin causes the blisters. *Lonomia* (a caterpillar in South America) venom contains anticoagulants and may cause severe bleeding. Centipedes bite with a cytolysin-based venom
- *Respiratory tract reaction*: House dust mites cause allergic reaction presented as asthma-like attacks. Other arthropods can cause allergic reaction in the respiratory tract as well.

CLINICAL PRESENTATION

- *Local*: In terms of skin or scalp presentation, arthropod contact ranges from no obvious sign to mild rash, papules, nodules, and necrotic tissue. The patient may have minimal complaints like light itchiness, light pain to severe itchiness, and pain.
- *Systemic*: Anaphylaxis, fever, sepsis, anemia, weight loss, and other signs may be present. Alternation in consciousness, coma, and even death, they may be caused by the contact alone or by the diseases transmitted.
- *Concerning features (red flags)*: More signs and more diseases may be present on top of the wound or rash after arthropod contact. Patients may not recall any bites, stings, or contact with an arthropod. Skin signs or wounds may not be obvious even for a poisonous widow spider. Clinicians are encouraged to seek more information about the arthropods that resided in their regions of practice. A patient may correctly recall an overseas trip, but details of a local trip may not be recalled as vividly. Offer hints like any contacts with wild or domestic animals, any local parks, woods, etc. For any patients with fever of unknown origin, unaccounted symptoms or signs, exposure to arthropods must be excluded. Warn a patient about delayed hypersensitivity, which may have an onset in terms of days. A skin rash, wound, nodule, ulcer, etc., with a history of arthropod contact can be caused by other diseases. Exclude allergic reaction against an antigen other than an arthropod. Exclude melanoma, basal cell cancer, and squamous cell cancer. Think of other causes of anemia. Sometimes tests for allergens and biopsy may be needed. Psychiatric illness, substance abuse, and withdrawal should be excluded.

EVALUATION

- *History*: Bites are common in many regions, especially in tropical and subtropical areas, but a patient may not be aware. Ask for any possibility of arthropod contact. If there was an arthropod contact, ask what, where, when, and how the contact was. Check the arthropod, identity the body shape, wings, number of legs, mouth parts, stingers, etc. Adult arthropods may look very different from larval/developmental stages. **Figure 1** may help in identification. Characteristics of the place like plants may help. Travel history must be checked. In addition to overseas travel, a hiking trip in the neighborhood may result in arthropod contacts. Ask for details of the trip such as the location, water source, and plants. Check the photos taken during the trip may give some hints. Change in occupation,

residence, hobbies, or recent cleaning of lodgings may give rise to arthropod contact. Ask for similar presentation in family members and friends because they may share the same exposure.

- *Physical examination*: Do not take arthropod bites or contact lightly. More signs and more diseases may be present on top of the wound or rash.
  - Beware of life-threatening signs, either present or in progression. Look for signs of severe allergic reaction like difficulty in breathing and hypotension.
  - Do not focus only on the wound. Do a general examination. In the general examination, look for pallor, jaundice, edema, lymph nodes, and splenomegaly. Look for signs of possible diseases transmitted. Check for fever. A simple contact does not usually cause fever.
  - Check the wounds. Note the severity of swelling and the location. A swelling in the head, neck, and throat regions demands special care.
  - The pattern and distribution of the rash, if any, may give a hint of the culprit.
- *Interpretation of finding*: It is important to grade the result of the contact. Do not miss any life-threatening conditions. Think about the possibility of transmitted diseases. Think of the differential diagnosis. A skin rash, wound, nodule, ulcer, etc., with a history of arthropod contact can be caused by other diseases, even malignant ones. Psychiatric illness, substance abuse, and withdrawal should be excluded.
- *Investigations*: Most arthropod-related cases do not need any investigation. For those severe cases, use the white blood cell (WBC), blood film (e.g., malaria and other parasites), and viral titer, e.g., dengue virus (usually two titers are needed to see the trend). For patients with possible organ failure, check the renal function and liver function. For suspected myocarditis, arrange cardiac enzymes and echocardiogram. A skin rash, wound, nodule, ulcer, etc., with a history of arthropod contact can be caused by other diseases. Exclude melanoma, basal cell cancer, and squamous cell cancer. Think of other causes of anemia. Sometimes tests for allergens and biopsy may be needed.

TREATMENT

Treatment includes prevention of bites, prevention of arthropod-borne infection, local wound care, supportive care, allergy (mild to severe), and antivenom. As in every aspect of medicine, prevention plays an important role. Avoid contact with arthropods.

Prevention

- *Personal protection*: Avoid using perfume in the wild because perfume may attract arthropods. Similarly, sweat may attract arthropods. Avoid contact with ants because they may be fire ants. Do not go near bee hives. Avoid contact with wild animals. For domestic animals such as pet dogs, use tick and flea collars or other products to repel ticks and fleas. Regular washing with antiarthropod shampoo helps to remove fleas and ticks. For other domestic animals such as horses, seek advice from veterinary surgeons for prevention of arthropods. Do not handle any sick or dead animals, even pets, unprotected. Always wear gloves, etc. For bedbugs, professional pest control may be needed. Wear long sleeves, long pants, etc., to protect the skin. Proper use of repellents such as DEET (N, N-diethyl-meta-toluamide) or the use of insecticides in the garden may help. Beware of allergies caused by repellents and insecticides. Beware that many commercial insect repellents or folk remedies may not work. Arthropods may hide in shoes, socks, pockets of shirts, blankets, bed linens, etc. Flip and check before use.
- *The environment*: General hygiene and proper handling of food and wastage can reduce the chance of survival of cockroaches, flies, and other arthropods. The mosquito *Aedes aegypti* can spread dengue fever, yellow fever, Zika virus, and chikungunya. Avoid stagnant water so that its eggs cannot develop properly. *Aedes aegypti* is most active just after sunrise and just before sunset but can bite at night. Anopheles mosquitoes, the vector for malaria, are active at dusk or dawn and active at night. Plan the activities accordingly. Mosquito nets, window screens, and bed nets can reduce the chance of mosquito contact. Dust mites can be prevented by regular and proper mattress cleaning. Furniture can be treated with both heat and steam. Isolation, either of a patient or others, is needed for scabies and hair lice until treated.
- *Vaccines and prophylaxis*: A vaccine is available for yellow fever. Prophylaxis against malaria is also available. Advice from a travel clinic will be useful. Make sure to receive a consultation as early as possible. Some vaccines or prophylaxes need repeated doses. For yellow fever, usually only government agencies have the drugs and appointments may be tight.
- *Food storage and preparation*: Food, raw or cooked, should be stored properly to prevent contamination by arthropods. Food must be properly cooked before consumption.

After Exposure

- *Do not crush the arthropod*: Crushing a mosquito while it is biting on the skin may be a second reflex for many people. Crushing a mosquito is relatively safe. For some arthropods, it may not be that safe. Epidemic typhus (*Rickettsia prowazekii*), trench fever (*Bartonella quintana*), and louse-born relapsing fever (*Borrelia recurrentis*) are transmitted by crushing the lice and their feces on the skin. Crushing also destroys the identity of the arthropod. Take a photo of the culprit if safe. Take note of the number of legs, color, shape, etc., of the arthropod.
- *Local wound*: The usual wound care must be conducted. Check for foreign bodies. Look for unusual swelling, necrosis, or sign of infection. In terms of treatment of local wounds, think of AI's: antihistamine, analgesics, antibiotics, antitetanus, [adrenaline/epinephrine (for anaphylaxis)], ice, and steroid. The possible route of administration can be topical, oral, intramuscular, subcutaneous, and intravenous. Local antihistamine cream may work for simple itchiness. Oral analgesics are usually good enough. Consider local antibiotics cream. Oral or even IV antibiotics may be needed for infected wounds. Because bites or stings may carry soil, the antitetanus status of the patients should be checked. Adrenaline is included here so as to stress the importance to exclude anaphylaxis. Steroid cream may be needed for severe itchiness. Beware of the adverse effects of treatment especially for ice and steroid.
- *Blockage of orifice*: If an arthropod blocks an orifice, removal must be done carefully. Light may sometimes

guide an arthropod to exit an orifice. Olive oil may float an arthropod out of the orifice. Removal of embedded arthropods such as maggots must be planned carefully. Breakage of the maggots may lead to hypersensitivity. Consult a clinical microbiologist, entomologist, a poison center, or a veterinary surgeon for the necessary precaution and prophylaxis before removal.

- *Remaining stings and ticks*: Removal of a remaining sting must be done carefully so as not to squeeze remaining toxin and chemicals into the skin. Consider using a card to scrub the sting out. Ticks can be removed with forceps or a tweezers with gentle traction. Consult experts if in doubt.
- *Systemic*: Look for signs and symptoms of allergic reaction. Antihistamine local or oral is usually enough for mild reaction. Add steroid if needed but with caution. IV antihistamine (e.g., diphenhydramine 1 mg/kg) and IV steroid are necessary for moderate reaction. Adrenaline, subcutaneous (SC), intramuscular (IM), or Intravenous (IV) is needed for severe life-threatening reaction. Some patients carry an EpiPen with them. In the prehospital setting, these patients may need help in the administration of EpiPens. Ventolin puff can relieve bronchospasm. Support the airway, breathing, and circulation with oxygen supply, intubation, IV fluid, and inotropes as the conditions require. Anaphylaxis means Intensive Care Unit (ICU) care. Always think of delayed hypersensitivity. If in doubt or because of a relatively high number of bites or stings, admit the patient for observation.
- *Specific treatment*: Permethrin can kill *Sarcoptes scabiei* (scabies) and lice. Other treatments are also available. Isolation, conduct contact tracing, and treat all the contacts. Careful surgical exploration and removal may be needed in some types of myiasis. Bursting of the maggots must be avoided. Infested tissues may be cleansed with nitrofurazone. Antivenoms exist for certain bites and stings (e.g., for certain species in scorpions and black widow spiders). Please contact a local poison center for advice. Professional pest control may be needed for certain arthropods. Please refer to the relevant chapters of this book for the treatment of the diseases transmitted. Please consult a microbiologist, entomologist, veterinary surgeon, or poison center if needed.
- *Follow-up*: For most bites, follow-up is not necessary. Arrange follow-up, if there is any worry about wound infection. Check for similar contacts with family members or colleagues. Arrange treatment if needed.

SCORPION STING

Scorpions are easily recognized, have 8 legs, have venomous stings, and there are 25 species, which can prove to be fatal to humans. Scorpions are widely distributed worldwide. Toxic varieties of scorpion are found in Middle East, India Mexico, South America, and Trinidad. There are 2,000 species of scorpions only about 25–40% are lethal. India is home to the most toxic and dangerous, lethal species of scorpion. Indian red scorpion (*Hottentotta tumulus*) is also known as eastern Indian scorpion of family Buthidae, which is found in India, eastern Pakistan lowlands of Nepal, and Sri Lanka.

They sting when stepped upon or threatened, fatality rate is 8–40%, are not aggressive. Its children who are mostly the victims as at times they may be barefoot. Its venom delays closing of neuronal sodium channels which results in autonomic storm, as there is sudden pouring of catecholamines into the circulation. Autonomic storm is seen by transient, parasympathetic, and prolonged sympathetic stimulation. Venom produces local as well as systemic manifestations. Local reactions my lead to itching, edema, ecchymosis with severe burning, pain, cardiac manifestation, with giddiness, bradycardia, hypovolemia restlessness, tachycardia, and pulmonary edema. Myocardial damage, caused by scorpion venom is due to pathogenic mechanism. Release of vasoactive inflammatory peptides and amine constituents (histamine, serotonin, bradykinin, leukotrienes, and thromboxane) induces coronary artery vasospasm and causes aggregation and thrombosis. Cardiotoxic effect of this scorpion venom causes myocarditis causes reduction of sodium-K ATPase, by releasing adrenaline, noradrenaline from neurons, ganglia, and adrenals causing increase in myocardial oxygen demand by direct inotropic and chronotropic effect on already compromised blood supply.

Scorpion venom also causes anaphylaxis by releasing allergic proteins, leading to anaphylactic shock in some victims of scorpion sting. Scorpion venom inhibits angiotensin, converting enzyme which results in accumulation of bradykinin, which ultimately leads to pulmonary edema. Cardiovascular system and pulmonary system are affected, which lead to death from pulmonary edema. Antivenom shows little effectiveness, however, mortality is reduced to <4% if prazosin is used in blood pressure. Scorpion venom is a water soluble, antigenic complex mixture of neurotoxin, cardiotoxin, nephrotoxin, hemolysin, phosphodiesterase, hyaluronidase, histamine, and other. Scorpion venom is used as immunosuppressants for various autoimmune disorders, such as rheumatoid arthritis, multiple sclerosis, also is used as an antimalarial.

Clinical Feature

Scorpion venom causes excessive depolarization due to opening of neuronal sodium channel. Symptom ranging from severe pain at the side of sting to vomiting breathlessness, sweating jerking movement of the extremities, and tachycardia with severe agitation. Symptoms can continue till 24–48 hours. Pulmonary edema, cardiac dysfunction, bleeding disorder, DIC, and pancreatitis are seen in sting from the lethal variety of scorpion from Asian and African countries.

Diagnosis

Tap test: Physician will tap at the site of the sting to see if pain gets severe, reaction is the indicator of a scorpion sting. There is over stimulation of sympathetic, parasympathetic, and central nervous system stimulation due the venom effect, hence after an hour of the scorpion sting, there is increase in blood pressure, heart rate tachyarrhythmias may develop. Elderly and pediatric patients are at special risk. "Roving eye" movement is common in children, along with twitching and muscle fasciculation weakness, agitation and opisthotonos, severe ataxia, and respiratory distress are also seen though less common.

Treatment

Wash the sting with soap and water, remove any jewelry example ring from finger if sting on finger. Apply cool compress 10 minutes on and 10 minutes off at the place of sting. Analgesics acetaminophen, tetanus prophylaxis to be given, benzodiazepines and opioids to be given for muscle

spasm and agitation, Tachyarrhythmias and hypertension to be treated with beta-blockers labetalol and esmolol. Prazosin has found to be effective in hypertensive therapy in children. Advance life support, critical care setting may be required for severe scorpion sting. It is recommended victims with systemic manifestation to be admitted in hospital and those with mild symptoms with localized pain at site of sting can be discharged home with adequate pain medication. Antibiotics to be given if secondary infection. Antivenom to be given if required. Like all animal derived antivenoms immediate and delayed allergic reactions are possible.

SUMMARY

Arthropod contact is common. Contact may cause local wound, systemic presentation, and infection (local and systemic). This chapter is summarized in **Flowchart 1**.

ACKNOWLEDGMENT

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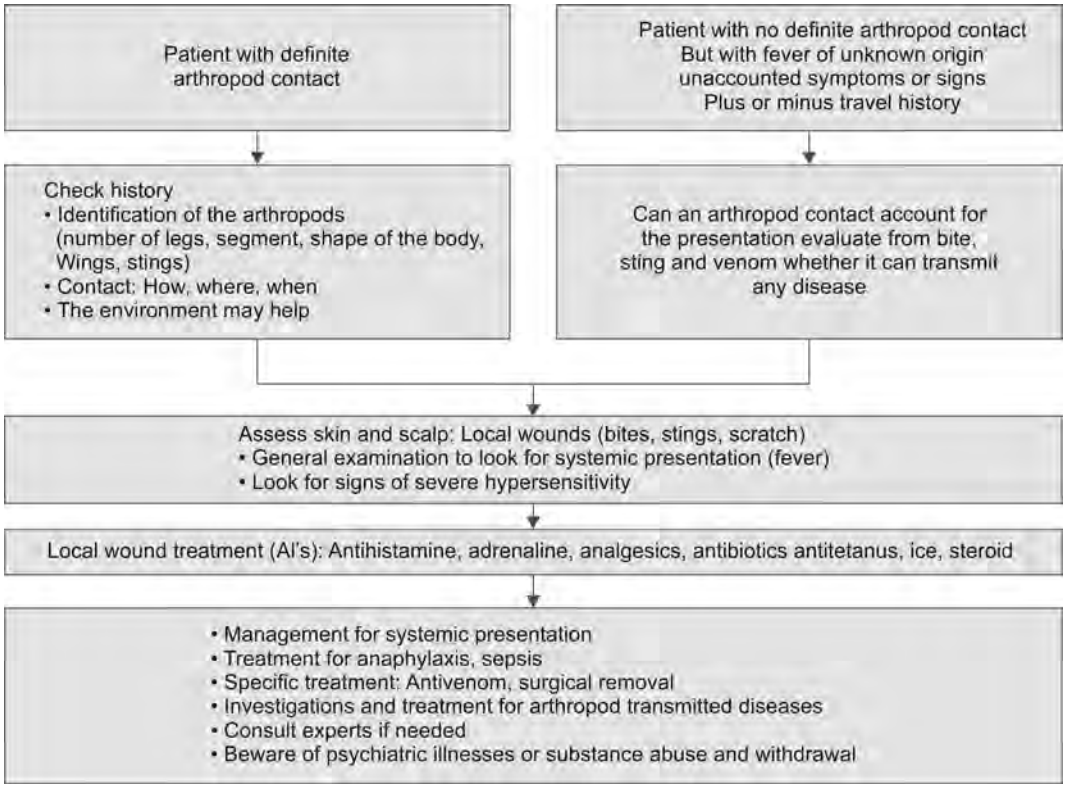
Patient with definite arthropod contact
Patient with no definite arthropod contact But with fever of unknown origin unaccounted symptoms or signs Plus or minus travel history
Check history
• Identification of the arthropods (number of legs, segment, shape of the body, Wings, stings)
• Contact: How, where, when
• The environment may help
Can an arthropod contact account for the presentation evaluate from bite, sting and venom whether it can transmit any disease
Assess skin and scalp: Local wounds (bites, stings, scratch)
• General examination to look for systemic presentation (fever)
• Look for signs of severe hypersensitivity
Local wound treatment (Al's): Antihistamine, adrenaline, analgesics, antibiotics antitetanus, ice, steroid
• Management for systemic presentation
• Treatment for anaphylaxis, sepsis
• Specific treatment: Antivenom, surgical removal
• Investigations and treatment for arthropod transmitted diseases
• Consult experts if needed
• Beware of psychiatric illnesses or substance abuse and withdrawal

FLOWCHART 1: Summary evaluation and management of insect bite.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Marine Envenomation

Deepak Singhal, Devendra Richhariya

INTRODUCTION

Aquatic animals may be venomous and may be dangerous to life of the swimmers, surfers, divers, and fishermen. Most of the victims may not seek medical care because most marine exposures are mild, e.g., mild stings, bites, abrasions, and lacerations. Aquatic animals who produce envenomation through dermal contact are summarized in **Table 1**. Marine envenomation through puncture and laceration is summarized in **Table 2**. Severe and life-threatening envenomation occurs due to box jellyfish, Irukandji jellyfish, cone snails, blue-ringed octopus, stonefish, or sea snakes. In these cases, immediate and effective treatment is given to patient to improve the symptoms (decrease pain, stabilize systemic symptoms, and treat anaphylaxis) and early treatment reduces the secondary complications (local allergic response, infection, and wound complications). Tetanus immunization prophylactic or therapeutic antibiotics are the key for the treatment of all marine envenomation.

SPONGES

Sponges attach to the ocean floor and are acellular creatures. They have spicules of silicon dioxide or calcium carbonate. Sponges such as fire sponge (*Tedania ignis*), poison bun sponge (*Fibularia nolitangere*), and red moss sponge

TABLE 1: Marine envenomation through dermal contact their presentation and treatment.

Marine species	*Clinical presentation*	*Treatment*
Portuguese man-of-war; blue bottle	Local pain, skin blisters, nausea, vomiting, abdominal pain, muscle cramps, and dyspnea	Remove tentacles hot water (upper limit 45°C) immersion
Box jellyfish	Excruciating pain, hypotension, paralysis, respiratory failure, cardiac arrest, skin blisters, and necrosis	Apply acetic acid 5% then remove tentacles, support airway and breathing antivenom if severe symptoms, avoid hot water immersion or pressure immobilization
Irukandji jellyfish	Catecholamine release, muscle pain, abdominal pain, hypertension, troponin leak, heart failure, and pulmonary edema	Remove tentacles, apply acetic acid 5%, cardiac monitoring, blood pressure control (avoid b-adrenergic blockers), respiratory support
Jellyfish	Mild pain, irritant dermatitis	Remove tentacles, apply acetic acid 5%, lidocaine containing product, or hot water (upper limit 45°C) immersion
Sea bather's eruption	Pruritic papules resembling insect bites in distribution of swim suit	Treat skin with acetic acid 5%, or lidocaine-containing first aid remedy, wash swim suit with hot water and detergent, then machine or sun dry
Sea anemone	Erythema and pruritus petechiae, blisters, and ulceration	Acetic acid 5%, may require prolonged wound care
Feather hydroid; fire coral	Stinging pain, urticaria, petechiae, ulceration, and residual hyperpigmentation	Acetic acid 5%, may require prolonged wound care
Sponge	Pruritic irritant dermatitis, blisters, and delayed desquamation	Remove spicules with tape, rubber cement, or facial peel acetic acid 5%
Bristle worm	Painful urticarial rash	Remove bristles with tape, rubber cement, or facial peel, acetic acid 5%

TABLE 2: Marine envenomation through puncture and laceration their presentation and treatment.

Marine species	*Clinical presentation*	*Treatment*
Crown-of-thorns starfish	Dusky puncture wound, pain, bleeding, edema, multiple punctures cause nausea, vomiting, paresthesia	Hot water to tolerance (maximum 45°C) for 30–90 min local anesthetic, locate retained spines, surgical removal if spines near nerve, tendon, or joint
Sea urchin	Red, purple, or black puncture wounds; local muscle aching; edema, multiple punctures cause nausea, vomiting, and paresthesia	Hot water to tolerance (maximum 45°C) for 30–90 min local anesthetic, locate retained spines, surgical removal if spines near nerve, tendon, or joint
Cone snail	Puncture wound resembling bee sting, local cyanosis, limb paresthesia, paralysis, respiratory failure, cerebral edema, coma	Pressure immobilization, support breathing, consider edrophonium, 10 mg IV, for paralysis, consider naloxone, 2–4 mg, for severe hypotension, hot water to tolerance (maximum 45°C) for 30–90 min, local anesthetic, remove retained radula
Blue-ringed octopus	Painless small puncture wounds, facial numbness, paralysis, and respiratory failure	Support breathing, supportive care
Lionfish and scorpionfish	Painful puncture wound, blistering, nausea, and vomiting	Hot water to tolerance (maximum 45°C) for 30–90 min, local anesthetic or nerve block, locate retained spines, surgical removal if spines near nerve, tendon, or joint
Stonefish	Severely painful cyanotic puncture wound, necrotic ulceration, altered mentation, fever, nausea, vomiting, seizures, paralysis, heart block, heart failure, and pulmonary edema	Antivenom for severe envenomation, hot water to tolerance (maximum 45°C) for 30–90 min, local anesthetic or nerve block, locate retained spines, surgical removal if spines near nerve, tendon, or joint, debride necrotic tissue
Stingray	Dusky painful laceration, local hemorrhage and necrosis, barb lodged in victim, large envenomation: nausea, vomiting, muscle cramps, syncope, and arrhythmias	Hot water to tolerance (maximum 45°C) for 30–90 min, local anesthetic or nerve block, locate retained barb, surgical removal of barb, treat retained barb as stab wound if barb in thorax, abdomen, groin, or neck, serial debridement of necrotic tissue
Sea snake	Painless pinhead-sized fang marks, muscle pain and stiffness, nausea, vomiting, ascending paralysis, respiratory failure, muscle necrosis, and renal failure	Pressure immobilization, maintain airway and breathing, antivenom if any symptom, monitor electrolytes and urine output, alkalinize urine if myoglobinuria, dialysis as needed for renal failure and hyperkalemia

(*Mammillaria prolifera*) produce dermal irritants known as crinotoxins. Skin edema, vesiculation, joint swelling, and stiffness are the manifestation of the crinotoxins. Clinical manifestation if mild in nature, reactions subside within 7 days while extensive exposure may induce fever, chills, malaise, dizziness, nausea, muscle cramps, and formication. If spicules remain in the skin, these can result in persistent bullae that take months to heal. Erythema multiforme or dyshidrotic eczema may develop as a delayed systemic complication. In severe cases, surface desquamation may follow. Treatment consists of removal of spicules using adhesive tape, a thin layer of rubber cement, or facial peel. Apply 5% acetic acid (vinegar) soaks. For symptomatic relief steroid cream or an oral antihistamine may be used. For severe allergy, erythema multiforme or dyshidrotic eczema, considers systemic corticosteroids. Antibiotic therapy is considered for wound infections.

HYDROIDS AND FIRE CORAL

Hydrozoans are plumelike species, multiorganism colonies of diverse configurations. Feather hydroids found in tropical waters. Fire coral is identical to hard coral. An example is *Millepora*, distributed in shallow tropical waters and dangling tiny nematocyst-bearing tentacles. The stinging tentacle-bearing Portuguese man-of-war (Physalia physalis) and blue bottle (Physalia utriculus) are widely distributed. Feather hydroids and fire coral clinical manifest as immediate pain and urticaria, progressing to hemorrhagic or ulcerating lesions. Pain usually resolves within 1–2 hours and inflammation resolves by 6–7 days, with occasional residual hyperpigmentation. Pain may persist for hours, and local symptoms resolve within 72 hours. Patient may experience severe systemic symptoms such as nausea, vomiting, muscle cramps, dyspnea, anxiety, abdominal pain, and headache. Treatment for feather hydroid and fire coral envenomation, apply acetic acid 5% (vinegar) to the skin. For symptomatic relief, consider steroid cream or an oral antihistamine; administer systemic corticosteroids, if the reaction is eczematous or indolent. A lidocaine-containing product may be equally effective. Systemic corticosteroid can be used for severe reactions.

JELLYFISH

Scyphozoans are single-organism jellyfish that range in size from 2 cm to 2 m across the bell and have different forms, including free-floating larva, sessile polyp, and large swimming

medusa mauve stingers. Multiple species of stinging larval forms are found in warm waters; the thimble jellyfish larvae are of pinhead-sized. Stinging pain and localized erythema occur when skin comes in contact with tentacles, symptoms resolve in hours to days. Sea bather's eruption occurs when a person comes in contact with the larval forms; pruritic papules occur in a bathing suit distribution (within which larvae are trapped) itching remains for 2–14 days. Fever, headache, chills, malaise, vomiting, conjunctivitis, and urethritis are the other symptoms.

Management includes topical acetic acid 5%, hot water immersion, and corticosteroid or antihistamine cream, and systemic corticosteroid in severe cases. A lidocaine-containing product may be effective as a topical decontaminant. To minimize or prevent sea bather's eruption, change swimwear on leaving the water. Before reuse of swimwear, wash them with detergent and hot water detergent and full drying.

SEA ANEMONES

Sea anemones and soft corals consist of tentacles and have stinging cnidocytes and which secrete mucus that may contain cytolytic and hemolytic toxins, neurotoxins, cardiotoxins, and proteinase inhibitors.

Sea anemones and soft corals envenomation present as painful skin lesions with central pallor and a halo of erythema and petechial hemorrhage, sometimes progressing to vesiculation and necrosis. Fever, chills, malaise, weakness, nausea, vomiting, muscle spasm, and syncope are rare. Mild envenomation resolves within 48 hours. Severe reactions may become indolent, leading to hyperpigmentation, hypopigmentation, or keloid formation. Severe dermatitis may require prolonged wound care with debridement and antibiotics for secondary infection.

BOX-SHAPED JELLYFISH

Some box-shaped jellyfish found in tropical waters are highly venomous, e.g., Hawaiian box jellyfish, Japanese box jellyfish, and Australian box jellyfish, each delivers potentially deadly venom. Irukandji jellyfish are 1–2.5 cm box jellyfish. The "Irukandji syndrome" is local vasoconstriction and high blood pressure attributed to sympathetic nervous system stimulation. Box jellyfish stings cause excruciating with rapid blistering, muscle spasm, hypotension, and sometimes paralysis. Victims may have respiratory failure and cardiac arrest within 1–2 minutes. Most deaths occur 5–20 minutes after the sting. Skin necrosis is common. Symptoms begin in 20–30 minutes poststing with muscle pain, abdominal and chest pain, nausea, vomiting, and respiratory failure in Irukandji envenomation. Massive catecholamine release precipitates severe hypertension and tachycardia, leading to cardiomyopathy, pulmonary edema, cerebral edema, troponin leak, and hypokinetic heart failure.

If box jellyfish sting is suspected, airway support should be provided with artificial ventilation. Sting sites should be poured with 5% acetic acid (vinegar) immediately for at least 30 seconds before removing adherent tentacles. Administer specific antivenom one vial intravenous (IV) or three vials intramuscular (IM) at three different sites. Repeat as needed every 10 minutes up to three times immediately and then once or twice every 2–4 hours until there is no further progression of systemic symptoms. Antivenom use is under scrutiny because of poor efficacy noted during in vitro studies. However, until further notice, it remains recommended. For Irukandji envenomation, treatment measures are supportive therapy, serum troponin, and cardiac monitoring should be done.

ANNELID WORMS

Bristle worms that easily penetrate skin and are covered with chitinous bristles. When they come in human contact cause bristles to break off into the skin, causing pricking sensation and urticarial rash with rare necrosis. Pain subsides in a few hours, but urticaria may persist for 2–3 days and skin discoloration for up to 10 days. Secondary infection and cellulitis may occur. Bristles should be removed with the help of tape, facial peel, or a thin layer of rubber cement. Next, apply acetic acid 5% soaks. Consider an oral antihistamine or corticosteroid for severe inflammatory reaction.

STARFISH AND SEA URCHINS

Starfish and sea urchins are included in the phylum Echinodermata. The crown-of-thorns starfish produces a toxic slime which is poisonous and that coats the spines. Toxic slime causes are hemolysis, myonecrosis, hepatotoxicity, and anticoagulation. Sea urchins have venom-bearing globular bodies covered by calcified spines have rounded at the tip or hollow. Venom of sea urchins contains steroid glycosides, hemolysins, proteases, serotonin, and cholinergic substances.

Crown-of-thorns starfish causes puncture wounds with immediate pain, bleeding, and edema on the skin. Wounds become dusky and tenosynovitis may develop. Multiple punctures can cause systemic reactions with paresthesia, nausea, vomiting, lymphadenopathy, and paralysis. Pain persists for 30 minutes to 3 hours. Retained spines can cause granulomas. Painful puncture wounds with severe local muscle aching lasting up to 24 hours are the hallmark of sea urchins' venom. Frequently, spines break off within the skin and can cause synovitis. Systemic symptoms include nausea, vomiting, paresthesia, and infections are common.

Treatment includes immersion of puncture wounds in hot water to tolerance (upper limit 45C) for 30–90 minutes or until there is significant pain relief. Nerve block or local anesthetic infiltration may be required for pain control. Wounds should be irrigated and explored for spines and should be removed as soon as possible. Surgeon should be consulted if spines have entered a joint or in close to neurovascular structures. For spine localization and removal, radiography, ultrasound, computed tomography, or magnetic resonance imaging (MRI) may be helpful. Reactive neuropathy may respond to a systemic corticosteroid. Secondary infections are common. Retained spine fragments causes granulomas and should be removed by excision or ablation, and retained spines may also cause arthritis which requires synovectomy.

MOLLUSKS

Cone snails are shelled mollusks. Venom-containing radular tooth stabs the victim and causes envenomation. Conotoxins target receptors and channels that mediate neuromuscular blockade. Blue-ringed octopuses are characterized by

presence of iridescent blue rings, are found in shallow waters of Indo-Pacific oceans. Venom is injected through parrot-like beak that causes paralysis. Bee sting–like puncture wound with local cyanosis occurs due to cone snails. Local paresthesia may be extended as paralysis that can lead to respiratory failure within 1 hour. Nausea, blurred vision, malaise, and weakness for a few hours occur in mild stings. Severe envenomation-induced paralysis lasts for 12–36 hours and takes weeks for symptom resolution. Blue-ringed octopus bites create one or two small puncture wounds that often go unnoticed. Within 15 minutes, oral and facial numbness begin that may rapidly progress to paralysis and respiratory failure. Cardiac arrest may follow. Other symptoms include numbness and discomfort of the affected limb, nausea, vomiting, and chest tightness. Cardiovascular and respiratory support takes priority in the management of cone snail envenomation. Pressure immobilization is recommended during transport. Edrophonium (10 mg IV adult dose) can be given for paralysis. Adverse reactions to edrophonium are treated with atropine, 0.6 mg IV. If hypotension use of naloxone, 2–4 mg, has been suggested. The wound should be irrigated with hot water to tolerance (upper limit 45°C) for 30–90 minutes and foreign bodies (radula) should be removed. Consider local anesthetic injection. Treatment of blue-ringed octopus bite centers on cardiovascular and respiratory support. Provide artificial ventilation if paralysis occur. Paralysis lasts after 4–10 hours, paralysis recovers, and hypoxia improves rapidly with complete recovery in 2–4 days.

SCORPIONFISH

Scorpionfish comes under family Scorpaenidae, these species have spines and venom glands covered by integumentary sheaths. With increasing order in toxicity lionfish are the least toxic, followed by scorpionfish with moderate toxicity, and stonefish with potent toxicity. Lionfish is very attractive, with long slender spines. Venom may induce local paresthesia and paralysis. Scorpionfish are camouflaged against their surroundings (ocean bottom and rocks) and have medium-length spines. Scorpionfish venom highly toxic to connective tissue, causes hypotension and pulmonary edema, and can cause paralysis. Stonefish remain motionless, hide, and possess short stout spines. Pain is main presenting features, starts immediately, and peaks at 60–90 minutes. With serious envenomation, pain may cause delirium and persist for hours (scorpionfish) or days (stonefish). The puncture wound is initially ischemic and cyanotic with progressive vesiculation, tissue sloughing, cellulitis, and necrotic ulceration. Systemic manifestations include anxiety, headache, skin rash, fever, nausea and vomiting, diarrhea, abdominal pain, seizures, paralysis, pericarditis, atrioventricular block, congestive heart failure, and pulmonary edema. Death from a stonefish sting can occur within the first 6–8 hours. Wounds healing occur in 4–8 weeks.

The wound should be immersed in hot water to tolerance (upper limit 45°C) for at least 30–90 minutes. Consider local anesthetic infiltration or regional nerve block. The wound should be thoroughly cleansed. If the spine has penetrated deeply into the sole of the foot or hand, surgical exploration should be performed. In a case of severe systemic reaction, stonefish antivenom may be administered IV or IM. As a rough estimate, one vial of antivenom should neutralize one or two significant punctures, with additional vials administered for recurrent severe pain or systemic manifestations.

STINGRAYS

Stingrays are flat cartilaginous fish with caudal appendages with bilateral retro serrate barbs and associated venom glands. Venom contains serotonin, 5'-nucleotidase, and phosphodiesterase. Toxin may induce peripheral vasoconstriction, bradycardia, tachycardia, atrioventricular block, and seizure activity.

Stingray envenomation can cause large lacerations, most often on lower extremities. There is intense pain, edema, and bleeding peaking at 30–60 minutes and lasting up to 48 hours. The wound starts with dusky coloration and may progress to hemorrhagic necrosis. Systemic manifestations include weakness, nausea, vomiting, diarrhea, diaphoresis, muscle cramps, headache, syncope, seizures, and arrhythmias. Treatment mainly consists of measures of pain relief, soak in hot water to tolerance (upper limit 45°C) for 30–90 minutes. Narcotics, local anesthetic infiltration, or a nerve block may be needed. The wound should be irrigated and debrided, and imaging should be obtained to rule out a retained spine. If a spine is lodged in the chest, abdomen, or other vital structure, it should remove surgically in the operating room. Wounds are preferably treated with delayed primary closure and should be observed closely because ulceration, necrosis, and secondary infection are common.

SEA SNAKES

Sea snakes are found mostly in tropical Pacific and Indian oceans. Sea snake venom contains hemolytic and myotoxic compounds (peripheral neurotoxins acting at the acetylcholine receptor), and causes muscle necrosis, hemolysis, and renal tubular damage. Sea snake species, which cause serious envenomation, are *Astrotia stokesii*, *Enhydrina schistosa*, *Hydrophis ornatus*, *Hydrophis cyanocinctus*, *Lapemis hardwickii*, *Thalassophina viperina*, and *Pelamis platurus*. Because fangs are short and easily dislodged, approximately 80% of bites do not result in envenomation. Presentation sea snake bites cause minimal pain and may resemble mere pinpricks. Nausea, muscle stiffness, swallowing dysfunction, blurry vision, and paralysis occur within 30–60 minutes. There has rarely been envenomation, if symptoms do not develop within 6–8 hours. Life-threatening complications include respiratory distress, paralysis, electrolyte disturbances, and myoglobinuria with acute renal failure leading to death. Treatment includes pressure immobilization during transport. Administer sea snake antivenom IV as soon as possible. Anticipate respiratory failure and provide mechanical ventilation. Hyperkalemia, rhabdomyolysis, and renal dysfunction are common so monitoring of serum electrolytes and renal function is important. If myoglobinuria is detected, alkalinize urine with sodium bicarbonate and administer diuretics. Acute renal failure may require dialysis.

TREATMENT AND COMPLICATIONS

Antivenom and Anaphylaxis

An envenomation or antivenom administration can cause anaphylaxis and presents as hypotension, bronchospasm, facial and airway swelling, pruritus, urticaria, nausea, vomiting, and diarrhea. Most reactions occur within 15–30 minutes and nearly all occur within 6 hours. A recipient of antivenom should be pretreated with 50–100 mg of IV diphenhydramine (1 mg/kg in children). Antivenom should be administered one vial over 5 minutes. If anaphylaxis develops, after antivenom injection, 0.1- to 0.2-mL aliquots of antivenom should be alternated with 0.03- to 0.1-mg IV doses of epinephrine, or an epinephrine drip administered (maintain heart rate <150 beats/min).

Serum Sickness

Serum sickness presents with fever, arthralgias, malaise, urticaria, lymphadenopathy, rashes, peripheral neuritis, and swollen joints. Formation of IgG antibodies in response to antigens in antivenom causes deposition of immune complexes that induce vascular permeability, activate complement, degranulate mast cells, and trigger release of proteolytic enzymes. Serum sickness is managed with systemic corticosteroids until symptoms resolve, followed by a 2-week taper.

SUMMARY

It is important to know the marine creatures in our clinical practice area. Every emergency physician should be able to manage anaphylaxis or acute life-threatening envenomation from box jellyfish, Irukandji jellyfish, stonefish, cone snail, blue-ringed octopus, or sea snake. If marine envenomation is suspected, evaluation is performed as summarized in **Box 1**. Know where to obtain antivenom. Immediate topical decontamination followed by removal of tentacles is helpful. Provide adequate medication for pain control. Early initiation of appropriate antibiotics is helpful in controlling the secondary infection caused by marine bacteria. Various therapeutic options (pharmacologic, nonpharmacologic, and surgical) to manage marine envenomation are summarized in **Table 3**.

BOX 1: Evaluation and management marine envenomation.

Immediate evaluation

- ABCs
- Attempt to identify causative agent
- Consider the geographic location where the injury took place, wheal and flare reactions are nonspecific
- Bug bite–type reaction located in areas of a swimsuit is classic for sea bather's eruption
- A gaping laceration, particularly of the lower extremity, with cyanotic edges suggests a stingray wound
- Multiple punctures in an erratic pattern with or without purple discoloration or retained fragments are typical of a sea urchin sting
- Fang marks with weakness, respiratory paralysis, myalgias, blurred vision, and vomiting indicate a sea snake bite
- An ischemic puncture wound with a red halo and rapid swelling and pain not relieved by hot water immersion suggests scorpionfish envenomation
- Blisters often accompany a lionfish sting. Painless punctures with rapid neuromuscular paralysis suggest a blue-ringed octopus bite The site of a cone snail sting is punctate, painful, and ischemic
- Rapid (within 24 hours) onset of skin necrosis suggests an anemone sting
- "Tentacle prints" with cross-hatching suggest a box-jellyfish envenomation
- Hypertension, muscle aches, and vomiting suggest Irukandji syndrome
- Ocular, intraoral, or genital lesions may come from fragmented hydroids, coelenterate tentacles, or Scyphozoans larvae
- Decontaminate (specific to causative organism)
- Stabilize and treat

Long-term recommendations

- Prevention:
  - Do not touch marine life when snorkelling, diving, or swimming. Avoid touching the bottom or grasping ledges or overhangs
  - Wear protective gear that covers all exposed skin
  - Shuffle feet when walking in shallow sandy areas
  - Do not stand or walk on reefs
  - Life-threatening envenomation benefits from rapid decontamination and cardiopulmonary support, and may benefit from antivenom administration
  - Provide tetanus prophylaxis in all cases and have a low threshold for initiating antibiotics
  - Marine envenomation often heals slowly and poorly, so arrange for follow-up

TABLE 3: Therapeutic options for marine envenomation management.

Nonpharmacological options		
Option	*Indication*	*Use*
Hot water immersion	• Jellyfish • Stingrays • Venomous spined fish	Hot water to tolerance (maximum 45°C); immerse for 30–90 min or until pain relief; check water temperature frequently
Adhesive tape, rubber cement, and facial peel	Sponge bristle worm	Apply gently over wound and peel to remove spicules or bristles
Pressure immobilization	Cone snail sea snake	Wrap an elastic bandage with a wide margin over the envenomation site at venous-lymphatic occlusive pressure; keep the limb immobile
Scrape with razor	Jellyfish, fire coral, hydroid, and anemone	Apply a layer of shaving cream and scrape with a razor to remove nematocysts
Pharmacologic option		
Drugs	*Indications*	*Doses*
Acetic acid 5% (vinegar)	All-purpose skin sting decontaminant	Apply topically
Lidocaine or bupivacaine without epinephrine	Local anesthetic infiltration or nerve block for pain control	Lidocaine, max dose 3 mg/kg bupivacaine, max dose 2.5 mg/kg
Prednisone (or equivalent corticosteroid)	Severe local inflammation or allergic reaction	60–100 mg PO QD adults 2–5 mg/kg (max dose 50 mg) children PO QD tapered over 10–14 day
Hydrocortisone 1% cream	For local inflammation and symptomatic relief	Apply BID
Antibiotics	Prophylaxis for puncture wounds and at first sign of infection Should cover *Staphylococcus*, *Streptococcus*, and microbes of marine origin, such as *Vibrio*	Ciprofloxacin, 500 mg PO BID Trimethoprim/ sulfamethoxazole, 160/800 mg PO BID doxycycline, 100 mg PO BID
Stonefish antivenom	Hyperimmune horse globulin preparation used to neutralize stings of stonefish	*Initial dose*: One vial per two puncture wounds, repeat for recurrent pain
Box jellyfish antivenom	Hyperimmune sheep globulin preparation used to neutralize the stings of *Chironex fleckeri* and *Chiropsalmus*	• *Initial dose*: 1 vial IV or three vials IM • Repeat up to three times every 10 min as needed, and then every 2–4 h until no further worsening
Sea snake antivenom	Hyperimmune horse globulin preparation used to neutralize the bites of most sea snakes	*Initial dose*: 1–3 vials Up to 10 vials may be required
Surgical treatment options		
• Debridement • Spine extraction or laser ablation • Tendon repair, synovectomy, or granuloma removal		

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

Preparation for International Travel

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INTRODUCTION

About 1 billion tourists have travelled across the globe in the initial 9 months of 2016. This data has a 4% spike when compared to 2015. According to the World Travel and Tourism Council, this number is likely to increase to 1.8 billion people travelling internationally in the year 2025. It is estimated that approximately 22–64% of the international travelers will experience ailments such as respiratory tract infection, gastrointestinal diseases, and/or skin infections based on the country or continent they had visited. The extent of the disease cannot be anticipated; however, such situations can be avoided if consulted prior to the date of travel with a healthcare practitioner. An average traveler during a 2-week trip may lose an average of 3 days due to ailments acquired during or post travel. About 20% of them continue to in poor health after their trip and 10% of them require medical help for their condition. However, with the current situation of global pandemic this study cannot be held valid. The near future does not hold valid for the calculations of the past. In every 100,000 international travelers, it is observed that 50,000 people contract an illness during the travel. While 8,000 people need to seek medical attention, of which 5,000 are in need to be confined to rest. About 300 people are hospitalized for medical intervention, 50 travelers require to be evacuated by air transportation, and 1 patient dies.

However, with the current situation of global pandemic of coronavirus disease-2019 (COVID-19) this study cannot be held valid. The near future does not hold valid for the calculations of the past. As per the World Health organization (WHO) statement released on 30th January 2020, the Director-General of the WHO, following the advice of the Emergency Committee convened under the International Health Regulations (2005), declared the current outbreak of COVID-19 a public health emergency of international concern and issued Temporary Recommendations.

CONSIDERATIONS: PRIOR TO TRAVEL

In most of the situations, travelers across the globe underestimate the health and safety risks involved. In very few cases, an international traveler seeks consultation about proper travel counseling prior to the date of departure. People travelling to higher risk countries to meet relatives or family members are more prone to contract gastrointestinal infections along with malaria and dengue fever. They tend to stay for longer periods, eat local food, and do not practice safe hygienic methods as a precaution. They neglect the severity of the contractible disease and pretravel counseling and safety measures. There is link between those avoided pretravel consultation and then contracting diseases like malaria, leading to consequences on health of travelers. Pretravel counseling includes individual approach on risk assessment, immunization schedule reviewed, details of arthropod-related diseases and protective measures, prophylaxis for malaria, traveler's diarrhea along with risk reducing measures, and travel-related education. This serves to be a helpful aid to a person travelling to developing countries, for adventure sports or activities, extended travel plan, travelling with a chronic medical condition or immune-compromised state, and travelling with children or pregnant mothers. It is ideal to undertake a medical consultation at around 6 weeks before the date of departure. This enables adequate time for the effect of immunization and preparation. However, it is obvious that medical attention can be taken at any time of travel during transit or stay or even after returning back to the maiden country.

RISK ASSESSMENT: INDIVIDUAL APPROACH

Factors that must be considered during analysis of individual risk assessment of a traveler:

- Country of destination
- Time of stay
- Season at the time of travel
- *Medical condition of the traveler*: It should include the complete list of medications taken currently, immunization status, any disabilities, previous history of surgeries, allergies history, and pregnancy status or postpartum.
- Any past history of traveler
- *Activities during the period of stay*: Attending mass gatherings, accommodation, and financial aids for medical help.

IMMUNIZATION: PRIOR TO TRAVEL

Pretravel Immunization

Proper screening of all travelling persons should be done at least 6 weeks before the date of departure after a step by step assessment of previous and current immunization. Additional immunization may be required specific to the destination (**Table 1**). All travelers should be screened to determine their need for pretravel immunizations including a review of their current immunization history. In addition to routine or domestic vaccinations, additional destination-specific vaccinations may be required activities and duration of stay. Please note that due to associated risks to health, live vaccines cannot be administered to pregnant mothers and immune compromised patients such as measles, mumps, rubella, oral dose of polio, rotavirus, varicella zoster, influenza, typhoid fever, yellow fever, Bacillus Calmette–Guérin (BCG) [for tuberculosis TB]. Administration of live vaccinations should be either 4 weeks apart or the same day, to prevent chances of failure.

Routine Vaccination

International travelers are more prone to contract vaccine preventable diseases such as influenza and hepatitis A, when compare to more country-specific vaccine preventable diseases like typhoid or Japanese encephalitis. As a result, it is more beneficial for a person travelling internationally to review with their current immunization status and ensure adequate booster dose, if required before travelling to other countries.

ARTHROPOD-SPECIFIC PROTECTION GUIDELINES

Arthropods such as mosquitoes, ticks, flies, and chiggers aid to the transmission of infections such as malaria, dengue fever, and rickettsia diseases. These diseases are primarily prevented by protective measures and maintaining adequate sanitary conditions around them. These types of infection are the most common cause of systemic febrile illness presented by patients after they return back home. A large number of risk factors include the destination of travel (urban or rural, developing countries), duration of stay, season (rainy and monsoon), and type of accommodation (overcrowded spaces and endemic areas). The female anopheles mosquito tends to bite between dusk and dawn. However, other vectors such as mites and ticks bite all day and night. Preventive and protective methods must be practiced in order to reduce the possible chances of acquiring arthropod-specific infection during the course of travel (**Table 2**).

TABLE 1: Routine vaccinations for travelers.

Standard vaccination	*Indication*	*Route*	*Scheduled dose*	*Accelerated dose*	*Estimated time of protection*
Haemophilus influenzae type b	• Infants/adults asplenia • Sickle cell disease leukemia—after chemotherapy or bone marrow transplant • 5–18 year: HIV patient	IM	• Three to four doses: At 2nd, 3rd, and 6th months and between 12th and 15th month • Three to four doses: 2, 4, 6, and 12–15 months		
Hepatitis A (inactivated virus)	Age >1 year	1 mL, IM	• First dose: Day 0 • Second dose: 6–12 months	• Combined dose • Hepatitis A and hepatitis B	• More than 20 years (seropositivity) • More than 40 years (antibody modeling)
Hepatitis B (recombinant hepatitis B surface antigen)	All international travelers	IM	• First dose: Day 0 • Second dose:1 month • Third dose: 6 months	• Combined dose • Hepatitis A and hepatitis b	30 years
Combined hepatitis A and B: Inactivated virus and recombinant hepatitis B antigen	Age >1 year	1 mL, IM	• First dose: Day 0 • Second dose: First month • Third dose: 6 months	• First dose: Day 0 • Second dose: 7th day • Third dose: 21st day • Fourth dose: 12 months	More than 15 years
Herpes zoster (shingles)	Geriatric (older than 60 years)	SC	Single dose		
Human papilloma virus (HPV)	Children and young adults	IM	• First dose: Day 0 • Second dose: 1–2 months • Third dose: 6 months		

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Standard vaccination	Indication	Route	Scheduled dose	Accelerated dose	Estimated time of protection
Influenza (inactivated virus or recombinant, trivalent or quadrivalent)	Age >6 months	0.5 mL, IM 0.1 mL, ID	Single dose	NA	1 year
Influenza (live-attenuated virus and quadrivalent)	Age >6 months	0.1 mL in each nostril	Single dose	NA	1 year
Measles, mumps, and rubella (MMR) (live-attenuated virus)	All international travelers	0.5 mL, SC	• First dose: Day 0 • Second dose: Fourth week		Lifetime, if two doses are administered at any time in life
Meningococcal disease (quadrivalent ACYW-135, bacterial polysaccharide, conjugated DNA)	• As a routine at 11 and 12 years • Booster at 16 years • Travel to belt of meningitis: Africa or Saudi Arabia (for pilgrimage)	0.5 mL, IM	Single dose	NA	3–5 years
Pneumococcal disease	• Infants • Adults: More than 60 years	IM/SC	• Infant: • First dose: 2nd month • Second dose: 4th month • Third dose: 6th month • Fourth dose: Between 12th and 15th month		
Poliomyelitis (inactivated virus)	• Travelers to countries with ongoing transmission • More than 4-week travel to Afghanistan or Pakistan	0.5 mL, SC	If previously immunized: Single dose	NA	Lifelong, if primary dose + booster at 18 years or more
Rotavirus	Infants	Oral	• First dose: 2nd month • Second dose: 4th month • Third dose: 6th month		
• Tetanus, diphtheria, and pertussis • Acellular pertussis (Tdap) or tetanus-diphtheria (Td): Toxoid and protein antigen	All international travelers	0.5 mL, IM	If previously immunized: Single dose	NA	• 10 years • 5 years for traveler—adventurous activities, injuries, in places with substandard medical care
Varicella (chicken pox)	All international travelers	SC	• Below 13 years • First dose: 12th–15th month • Second dose: 4–6 years • Above 13 years: Two doses at 28 days apart		
Typhoid (bacterial cell wall polysaccharide)	Travel to low income nation	0.5 mL, IM	Single dose	NA	2–3 years

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Yellow fever (live-attenuated virus)	• Travel to endemic area (tropical countries: South America and Africa) • Avoid in children <9-month-old	0.5 mL, SC	Single dose	NA	10 years
Cholera (Live attenuated bacteria)	Adults 18–60 years High risk	1 sachet, oral	Single dose	NA	3–6 months
Japanese encephalitis inactivated virus, from cell culture	Travel to endemic areas	0.5 mL, IM	• First dose: Day 0 • Second dose: Day 28	• First dose: Day 0 • Second dose: Day 7	• 1–2 years after initial dosage • More than 6 years if boosted at 1–2 years
Rabies	Travel to rabies infested zoo, extended stay	IM	3 doses before exposure: 0, 7, and 21–28 d	Two additional doses (days 0 and 3) after exposure	Rabies travelers to rabies enzootic areas (especially remote, rural, or extended stay)
Tick borne encephalitis	Travelers to Europe, Soviet Union, and Asia	IM	Three doses: Day 0, 1–3 months, and 5–12 months	3 years	
Tuberculosis (BCG)	To be considered in healthcare workers travelling to high risk areas, with isoniazid and rifampicin	ID	Single dose	10–15 years	

Note: Meningococcal and poliomyelitis are childhood vaccines that may require boosters in adult travelers with specific itineraries.

(BCG: Bacillus Calmette–Guérin; DNA: deoxyribonucleic acid; HIV: human immunodeficiency virus; ID: intradermal; IM: intramuscular; SC: subcutaneous)

TABLE 2: Preventive and protective methods for arthropod infections.

Practice precluding	• Avert from regions endemic to malaria or outbreaks • Avert areas with water pooling or stagnant water bodies collecting and vegetations around the place of accommodation (chiggers/ticks) • Try to avoid travelling outside during dusk and dawn
Background check	• Prior check of type of accommodation and surrounding area • Check for rooms with adequate ventilation and air conditioning • Close the windows at the time of sunset
Garment check	• Avoid exposing areas of skin: Wear long sleeved shirts, jackets, or coats • Clothes of lighter shades and heavy weighted to prevent mosquito bites, sand flies, or tsetse flies
Additional insecticide application	• Application of permethrin on garments (shirts, t-shirts, and jackets), shoes, and camping gear • Carry insecticide impregnated clothing • Reapply insecticide after 5 washes
Application of repellent	• Repellent-containing diethyltoluamide (DEET) (20–50%) or picaridin (20%) can be applied over hands, palms, face, forearms, and legs and feet • Reapply after 6–8 h of DEET and every 4 h for picaridin • Day time application for *Aedes* mosquitoes and night time for *Culex* and *Anopheles* mosquito • Safe in pregnancy and infants above 2 months of age
Bed nets with insecticide impregnated	• Practice sleeping under bed nets impregnated with pyrethroid in countries endemic for malaria • Retreatment of nets for effectiveness • Can be used for months
Insect repellents	Use repellents such as mosquito coils, candles, plastic strips, heat generating equipment, and insecticide spray at the time of dusk
Tick check	Full-body and clothing check after activity and at the end of the day, using a mirror or companion

MALARIA—CHEMOPROPHYLAXIS

Chemoprophylaxis is highly recommended to travelers to endemic regions in order to prevent malaria since there is no definitive vaccine for malaria (**Table 3**). Immunocompromised patients, asplenic or human immunodeficiency virus (HIV), are under higher risks of being infected with malaria. They would have more serious consequences compared to the general population. The course of treatment is started few weeks before travel and continued after return depending upon the efficacy of the drug. Avoiding taking proper doses of prophylaxis can pose as one of the many causes of being infected by malaria.

TRAVELER'S DIARRHEA

Traveler's diarrhea affects about 10–20% of international travelers during the first 2 weeks with presenting symptoms lasting for an average of 3 days. Route of transmission if fecal-oral, with bacterial case accounting for 80–90% cases. Use of antacids and proton pump inhibitors (PPIs) causes

TABLE 3: Chemoprophylaxis for malaria.

Drug	*Typical adult dosing*	*Typical pediatric dosing*	*Start (preexposure)*	*Continue (postexposure)*	*Advantages*	*Disadvantages*
Chloroquine	500 mg salt (300 mg base) oral once a week	8.3 mg salt (5 mg base)/kg/week up to the adult dosage	2 weeks	4 weeks	• Safe and well tolerated • Can be used during pregnancy • Can be used in children (all ages)	• Global resistance outside of the Caribbean and Central America • May exacerbate psoriasis
Doxycycline	100 mg oral once a day	2 mg/kg/day up to adult dosage (for children ≥8 years) up to the adult dosage	2 days	4 weeks	• Least expensive • Can prevent leptospirosis and rickettsia • Good last-minute choice • Widely available globally	• Esophageal irritation/ulceration • Skin photosensitivity • Vaginal yeast infections • Not for use in pregnancy and children <8 years old
Mefloquine	250 mg salt (228 mg base) oral once a week	• ≤9 kg: 5 mg/kg (4.6 mg/kg base) once per week • >9–19 kg: One-fourth of 250-mg tablet weekly • 20–30 kg: One-half of 250-mg tablet weekly • 31–45 kg: Three-fourths of 250-mg tablet weekly • >45 kg: 250 mg once per week	2–3 weeks	4 weeks	• Weekly dosing • Good long-term regimen • Can be used during pregnancy • Can be used in children (all ages)	• Some areas of mefloquine resistance (Southeast Asia) • Neuropsychiatric side effects • Avoid in patients with depression, psychosis, seizures, and atrioventricular conduction abnormalities
Atovaquone/Proguanil	250 mg atovaquone/100 mg proguanil oral once a day	• 5–8 kg: One-half of a children's tablet (62.5 mg atovaquone/25 mg proguanil) daily • 9–10 kg: Three-fourths of a children's tablet daily • 11–20 kg: 1 child's tablet daily • 21–30 kg: 2 children's tablets daily • 31–40 kg: 3 children's tablets daily • >40 kg: 1 adult tablet daily	2 days	1 weeks	• Well tolerated • Good for short trips • Good last-minute choice • Can be used in children (≥11 kg) and off-label in children (≥5 kg)	• Expensive • Avoid with renal impairment • Not recommended for pregnant women, breastfeeding mothers, and children <5 kg

reduced gastric acidity making the travelers more prone to gastrointestinal infections. Immunocompromised patients, pregnant mothers, and young children are at a higher risk of contracting the disease.

Recommendations for Safe Travel

- Avoid eating at restaurants with poor sanitation and unhygienic conditions.
- Avoid raw food, uncooked fish or meat, eggs shellfish, or mayonnaise.
- Always consume bottled or packaged water. Ensure the source of water is disinfected and water is filtered and treated well.
- Consume well-cooked meals.
- Avoid eating from street vendors or locally from market stalls. Avoid eating cut fruits, salads, and cold sauces.
- Consume dairy products that are pasteurized.
- Avoid consuming unrefrigerated or nonpackaged food.
- *Proper hand hygiene*: Washing hands with soap and water can reduce the risk of travelers' disease by 30%. If not available, 60% alcohol-based sanitizer can be used.
- Prophylaxis is not routinely recommended.

Self-treatment

- *Mild dehydration*: Encourage oral fluids like water or unsweetened juices to replenish the loss of water due to dehydration. Avoid Gatorade or soft drink due to their high sugar content and low salt content.
- *Moderate-to-severe dehydration*: Oral rehydration salts (ORS) are ideal for adequate rehydration, which is available in markets or can be made at home too. ORS is prepared by mixing half a teaspoon of salt and six level teaspoons of sugar to 1 L of bottled water. Early treatment of diarrhea with antibiotics and adequate hydration is effective in reducing the prolongation of duration of symptoms.
- *Severe diarrhea*: Consider single dose of quinolone (tablet ciprofloxacin 500 mg or levofloxacin) or tablet azithromycin 1 g for rapid cessation. In Southeast Asian countries, azithromycin is preferred due to fluroquinolone-resistant enteropathogens.

PREVENTION OF INJURY

Injuries are preventable to a certain extent; however, recent studies show that international or domestic travelers are more prone to injuries than acquiring an infection. Among the most common deaths, road traffic accidents account for 56% and drowning about 25%. One is three times more prone to drown in an overseas country than at home. Travelers are around new surroundings and situations in a foreign land. Hence, it is more likely that they are injured in road traffic accidents, especially during monsoon (heavy rainfall), at night, or during national and public holidays.

Precautionary Measures

- Restrict travel time during the night time to unknown locations, especially without the presence of local travel guide. Look out for excessive fog, rain, and snow at the destination or during travel.
- If you have an infant/children travelling, carry child safety seats (in most of the countries it is not mandatory to have car seats for infants and toddlers).
- Collect basic information about the transport vehicle and ensure airbag safety and functional seatbelts. Wear seatbelt at all times during the journey and give preference to sit at the backseat.
- Restrict using two wheelers for transportation. If so, ensure you wear properly fitting helmet and safety gears.
- As legally mandated, avoid driving under the influence of alcohol and/or with someone who has consumed alcohol or other recreational drugs.
- Pedestrians often do not follow precautions while crossing the road or walking on the causeway. In addition, avoid using roads with limited visibility for commuting.
- Avoid travelling in cars, minivans, buses, or two wheelers overcrowded with passengers.
- For water sport activities, ensure floating devices are available at the location or carry them beforehand, if possible. Constant look out for children around water bodies such as lakes, ponds, river streams, or at the beach. Supervision should be by an adult not under the influence of alcohol. Do not participate in water sport activities after consumption of alcohol. Prior homework about the location, safety guidelines of water sports, and weather conditions should be done.

TRAVEL WITH CHILDREN/INFANT

In children, acute diarrheal diseases lasting up to 2 weeks are the most common cause of gastrointestinal infections, especially bacterial (one-third of all cases).

Precaution Prior to Travel

- Adopt the principle of cleaning, boiling, and cooking before consuming any food products in a foreign land.
- Adopt the practice of hand sanitization and hygiene at regular intervals.
- Most cases of moderate dehydration associated with gastroenteritis can be treated with adequate rehydration. ORS is adequate and ideal for most conditions.
- Antiemetics should be prescribed for children with symptoms of nausea or vomiting.
- Due to its lower resistance rates, azithromycin is more preferred in comparison to fluoroquinolones (same as in adults).
- *Malaria in endemic areas*: Follow malaria and arthropod specific guidelines as discussed earlier in this chapter. Bed should be covered with adequate nets; permethrin-treated clothing should be worn at most of the times during dusk, dawn, or daytime. Wear long-sleeved shirts or T-shirts, cover most parts of body with either socks for the feet or scarf around the neck. Local application of diethyltoluamide (DEET) (25–50%) and picaridin (KBR3023) (20%) over the exposed areas of skin is carried out as a preventive measure for children. Pay attention to areas around mucous membranes and hand in children. A combination of permethrin and insect repellent coils or devices can be very helpful in prevention of breeding of mosquitoes in the surrounding.

- Administration of medicines are challenging in younger patients. As a result, crushing medicines and mixing with juices, peanut butter, yogurt, or other thicker, sweet foods, or water can be effective in removal of the bitter taste.
- Prior check with the airlines for restraint seats availability for children/infants/toddlers.
- Children and infants are more prone to motion sickness in longer durations of travel. Symptoms such as ataxia are predominant in children <5 years, whereas, older children have classical complains of headache, vomiting, nausea, pallor, and dizziness with sweating.
- Make sure the child is fed at least 3 hours prior to the start of travel and maintain a stable head and body posture to decrease the effects of sickness during travel.

JET LAG

The phenomena of jet lag are based on rapid difference in time zone while traversing different countries which gets affected. The internal clock—circadian rhythm versus the day night cycle in external environment is altered to an extent that the body is unable to cope up. This causes in awakened nights and sleepy mornings due to disrupted sleep patterns. Jet lag tends to worsen with age. Exposure to light is one of the powerful factors determining the circadian rhythm. Melatonin can be helpful in enhancing the adaption to new time zone, if appropriately timed. Jet lag is determined by various other factors such as the extent of difference of time zone, probable duration of stay at the new place, and direction of travel. In case of shorter duration of trips lasting <3 days, it is advisable to stay in sync with the time of origin country. In order to adapt to the destination time zone readily, it is advisable to move bed time and wake up time with respect to the destination time zone 3 days prior to the date of departure. However, this may not possible in practical situations. If possible, modification in sleeping and waking time can help one get acquainted with the new time zone better. Avoid consumption of sedative or hypnotic medication prior or during the journey. In some cases, it can be helpful to avoid early morning light and expose to late morning or afternoon light. At the destination, continue the same sleep wake pattern established prior to the journey. Set your clock on mobile phone to the new time zone.

INSURANCE OF TRAVEL

It covers medical, dental, and travel expenses; usually that are not covered in regular health or other insurance plans. Premium insurance plans range for 24 h/day for 7 days or during the period of stay, in the destination country. It connects the traveler to the best doctors available around their locality round the clock, in the event of emergencies or for aeromedical evacuation, if necessary. Frequent travelers can avail for yearly insurance plans or for individual trips as per their convenience. In most travel insurance policies, basic healthcare facilities are included. However, additional policies may be excluded. About 6–8 weeks prior to departure, travelers are recommended to review their current plan of insurance policy, check for options not available and payment options including credit card, debit card, or online transfer. Coverage for international travel must include medical care costs and aeromedical evacuation at least. Apart from these, dental care, personal liability, cancellation charges coverage, personal effects lost, and carrying body of relative after death. In some policies, even loss of income, relatives and family members' transportation, and daily allowance are included. Travel to war zones, certain infectious diseases, pregnancy, and travel for adventure sport activities are usually not included in insurance policies. It is always advisable to check with the insurance company to include other policies to ensure safe and insured travel to an unknown destination. In case of travelers above 60 years or age or existing premedical conditions, where insurance policies cannot be availed, it is advisable to study about bilateral government healthcare agreements. In case of worse case scenarios, at the least, arrangement to travel back to home country must be prepared.

Patients with ongoing medical treatment and chronic medical conditions should carry a detailed history of their condition, medication history and past history of surgery, and allergy history. This can be obtained from their healthcare personnel prior to departure. Their travel insurance agency number and emergency contact of family member or spouse should be mentioned in this document. It is advisable to carry the above documents in carryon luggage as it is helpful in case if the luggage goes missing. It is a hard and tedious job to obtain medications in a foreign land. Hence, it is advisable to take in to consideration the possibility of loss of medicines, articles of clothing, documents (medical or nonmedical), and money. One must be prepared beforehand in order to avoid mishaps during or after arrival at the destination.

SPECIFIC CONSIDERATIONS: HEALTHCARE PERSONNEL

Healthcare personnel (inclusive of practicing doctors, registered nurses, paramedical staff, cleaners, and sweepers) in contact with patient or relatives of patient are more likely to be infected with respiratory diseases through contact or droplet routes of transmission. The health and wellbeing of these healthcare workers are critical as they will be providing their care and medical help to the community they serving. In most developing countries, the access to clean and portable drinking water is scarce. It might be safe for people living in the locality since they develop resistance to the microbes due to long-standing exposure. Hence, new residents readily acquire these infections due to their low immunity status and resistance to these microorganisms.

For disinfection of water, use of iodine tablets or chlorine, commercial water filters, domestic appliance of water filters, or boiling water to 70°C (160°F) for 30 minutes. Solar radiation and UV filters are used to acquire clear water.

Use of Personalized Protective Equipment

Use of sterile gown/coverall suits, sterile glows, N95 mask or respirators, and knee length shoe covers should be encouraged in all cases. This enables the personal safety and protection of the treating doctor and nursing staff as well as prevents transmission of these contagious diseases to other patients and staff within the vicinity. Proper steps of handwashing before and after in contact with the patient must be practiced.

All healthcare personnel must take adequate precautionary steps in preventing any needlestick injuries to themselves or others around them. Vaccination for hepatitis B should be given to all doctors and staff as a precaution.

Postexposure Prophylaxis

In the event of contact of bodily fluids or needlestick injury from a HIV-positive patient, postexposure prophylaxis must be started at the earliest. Most commonly used regimen is tablet tenofovir 300 mg (one tablet) or tablet emtricitabine 200 mg once a day and tablet raltegravir 400 mg twice a day for up to 4 weeks.

SPORTS RECREATION

There are higher incidents of injuries and fatalities recorded with travelers during adventurous activities such as base jumping, water sports, snowboarding, sky diving, and alpine skiing. It is estimated that for every 60 participants for base jumping there is one fatality reported per year (1.75). The injuries rate for snowboarding is 6.1 incidents of injury/1,000 visits and 2.5 incidents of injury/1,000 visits for alpine skiing. However, it is a lower estimated risk but pose a higher degree of threat to serious injuries.

As a preventive measure, review with the company associated with the sport activity about the standard of safety equipment and ask for certification for authentication. Make sure all safety gears, harness belts, properly fitting helmets, and well-trained and certified staff are present at the time of activity. Proper medical evaluation before travelling is imperative and clearance of the same should be obtained to prevent any chances of syncope or collapse during the activity. Ensure that medical professionals are available in the nearest facility in case of an emergency. Make prior arrangements in the event of transporting any casualties or seriously injured patients to another location. The emphasis on certified and well-experienced guides is done to prevent the risks of morbidity or mortality, as it is observed that these injuries pertain to activities undertaken by individual groups with no proper certification or license as opposed to certified and licensed companies.

WATER ENVIRONMENT AND DIVING

Over the past 10 years, people traveling for water sport activities are exceedingly common, domestically and internationally. However, contrary to belief traumatic injuries are less frequent with water sports than with land-based activities. Water sport hazards may include collisions with equipment and land, drowning, failure of adequate oxygen supply, and submersion that pose a serious risk to life.

Scuba diving is most prevalent among water sport activities with drowning and decompression sickness being the most serious illness. It is advisable not to travel by air for 12–48 hours after diving. The degree of decompression sickness depends upon the length and depth of dives and the number of dives. However, the postdiving air travel can be avoided for initial 48 hours and after which it is best to consult for a medical evaluation before planning to return home.

Preparation for Water Related Environment/Water Sports

- *Exposure to sun*:
  - Apply sunscreen with high sun protection factor (SPF) and is water resistant.
  - Sunscreen must be applied prior to the application of DEET (containing insect repellent). If DEET is applied after sunscreen, it will decrease the time of effect of sunscreen.
- *Prevention of hypothermia*: Exposure to cold water–
  - Old aged individuals (>60 years) and children are more prone to hypothermia. Use of wet suits and dry suits is recommended. Make sure the exposure time is not unsupervised for a long period of time.
- *Seasickness*:
  - If a patient is known to have boat sickness, it is advisable to start the premedication prior to travel by boat in order to reduce the dizziness.
  - Sound knowledge about the hazardous marine life locally. Be aware of venomous and nonvenomous stings of marine life. Cover all exposed areas with appropriate wet suits. Always engage in water sport activities under the supervision of certified and licensed guide or company.
  - Avoid exposure to fresh water or stagnant water bodies to prevent infections of schistosomiasis and leptospirosis. Dry all areas of skin exposed to fresh water with fresh clean towel and apply DEET on skin.
  - For high-risk travelers, prophylaxis with tablet doxycycline 200 mg orally weekly can be started.
  - Exposure to brackish and salt water should be avoided. Proper and timely cleaning of wounds with antiseptic solution and clean dressing is recommended. If required, standard antibiotic regimen should be started at the earliest.
  - Make sure you are trained in swimming prior to undertaking any activities involving water bodies. Avoid consumption of alcohol during or prior to such activities. Check weather condition (high tides) around before the activity. Patient with high-risk conditions should undergo medical evaluation (cardiac disease and seizure disorders). Ensure that life preservers are present at all times during the water sport activity. Ensure the availability of pediatric-sized floating devices. If not present, carry your own.
  - Avoid musculocutaneous and soft tissue injuries by soft handling the equipment first. Prior study on instructions to use and handle them must be done to prevent injuries. One must acquaint themselves of first aid training, basic wound care, and management of minor cuts and bruises.

THROMBOSIS

Long hours of travel by air, usually >6 hours tends to draw a link between thrombosis and pulmonary embolism. This is due to immobilization of lower limbs while sitting for longer periods of time than usual. This can be risky for individuals with prior history of thrombotic events, post-coronary artery bypass grafting (CABG) status, and postorthopedic surgeries, obese individuals, or any healthy individual as well. Incidence of thrombotic events accounts for 1 in every 4,600 flights lasting >4 hours. Further, there is an increase in 18% for every flight lasting 6 hours or more. Passengers with risks mentioned above or other medical conditions are at higher risk.

Precautionary measures are undertaken like practicing foot and leg exercises every 2 hours to allow increased blood flow to the lower limbs. Adequate hydration throughout the

journey can be helpful in preventing any signs of dehydration. Use of compression stockings (15–30 mm Hg) for higher risk patients is recommended. However, some practitioners advise the use of low-molecular-weight heparin subcutaneously before departure and 24 hours after departure as prophylactic treatment for patients with previous history of thrombotic vents or thrombophilia. Aspirin is of no proven benefit as prophylaxis for passengers. Passengers may choose aisle seating option to allow more leg space for mobility of foot and leg.

ACUTE ALTITUDE ILLNESS

Acute altitude illness (AAL) is a consideration for all travelers ascending a height above 2,000 m (6,562).

Acute altitude illness comprises of:

- Acute mountain sickness (AMS)
- High-altitude cerebral edema (HACE)
- High-altitude pulmonary edema (HAPE)

Acute altitude illness is present in individuals ascending above 2,500 m (8,202) and 25% of travels that ascend rapidly. Prevention of acute altitude illness is to gradually ascend. In cases of high risk, prophylaxis treatment with tablet acetazolamide 125 mg twice daily for adults to be started 2 days prior to the ascend to 2,800 m or above and continue same treatment for 2 days beyond highest altitude attained. Pediatric dosage is 2.5 mg/kg/dose and can follow the same regimen as adults. In adults with sulfa allergies or those who cannot take acetazolamide, tablet dexamethasone 2 mg every 6 hours or 4 mg every 12 hours can be started 24 hours prior to the ascent and should be continued for 10 days.

TERRORISM/UNSTABLE POLITICAL SITUATIONS

Travel to countries involved in terrorist activities, ongoing war, famine, unstable political situations or with increased rates of violent crimes, rapes, murders, etc., can be very challenging and daunting. It is recommended to contact the embassy of your country in the country of destined travel about the magnitude of the situation. During the process of visa, make sure of arrangements made for a flight back to your home country in case of emergencies. While staying in hostile conditions, make sure to leave with a supply of medical kit and essentials in case of first aid or unavailability of medical help. Always try to make prior contacts of trustworthy local individuals who might offer help. However, one must look out for crooks and thieves during such conditions of instability. At the worst case, travel at times of uncertainty can be avoided until the situations in the destination are better or completely safe. In the end nothing is really important than assuring one's safety.

UPDATED WHO RECOMMENDATIONS FOR INTERNATIONAL TRAFFIC IN RELATION TO COVID-19 OUTBREAK

On 30 January 2020, the Director-General of the WHO, following the advice of the Emergency Committee convened under the International Health Regulations (2005), declared the current outbreak of COVID-19 a public health emergency of international concern and issued Temporary Recommendations. The committee asked the Director-General to provide further advice on these matters and, if necessary, to make new case-by-case recommendations, in view of this rapidly evolving situation. As of 27 February 2020, although China, particularly the Province of Hubei, has experienced sustained local transmission and has reported by far the largest number of confirmed cases since the beginning of the outbreak, lately the situation in China showed a significant decrease in cases. At the same time, an increasing number of countries, other than China, have reported cases, including through local transmission of COVID-19. As the epidemic evolves, it will be expected that many areas may detect imported cases and local transmission of COVID-19. *As of September 1, 2021 in total 32 million cases of COVID-19 have been reported from India meanwhile, worldwide total 220 million COVID-19 cases and 4.5 million deaths have been reported.*

Recommendations for International Travel during Ongoing Transmission

With the contamination of new patients on daily basis worldwide, it is not advisable to countries with more number of affected cases than your maiden country. While travelling internationally, healthy individuals may come in contact with sick or COVID-19 positive patients at airports, airplane, ships, trains, or buses. This may either lead to development of symptoms in the new patient or a carrier state. A carrier status in a passenger will be asymptomatic and may travel back home and further transmit the COVID-19 virus to other members of family. Recent studies of cases, both old or new, it is imperative that this disease is more serious and life-threatening to older individuals above 60 years of age, underlying medical conditions (diabetes mellitus, cardiac conditions, chronic renal diseases, and previous history of respiratory conditions: Pneumonia and interstitial lung disease), pregnant mothers, young infants, and immunosuppressed patients with chemotherapy ongoing. Healthcare institutions are becoming overburdened in developing countries like India, where the doctor to patient ratio is 1:1,800, in contrast to the WHO guidelines for recommended minimum doctor to patient ratio of 1:1,000. This limits the availability of medical attention to few individuals, leaving the majority of population helpless. With the rise in number of positive cases rising on a daily basis, many countries have restricted travel from highly affected countries to prevent increase in cross contamination. Primarily individual travelers will be screened for fever at evaluation, cough and cold, and sudden onset breathlessness at the entry point in airports.

Recommendations for International Travelers

Maintain adequate hand hygiene: Precaution is better than cure. With no definitive cure in the current situation and only supportive therapy, it is advisable for all travelers domestically or internationally to clean their hands with an alcohol-based sanitizer (at least 60% alcohol). If possible, it is recommended to wash their hands for 20 seconds for it to be effective. During the journey, always wear gloves and avoid touching your face, mouth, or nose.

Keep distance of 6 feet apart from contact for others. Social distancing should be maintained at all times prior to departure and during the time in the airport. Social distancing means staying out of crowded places, avoiding group gatherings, and

maintaining distance (approximately 6 feet or 2 meters) from others when possible.

Wear a N95 mask, surgical mask (3 Ply), or cloth-based mask to cover the nose and mouth.

While coughing or sneezing, raise your elbow to your face in order to cover your face and mouth. This will prevent spread to others in close proximity.

It is advisable not to travel under such times of crises and global pandemic if you are sick.

After reaching the destination, initial screening at the airport is done. After arriving in India, all international passengers would be quarantined at home or a hotel facility away from their family or friends. They are counseled about the need of informing designated authorities in case of development of symptoms.

In case of active symptoms mentioned above after travel internationally, the passenger is asked to be tested at the earliest. If he/she is stable, they are asked to stay at home quarantined for 14 days or admitted to a healthcare facility for further medical attention.

SUMMARY

In most of the situations, travelers across the globe underestimate the health and safety risks involved. In very few cases, an international traveler seeks consultation about proper travel counseling prior to the date of departure. Pretravel counseling includes individual approach on risk assessment, immunization schedule reviewed, details of arthropod-related diseases and protective measures, prophylaxis for malaria, and traveler's diarrhea along with risk reducing measures and travel-related education. This serves to be a helpful aid to a person travelling to developing countries, for adventure sports or activities, extended travel plan, travelling with a chronic medical condition or immune-compromised state, and travelling with children or pregnant mothers. It is ideal to undertake a medical consultation at around 6 weeks before the date of departure. Travelers should consider to carry travel medical kit (**Table 4**) along with them. In view of the recent COVID-19 pandemic, advisory by the WHO needs to follow.

TABLE 4: Travel medical kit.

Personal health documentation: • Allergy list • Current medications • Immunization record • Medical/Surgical history with list of diagnoses • Emergency contact information • Medical insurance information • Any prescription medicines	*Allergy:* • Epinephrine autoinjector (0.3 mg) • Short-acting antihistamine: Diphenhydramine 25 mg and meclizine 25 mg • Long-acting antihistamine: Cetirizine 10 mg, loratadine 10 mg, and fexofenadine 180 mg • Scopolamine patch 1.5 mg
Altitude illness: • Acetazolamide 125 mg • Dexamethasone 4 mg • Nifedipine 30 mg *Antiemetic:* • Ondansetron 4–8 mg oral dissolvable tablet • Promethazine 25 mg rectal suppositories	*Antibiotics:* • Amoxicillin 500 mg • Ciprofloxacin 500 mg • Azithromycin 250 mg • Trimethoprim/Sulfamethoxazole 160/800 mg • Cephalexin 500 mg • Amoxicillin/Clavulanate potassium 875/125 mg • Nitrofurantoin 100 mg
Antifungal: • Fluconazole 150 mg • Miconazole 2% cream • Clotrimazole 1% cream • Ketoconazole 2% cream *Antiviral:* • Oseltamivir 75 mg	*Antimalarial:* • Chloroquine 500 mg salt (300 mg base) • Mefloquine 250 mg salt (228 mg base) • Atovaquone-proguanil 250/100 mg • Arthropod avoidance • DEET 20–50% • Picaridin 20% • Permethrin 0.5% solution
Emergency contraception: • Levonorgestrel (Plan B One-Step) 1.5 mg • Ulipristal (Ella) 30 mg	*Eye care:* • Saline drops • Contact lens holder and spare glasses/contacts • Polymyxin B sulfate/trimethoprim ophthalmic drops • Erythromycin ophthalmic ointment

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Gastrointestinal: • ORS • Bismuth subsalicylate 262 mg • Loperamide 2 mg • Calcium carbonate 500 mg • Ranitidine 150 mg and omeprazole 20 mg • Calcium polycarbophil (FiberCon) 625 mg • Docusate sodium 100 mg	*Pain/Antipyretic:* • Acetaminophen 500 mg and ibuprofen 400 mg • Postexposure prophylaxis • Tenofovir 300 mg/emtricitabine 200 mg • Raltegravir 400 mg
Respiratory: • Nasal saline drops • Pseudoephedrine 60 mg • Albuterol metered dose inhaler	*Skin:* • Hydrocortisone 1% and triamcinolone 0.1% • Mupirocin ointment sunscreen • N-acetyl-5-methoxytryptamine (melatonin) 0.5–5 mg • Sleep aid zolpidem 5–10 mg
First aid supplies: • Commercial first aid kit • Adhesive strips (Steri-Strips) • Adhesive tape (Duct tape) • Alcohol wipes, antiseptic cleanser, and hand sanitizer • Band aids and dental kit • Disposable gloves • Elastic bandages and gauze (hemostatic gauze) • Local anesthetic • Moleskin/Molefoam	*Personal protective equipment:* • Safety pins • Scissors • Splint • Suture kit/sutures/stapler • Syringe/Needle • Thermometer • Tweezers • Wound glue

(DEET: diethyltoluamide; ORS: oral rehydration salts)

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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CHAPTER

In-flight Medical Emergencies

Devendra Richhariya

INTRODUCTION

A large number of people are travelling aboard through commercial airlines every year and in-flight medical emergencies are also increasing worldwide each year. A medical professional may get a sudden call for assistance in the unfamiliar surroundings of an airliner cabin. Medical professional who is experienced in "wilderness medicine" requires to adopt improvisational approach to address the medical issues. Physicians who are travelling in commercial flight need to assist the passenger who is having a medical emergency and most of them need hospitalization as well. So physician should be aware about the common in flight medical emergencies and their management in unique environment and the liabilities, they may incur when offering assistance. No mandatory reporting system exists in estimating the frequency of in-flight medical events is challenging because so this is likely to be an underestimated. This chapter briefly discusses on the unique conditions, challenges, and constraints of the flight environment and resource management to equipment required.

THE FLIGHT ENVIRONMENT, CABIN ALTITUDE, AND CABIN AIR

Modern commercial aircrafts roughly fly at equivalent to a cruising altitude of 32,000–45,000 feet between the troposphere and stratosphere. Panes fly more smoothly and experience less turbulence above the troposphere. Pressurized cabin of the aircraft protects the passengers from high-altitude atmospheric conditions by creating its own medical ramifications.

The ambient atmospheric pressure is roughly 0.2–0.3 ATM at cruising altitude (30,000–40,000 feet). The cabin must be pressurized for survival of patient and to operate in this environment. Typically pressure between 6,000 and 8,000 feet above sea level is maintained in the cabin of the aircraft. Maintaining the cabin pressure at sea level is difficult to maintain would make the plane unacceptably heavy and expensive to build and operate. So, preventing passengers from becoming hypoxic in aircraft, compromise is made that is the most efficient for weight/strength/expense. Newer aircraft can pressurize the cabin to lower altitudes, equal to about 6,000 feet, and even in the upper flight levels. The fractional oxygen content of the air in the cabin is the same as that at sea level, approximately 21%. Atmospheric pressure changes with increasing cabin altitude. At a typical cruising altitude, the atmospheric pressure in the cabin is decreased by about 25–30% and results in a similar decrease in the partial pressure of inspired oxygen. Slight hypoxemia, with a corresponding decrease in oxygen saturation and a mild compensatory hyperventilation and tachycardia may occur in a traveler because of lower partial pressure of oxygen in the aircraft cabin results. Physician, who is attending the inflight medical emergencies, should be aware of physiologic changes like decreases in arterial oxygen saturation in the range of 3–5%, even in healthy individuals.

The risk of getting infection during a commercial flight arises from the close proximity to potentially infected passengers, and not from the quality of air in the cabin. A crowded airplane has similar risk of getting infection than other enclosed spaces. About 40–50% portion of the cabin air is recirculated and passes through high-efficiency particulate air filters and 94% and 99.9% of all airborne microbes are filtered during this process.

Low Humidity of Cabin Air

Typical humidity levels in most airliners are about 2% and airline cabin is usually dry. Airplane designers are happy to minimize moisture to help inhibit structural corrosion. Maintaining optimal cabin humidity (40–70%) is prohibitive because of the increased cost and weight of equipment. Low cabin humidity levels can lead to dehydration, so passengers are encouraged to increase water intake. Dry eyes may occur in patient with preexisting eye problem, and soft contact lens wearers so carrying "artificial tears" is beneficial. Dry-inflamed upper respiratory mucosa can produce cough and exacerbate reactive airway disease.

PRESSURE AND DYSBARISM

Middle Ear

Reduction in aircraft cabin pressure can lead to volume expansion of closed gas containing compartments in the

human body. Symptoms develop due to expanding volumes of air in the paranasal and frontal sinuses, but the most common manifestation of dysbarism is barotitis media resulting in to ear pain. Risk factors for barotitis media are associated with to eustachian tube congestion secondary to upper respiratory infections, middle ear infections, chronic effusions, or allergies. Mild barotrauma may occur as the aircraft ascends (increase in pressure and expansion of gases) or with descends of aircraft (decreased pressure in the middle ear). Mostly mild discomfort in ear is the typical presentation, in rare cases, rupture of the tympanic membrane may also occur with change in pressure. Swallowing (chewing gum or sucking on hard candy) is the simplest and commonly used method to open the eustachian tube. During descent, infants should be given a bottle or pacifier to suck on to facilitate swallowing. Older children and adults may benefit from performing a Valsalva maneuver. This is performed by pinching the nostrils and attempting exhalation through the nose. This maneuver is familiar to most scuba divers, because the same technique is used for equalizing ears during descent. Another useful technique is attempt swallowing while pinching the nostrils closed. Various pressure equalization techniques are helpful:

- *Voluntary tubal opening*: Traveler can attempt to yawn or by wiggling the jaw.
- *Valsalva maneuver*: Gently blow through your nose after pinching the nostril.
- *Toynbee maneuver*: Swallow (good technique during ascent) after pinching the nostrils.
- *Lowry technique*: Pinch your nostrils, and gently try to blow air out of your nose while swallowing.

Dental

Patients with preexisting dental disease such as a dental abscess (barodontalgia) may experience toothaches due to changes in cabin pressure.

Abdomen

Travelers may experience abdominal discomfort due to intraluminal gas expansion caused by decreased cabin pressure. Complications may occur during flight subsequent to recent abdominal surgery and surgical ligature. Surgeon's advice should be taken before planning the air travel. Travelling should be avoided for 10 days after abdominal surgery. It is advisable to avoid travel by air for 24 hours after colonoscopy, where a large amount of gas has been introduced into the colon, after laparoscopic intervention and neurosurgical intervention. It may be necessary to delay travel for approximately 2 weeks after ophthalmologic procedures for retinal detachment involve the introduction of gas by intraocular injections, which temporarily increase intraocular pressure.

Gas Expansion and Medical Devices

Fixed quantities of air are used in various medical devices include pneumatic splints (air splints), feeding tubes, urinary catheters, cuffed endotracheal tubes, and cuffed tracheostomy tubes. During rapid ascent in unpressurized and pressurized aircraft, trapped gas within these devices expands and known to cause barotrauma. During flight, air can be replaced with water in these devices to eliminate the effects of gas expansion, if not contraindicated. These devices need careful monitoring during air travel; cuff should be partial deflated if overexpansion is suspected. Caps of feeding and infusion tubes should be opened.

Pneumothorax

As air expands within the pleural space during ascent, patient with a small, asymptomatic pneumothorax can develop in to more significant pneumothorax. Risk of flight-related pneumothorax during air travel is increased in patients with preexisting pulmonary disease, cystic lung disease, recent pneumothorax, thoracic surgery, and chronic pneumothorax.

ON-BOARD MEDICAL RESOURCES

Airlines carry first-aid kits to assist medical emergency providers. First-aid kits consist of basic supplies such as bandages and splints, additional items are listed in **Table 1** and should have at least one automated external defibrillator (AED). Airlines usually contract with ground-based medical consultation services because health professionals are not aboard in every flight. Patient at these centers can get treatment recommendations by specialist. During emergency, on-board volunteer providers can also consult these services. Flight attendants should receive cardiopulmonary resuscitation (CPR) and the use of AEDs training every other year.

AUTOMATED EXTERNAL DEFIBRILLATORS

If there is a cardiac arrest on-board, and if one considers the 20–30 minutes required for an emergency landing from cruising altitude, plus a 10-minute taxi time to the gate, it is clear that these patients rarely survived. The successful introduction of AEDs for outside hospitals use has successfully improved survival rates after ventricular fibrillation. On these bases, airline organizations introduced AEDs into their aircraft fleet. If an AED is on-board, typically at least one cabin crew member should be trained in its use. Airlines allow only crewmember to manage the AED and cabin crew may assist or direct its use. If CPR is indicated, CPR can be started and cabin crew (trained in basic CPR) to assist. Modern AEDs may have electrocardiographic display (monitor) that shows the cardiac rhythm. AEDs with monitoring allow better decision-making when a passenger presents with chest pain, palpitations, dyspnea, or light-headedness. Recent modern equipment can monitor blood pressure, tympanic temperature, glucometer, oxygen saturation as measured by pulse oximetry, respiration and breath gas analysis, and electrocardiogram, and transmit these data to a remote physician for diagnosis. The device allows monitoring of electrocardiogram when used in conjunction with a smart phone.

Limitations of In-flight Automated External Defibrillators

Limitations of in-flight AEDs include the following—Inability to deliver the shocks because of patient movements interfering with analysis; prematurely turning off the AED, not able to follow instructions to deliver shocks, AED leads are off; misreading the AED screen instruction to start CPR; and inflight vibration may interfere in operating the AED even for trained healthcare professionals. Some airlines only allow cabin crew who is trained in CPR to operate on-board AEDs.

TABLE 1: On-board emergency medical kits.

Content	*Quantity*
Sphygmomanometer	1
Stethoscope	1
Airways, oropharyngeal (3 sizes): 1 pediatric, 1 small adult, 1 large adult or equivalent	3
Self-inflating manual resuscitation device with 3 masks (1 pediatric, 1 small adult, 1 large adult or equivalent)	3
Cardiopulmonary resuscitation mask (3 sizes): 1 pediatric, 1 small adult, 1 large adult or equivalent	3
IV administration set: Tubing with 2 Y-connectors	1
Alcohol sponges	2
Adhesive tape, 1-inch standard roll adhesive	1
Tape scissors	1
Tourniquet	1
Saline solution, 500 mL	1
Protective nonpermeable gloves or equivalent	1 pair
Needles (2–18 gauge, 2–20 gauge, 2–22 gauge, or sizes necessary to administer required medications)	6
Syringes (1–5 mL, 2–10 mL, or sizes necessary to administer required medications)	4
Analgesic, nonnarcotic, 325-mg tablets	4
Antihistamine, 25-mg tablets	4
Antihistamine injectable, 50 mg (single-dose ampule or equivalent)	2
Atropine, 0.5 mg, 5 mL (single-dose ampule or equivalent)	2
Aspirin tablets, 325 mg	4
Bronchodilator, inhaled (metered dose inhaler or equivalent)	1
Dextrose, 50%/50 mL, injectable (single-dose ampule or equivalent)	1
Epinephrine 1:1000, 1 mL, injectable (single-dose ampule or equivalent)	2
Epinephrine 1:10,000, 2 mL, injectable (single-dose ampule or equivalent)	2
Lidocaine, 5 mL, 20 mg/mL, injectable (single-dose ampule or equivalent)	2
Nitroglycerine tablets, 0.4 mg	10
Basic instructions for use of the drugs in the kit	1

ON-BOARD MEDICAL OXYGEN (PORTABLE OXYGEN BOTTLES)

Most of the airlines carry a minimum of one portable oxygen bottle (POB) per flight to fulfill the minimum oxygen requirement.

Flow Rates and Duration

If called to assist in an on-board emergency, keep in mind that POBs may have only two fixed settings—(1) high (4 L/min) and (2) low (2 L/min) constant flow. Selection is made via a knob mounted on top of the regulator. Alternatively, some airline POBs are adjustable between 2 and 8 L/min.

Personal Portable Oxygen Bottles

Portable oxygen bottles are considered as hazardous material as they contain compressed gas or liquid oxygen that so airlines prohibit the use. Airlines are allowed to carry a passenger's filled oxygen cylinder in the aircraft cabin but the passenger cannot use it. However, because of various requirements like written pilot notification, additional HAZMAT training, and manual documentation, most airlines do not offer this service. Passengers, who are planning to carry their own oxygen cylinder on-board for use, should check with the specific airline before travel because liquid oxygen is classified as a hazardous material. Passengers who are on continuous medical oxygen are either not allowed to travel, or may request, to submit "fit to fly" certificate from a licensed physician, that they can complete their flight without the use of medical oxygen.

Carrier-Supplied (Compressed) Oxygen (Portable Oxygen Bottles)

Passengers who need oxygen therapy during flight, they may contact the airline as some airlines provide, for a fee, compressed bottled oxygen during flight. Flow rates and available equipment, such as masks vary with airlines. And airlines do not provide oxygen for passengers before or after a flight (e.g., between connecting flights).

Personal Portable Oxygen Concentrator

Check with the specific airline to see if they allow portable oxygen concentrator (POC) devices to be brought onboard and for use during flight. Passengers can use *personal* POCs during long layovers or delays.

Continuous Positive Airway Pressure Devices

Continuous positive airway pressure devices are the requirement for patients with sleep apnea during long-duration flights. Most domestic and international flights permit portable continuous positive airway pressure devices because these devices are classified as "medical assist devices".

SPECIFIC MEDICAL CONDITIONS

Cardiac Arrest

Managing the cardiac arrest among all in-flight medical emergencies is challenging in the setting of an aircraft cabin, due to confined and restricted space for patient care and less than appropriate positioning of the patient, limited personnel with the appropriate skill set, and few supplies the potential interventions are limited. During flight, only basic approach is the most appropriate and only possible approach for the management of cardiac arrest. So inflight management of cardiac arrest by volunteer physician should consist of cardiac arrest recognition, compression-only CPR, and defibrillation with the use of an AED. If return of spontaneous circulation (ROSC) is achieved during resuscitation, diversion and

emergency landing are probably the most appropriate recommendations, if diversion is not immediately possible, the volunteer physician should continue best possible care and monitoring of the patient. Consider cessation of resuscitation efforts and pronouncement of death if a ROSC is not achieved within 20–30 minutes. If the patient does not have a favorable response, justify discontinuing of resuscitation particularly in austere environment of aircraft cabin. A shockable rhythm may prompt the clinician to continue resuscitation. Only a physician is allowed to pronounced death during flight.

Acute Coronary Syndromes

Chest discomfort, dyspnea, nausea, vomiting, and diaphoresis are the common symptoms of acute coronary syndrome. Other manifestations include syncope or presyncope, respiratory symptoms, and cardiac arrest. There are very limited management options for a suspected acute coronary syndrome in an in-flight patient. Aspirin is recommended in most adult patients with chest pain who are suspected of having an acute coronary syndrome; active, clinically significant hemorrhage, and a true allergic reaction the only absolute contraindications to administration of aspirin. Sublingual tablets of nitroglycerine present in the medical kits, and should be used with caution. In certain situations, nitroglycerine can cause or exacerbate hypotension and shock such as in acute inferior ST-segment elevation myocardial infarction with right ventricular infarction (a diagnosis that cannot be made on a commercial aircraft in flight). In an ill looking patient, intravenous access should be achieved; fluid bolus may be helpful in patients with hypotension. Supplemental oxygen should be started and the clinician can request a descent to a lower altitude to improve oxygenation if patient saturation is low. A patient who is in an unstable condition (sick looking), should prompt a possible acute myocardial infarction and recommendation to the crew for immediate diversion. A patient at lower risk for an acute coronary syndrome, in stable condition, should prompt a less urgent recommendation for diversion; the patient should be offered transfer to a hospital by emergency medical-service personnel on landing.

Stroke

Acute stroke can present in various ways. A passenger, who has an abrupt onset of neurologic symptoms, should be considered as potential diagnosis of acute stroke. Patient should be evaluated for focal neurologic deficits because performing a complete neurologic assessment is challenging in the confined environment of an aircraft. Suspected strokes as an in-flight medical emergency with evidence of respiratory compromise should consider providing supplemental oxygen, because neural cells must be protected from further hypoxemia injury. In view of limited available oxygen supply, use the lowest necessary flow rate. Aspirin is available in the emergency medical kit, but should not be given in flight for a suspected stroke because possibility of an intracranial. The blood sugar level should be measured, if possible because strokes can also be mimicked by hypoglycemia. Although some airlines carry glucometer as part of an emergency medical kit. If glucometer is not as part of the medical kit, healthcare providers can borrow from other passengers; the cleanliness of the device is utmost important to prevent the transmission of bloodborne pathogens. Finally, healthcare provider should recommend a landing on suspicion of an acute stroke.

Altered Mental Status

Various underlying neurologic conditions may be exacerbated during air travel and may cause altered mentation. The physician assisting such a passenger must be aware of a wide differential diagnosis such as metabolic derangement, infection, vascular pathology, intoxication, trauma, hypoxemia, and postictal states. Seizure thresholds are also potentially lowered by in-flight hypoxemia. Reversible causes of a patient's altered mentation (hypoglycemia, hypoxia) must be assessed and rectified by clinicians. The blood sugar level should be assessed and corrected by oral blood glucose or intravenous dextrose. Hypoxemia should be corrected by supplemental oxygen and the descent to a lower altitude should be requested. Altered mental status may be debilitating or fatal, so recommending an expedited landing or diversion is advisable.

Syncope

Out of all aircraft medical emergencies, syncope and presyncope are relatively common medical events; many passengers are somewhat dehydrated as passenger aircraft cabins are pressurized by air pumped through the engines, which results in a relatively dry environment. Other contributing factors like altered eating patterns, fatigue from delayed flights may also cause syncope. Passenger's blood pressure and pulse should be measured by attending physician because intravascular volume depletion or bradycardia can readily cause syncope or presyncope. Keeping the patient on the floor with the feet elevated may provide rapid relief. Intravenous fluids should be given in patients with persistent hypotension. The blood glucose level and oxygen saturation should be checked. Underlying medical conditions of the patient should be assessed, some of which may be potentially fatal. Passengers who have persistent symptoms or abnormal physical findings, especially in elderly passengers with serious cardiac disease the responding physician should consider recommending a diversion because these patients are at increased risk for death.

Trauma

Usually, minor trauma is a relatively common on commercial airlines, mostly resulting from blunt force trauma due to turbulence. Mostly these are nonlethal injuries, but specific factors such as age, medical conditions, and use of anticoagulants must be considered while evaluating the injury. Basic first aid, cold compresses, and analgesia are required for most of the traumatic injuries. If a fracture or dislocation is suspected, the patient should be placed in a nonweight-bearing position with appropriate splinting. A thorough history and a physical examination should be performed in head trauma even if it is minor. Frequent reassessment of injury helps in early recognition of severe injury and recommendation of expedited landing or diversion.

Dyspnea

Underlying respiratory diseases of the passengers can be exacerbated due to reduced oxygenation in aircraft cabin. Acute exacerbations of chronic obstructive pulmonary disease, severe hypoxemia in patients with pulmonary hypertension can occur as a plane gains altitude. Supplemental oxygen should be started in passengers with dyspnea. Permission to travel with additional oxygen should be provided to passengers with respiratory illnesses and a resting oxygen saturation <92%. Bronchospasm should be treated with albuterol metered-dose inhaler available in the medical kit. Clinician need to perform a needle thoracostomy using the on-board equipment on suspicion of pneumothorax in a patient who is in unstable condition. Descending to a lower altitude may also be beneficial, because cabin pressure is inversely proportional to the altitude of the aircraft.

Infectious Disease and Air Travel

Air travelers are subjected to long periods in enclosed spaces, which facilitate the spread of infectious disease in spite of clean cabin air, provided by modern airliners. Recently world is witnessing SARS-CoV-2 pandemic and learning about air travel with precaution, e.g., mask, social distancing, hand sanitization, personal protective equipment, and various outbreaks of serious infectious diseases have been also reported aboard commercial airlines including influenza, food poisoning, measles, tuberculosis, viral enteritis, severe acute respiratory syndrome, and smallpox. The risk of cross-infection from airborne pathogens in aircraft cabins increases with the longer duration of the flight (with 8 or more hours increases the risk) and proximity to infected passenger (seating within two rows associated with an increased risk). Ask the ill passenger to use a facemask, if a contagious disease is suspected. Medical kit and/or the first aid kit should have the mask and gloves. If a potentially contagious disease is suspected, the clinician should make an effort to isolate the patient and relocate neighboring passengers. Use of a facemask by the ill passenger, preventing them from moving around the cabin and relocation of neighboring passengers are the important measures, can reduce the risk of transmission. Discuss quarantining the passenger with the flight crew and any reporting requirements. When an acute infection is suspected performing compression-only CPR, isolation of body fluids should also be done. Potential quarantine and government reporting requirements also arise when a communicable disease is suspected and clinician should have a discussion with both ground-based medical services and the flight crew about.

Psychiatric Emergencies

Multiple stress factors such as lengthy check-in process, enhanced security measures, delayed flights, cramped cabins, and alcohol consumption may be responsible for in-flight medical psychiatric emergencies. Acutely agitated passengers pose safety concerns for other travelers, improvised physical restraints might be necessary to ensure the safety of other passengers (medical kit does not contain sedatives), physician must rule out any organic cause such as hypoglycemia. Various factors during air travel, which increase the emotional and physical stress, are the following—time pressures of travel, congestion in airport, cope up with connecting flights, stress and anxiety related to business travel, family related events, disruptions in circadian rhythms, lack of sleep and dehydration, and stress and anxiety associated with missed and cancelled flights.

Postdive (Scuba Diving) Air Travel

According recent studies, flying in a commercial aircraft even after a 24-hour in surface can produce bubbles in a diver's blood; Divers Alert Network advises for a 24-hour surface interval before flight.

Circadian Rhythm Sleep Disorder (Jet Lag)

Jet lag is a sleep disorder, develops in passengers who travel across three or more time zones. Jet lag occurs when the internal circadian rhythm "clock" adjusts slowly to the destination time. This disruption causes circadian rhythms to become out of synchronization with the destination time zone. The sleep-wake cycle is regulated by pineal gland by secreting melatonin. The melatonin synthesis and release is stimulated by darkness and suppressed by light. Symptoms of jet lag include poor sleep, sleep-onset insomnia, fraction of sleep, and early awakening; fatigue; mood changes; headache; irritability; poor concentration; depression; and mild anorexia.

Travelers can minimize jet lag by doing the following before travel: Shift the timing of sleep to 1–2 hours later for a few days before traveling westward. Shift the timing of sleep to 1–2 hours earlier for a few days before traveling eastward. If traveling westward, seek exposure to bright light in the evening, if traveling eastward seeks exposure to bright light in the morning. Rooster and Entrain, mobile apps are available to calculate and adhere to a light/dark schedule to help travelers to avoid jet lag.

For preventing jet lag, the use of the nutritional supplement melatonin (0.5–5.0 mg of melatonin during the first few days of travel) is controversial. Ramelteon, newer melatonin receptor agonists, recently has been approved for the treatment of insomnia, but has not been well studied for use in jet lag. Nonaddictive sedative hypnotics (nonbenzodiazepines), such as zolpidem, may be used to promote longer periods of high-quality sleep. Temazepam (short-acting benzodiazepine) is recommended to minimize over sedation. Caffeine in limited quantities promotes daytime alertness. Take short period of sleeps (20–30 minutes), shower, and spend time in the afternoon sun.

APPROACH TO PATIENT CARE DURING IN-FLIGHT EMERGENCIES

It is a challenge for the medical professional to assist someone in an isolated environment and without availability of specialized equipment. Responding physician can create a less stressful environment for the patient, crew, and other airline passengers by showing calm, competent, and professionalism. Licensed medical professionals, currently practicing medical provider only should respond to a call, should be ready to show a medical license that verifies your

training. It is appropriate to ask the patient for consent (if they are not altered) with a crewmember as witness before starting in-flight care. Ensure one flight attendant continues to assist responding physician assisting throughout the in-flight emergency, to maintain continuity and ensures that you have access to needed equipment and cockpit communications. Most of international flights have access to a ground-based consultant that is very helpful for any in-flight medical volunteer, if the passenger seems very sick, request the cabin crew to arrange ground-based consultation. If you have been drinking alcohol, do not respond or no other provider responds, make full disclosure to the flight crew and the patient. International airlines are not considered to be a covered entity regarding healthcare privacy, responding physician legally speaks to the flight crew about the medical issues of the sick passenger. Because of language barriers, history taking may be difficult, family members or another available passenger may act as an interpreter, request can be made via a simple cabin announcement. Obtain and record vital signs early in the event and focused physical examination is preferred because of limitations in space, vibration, and ambient cabin noise. Virtually, it is not possible to auscultate heart, lungs, or abdomen, patient should be moved to a larger area if a full resuscitation is indicated. You may be able to find additional medical equipment from other passengers, and do not hesitate to ask for additional help. Avoid performing procedures, if physician is unfamiliar with or announcement can be made for a nurse or emergency medical technician if physician out of practice, starting IV lines. Notify to the cabin crew, if the patient's presentation suggests a communicable disease. Despite the do-not-resuscitate order, the cabin crew may decide to continue resuscitation, if their company policy requires.

Cockpit Coordination

During management of the medical emergency, pilot in command or captain takes over the cockpit, copilot or "first officer" takes over the responsibility of flying the aircraft. Notification about medical emergency to air traffic controllers is given by nonflying pilot. Pilot/captain in consultation with a ground-based consultant always makes the decision to divert. Diversion is a complicated decision that must take into consideration factors such as fuel, costs, the ability of the aircraft to land at the closest airport, and the medical resources available at that airport. The most common reasons for diversion are cardiac, respiratory, and neurologic emergencies including nonrevolving chest pain, shortness of breath, severe abdominal pain, stroke persistent unresponsiveness, refractory seizures, and severe agitation.

Legal Ramifications

A medical responder who gives assistance develops a doctor–patient relationship, with its attendant obligations and liability risk. Law of that country determines the liabilities in which the aircraft is registered, but the law of the country in which the incident occurs or in which the parties are citizens could arguably apply. Provider should document all the events of the care and treatment given to the patient, should use airline-specific documentation as required. Providers should be careful about the patient's privacy rights and should not discuss the patient's care with third parties (e.g., media) without appropriate authorization from the patient. Provide all necessary medical management information to captain and cabin crew. The airline, considered to be a covered entity itself, is not obligated to follow regulations regarding healthcare privacy. It should be noted that all communications with medical ground consultants are recorded.

DEATH ON BOARD

International Air Transport Association Guidelines for death on board (January 2016) state that cabin crew trained to perform CPR, should continue CPR until one of the following occurs—(1) spontaneous breathing and circulation resume; (2) it becomes unsafe to continue CPR (e.g., heavy turbulence and/or forecasted difficult landing after liaising with the flight deck); (3) all rescuers are too exhausted to continue; or (4) the aircraft has landed and care is transferred to emergency medical service (EMS); airlines may choose to cease resuscitation and person is presumed dead if CPR has been continued for 30 minutes or longer with no signs of life, and no shocks advised by an AED. It may be advisable to avoid declaring death on board because the legal implications of declaration of death vary from country to country. Therefore, limit involvement to advising the cabin crew regarding the presumption of death.

FUTURE CHALLENGES

Challenges to be addressed in the future include the following—lack of standardization of the onboard medical care; lack of mandatory and standardized reporting system for a better understanding of the overall incidence of in-flight emergencies; lack of postflight follow-up to ascertain frequency of nonemergency medical issues (i.e., venous thromboembolism); and requirement of flight attendants to undergo training in AED and CPR every 24 months. Most airlines lack clear standardized medical protocols for flight attendants managing in-flight medical emergencies, including protocols for flight attendants on flights where no medical professionals are available to volunteer. Most of the airlines remain out of reach of modern telemedicine technologies despite recent advances in this field.

SUMMARY

In-flight medical emergencies are relatively frequent. Air travel can exacerbate the underlying diseases in passengers or new medical problem may arise during flight. Physicians should be prepared to provide care while traveling especially in medically austere environment. Physician must be aware of associated liabilities surrounding the delivery of in-flight medical care.

MULTIPLE CHOICE QUESTIONS

To access the MCQs of this chapter online, kindly refer to **jaypeedigital.com** also please follow the instructions mentioned on inside cover.

SHORT ANSWER QUESTIONS

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Occupational and Industrial Health

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CHAPTER

Devendra Richhariya

INTRODUCTION: A GLOBAL VIEW ON OCCUPATIONAL HEALTH

Occupational health (OH) problems are a substantial global burden. All fatal and nonfatal work-related injuries and illnesses cause economic burden with loss of 4% of all work-years globally, equivalent to a cost of approximately 3,000 billion US $ for low-, middle-, and high-income countries. This is roughly equivalent to 4% of the global Gross Domestic Product (GDP) worldwide. One of the biggest public health achievements in the 20th century is improvements in OH and safety with decreases in fatal occupational injuries, improvements in mining safety, successful vaccination against hepatitis B, reductions in communicable diseases, and many more advances can be added to the OH community's tally. Regular follow-up and continued vigilance is necessary even if old problems have disappeared. High quality OH interventions are required in view of newer health problems related to musculoskeletal and psychosocial problems, ageing workforce.

There are three major challenges related to health and safety at work challenges:

1. To improve implementation of existing health and safety rules.
2. To improve the prevention of work-related diseases by tackling new and emerging risks without neglecting existing risks.
3. To take account of the ageing of workforce.

Occupational health is an even more emerging issue. Fatal accidents are higher, great efforts must be made for the reduction of recognized occupational and work-related diseases by enforcing OH standards and legislation, limiting exposure to both new and known health hazards such as silicosis, asbestosis, lead toxicity, or pesticide poisoning. The majority of these diseases, injuries, and accidents are preventable and emphasis is given on the enormous potential of OH programs. These programs are important, not only for the health, safety, and well-being of the global working population, but also for employers. Improving health at the workplace can result in reduced absences from work, can increase economic productivity and competitiveness of its staff, can reduce insurance premiums or medical costs, and can yield a range of intangible gains such as improved company profiles and worker engagement.

VALUE OF OCCUPATIONAL HEALTH FOR ALL STAKEHOLDERS

A whole range of stakeholders—workers, worker's families, healthcare systems, insurance companies, businesses and shareholders, customers, and even other companies, are benefited by improving OH at work since all of these parties avoid costs when work accidents or diseases are prevented. Three main stakeholders: employees, employers, and society are the most important beneficiaries of investing in OH. Some of these benefits are seen immediately such as fines from legal violations and compensation of occupational diseases, while benefits which give delayed but sustainable results are workers' health gains, corporate image, and increase in worker productivity (**Fig. 1**).

Employee

It is important to protect and promote the health of employees during and beyond working life as most of the world's population (58%) spend one-third of their adult life at work. OH interventions help in preventing the accidents or injuries at work, the prevention or early detection of diseases, and the health benefits from return-to-work. Various programs for lifestyle changes and health promotion activities at work, e.g., smoking cessation programs and reduced alcohol consumption by professional drivers, help in creating a good healthy environment at work place. By implementing the health promotions, events can be averted at the work place are: income losses for employees, wage losses during sickness absence, and wage losses upon return to work. Various programs for lifestyle changes are helpful in reductions in medical treatment costs.

Business

Financial Factors

Occupational health programs implementations can improve productivity, because healthy employees have reduced sick leave (absenteeism) and increased productivity at work (presenteeism). Productivity impact is usually estimated through the calculation of lost working time from absenteeism and presenteeism, and converted into monetary

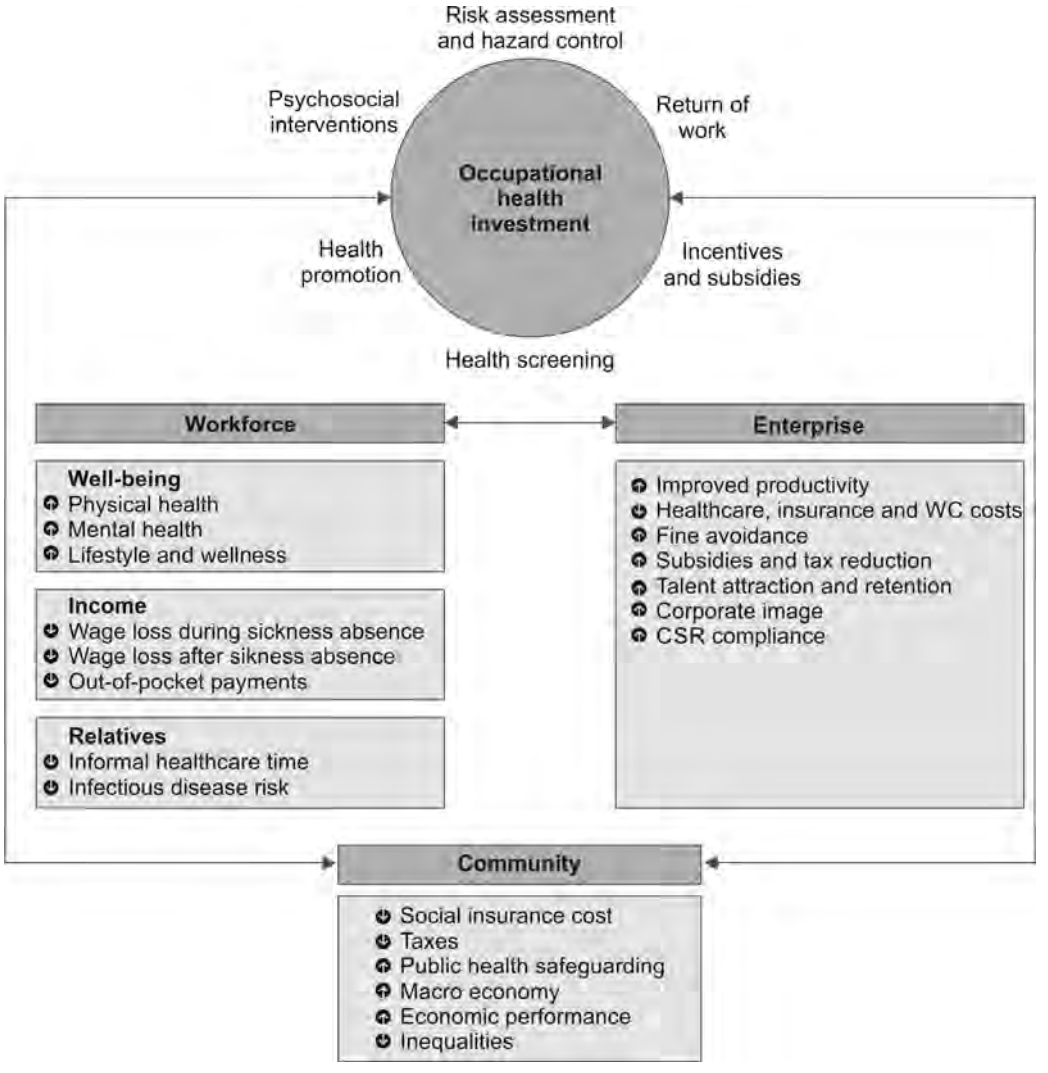

FIG. 1: Value of occupational health investments by category and interconnection between categories.

values by multiplying with the (average) employee wage. In many setting, OH programs are of crucial importance and cost-effective and shown to be helpful in the prevention of absenteeism.

Nonfinancial Factors

Full benefit of OH programs cannot be estimated by financial factors alone. Quality or efficiency is more important than to financial parameters. Companies investing in OH can attract more and more talented workers and lower recruitment and human resource (HR) management costs, finally affect the productivity of the firm.

Society

Public Health

Occupational health interventions can play an important role in safeguarding public health, particularly in outbreaks of infectious diseases or health-related disasters. Exposures increase the risk of acquiring communicable diseases, such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) in the healthcare worker. Vaccination reduces the risk of influenza hepatitis, tuberculosis, or HIV. OH can therefore play a crucial role in emergency response. The World Health Organization recommendations during outbreak of coronavirus disease 2019 (COVID-19) are to prevent infections at work, not only for healthcare, transport, or burial team members but also for employers and employees in general. Further protecting or vaccinating employees to avoid a communicable disease can prevent infection for many other parties, such as the employee's family, nonprotected coworkers, and customers. OH not only plays an important part in communicable diseases but can also be of significant in other disasters.

Economic Performance

At the national level, a link between economic performance and OH can be taken as good indicator. All stakeholders get benefits from investing in OH. Employees get improvement in well-being and health. Companies get increased productivity (through reduced absenteeism and presenteeism); decreased compensation and healthcare expenses; and improved reputation.

WORK ENVIRONMENT

Work place is assessed related to occupation, work, and work environment. Workplace should be inspected for actual

TABLE 1: Potential health hazards.	
Air contaminants	• *Particulate contaminants*: Dust, fume, mist, and aerosol fibers • *Gas and vapors contaminants*: Gases vapors
Chemical hazards	Harmful chemicals in the form of solid liquid and gas, mist, dust, fumes exerts toxic effects by inhalation, absorption, and ingestions
Biological hazards	Exposure to bacteria virus fungi and other living organism while working in laboratory can cause acute and chronic infections
Physical hazards	*Noise radiations*: Ionizing and nonionizing radiation and radiant heat exposure
Ergonomic hazards	Excessive vibration, noise, eye strain, repetitive motion, heavy lifting problem, poorly designed tools, and work area
Psychological factors	Stress, production pressure, low pay, and lack of recognition
Technique used in recognizing health hazards	
Material inventory	Check who is using inventory (purchasing staff, safety adviser, occupational hygienist doctors' nurses). Obtain information about nature of material, use of material, their storage handling and control procedure, administrative details, trade and chemical details, use, and waste disposal
Process inventory	Assess and document hazards associated with every process. Process inventory should include process, material involved, point of material entry and exit, operating procedure, and potential exposure
Walkthrough occupational hygiene survey	Preliminary assessment of premises plant operation should be done by walkthrough survey to identify potential hazards. Walkthrough survey is helpful in interacting with plant personnel, engineers, and foreman who know the problem in process and also able to tell complaints and symptoms among workers
Air sampling program	Essential for health risk evaluation, environmental protection, compliance, process control, source identification, and documentation of exposure
Controlling hazard	
Engineering control	Reducing or removal of hazard at source, elimination of toxic chemical, and installing general and local ventilation
Work practice control	Change in existing work process, maintain process and equipment in regular basis, good housekeeping, and prohibiting smoking and chewing tobacco in regulated areas
Administrative control	Limit hazard exposure by scheduling task and production, use of appropriate personal protective agents

hazard and unsafe worker behavior. Assessment of workplace environment is required to monitor stresses arising from workplace environment which may cause injury and sickness, impaired health and significant inefficiency among worker and also community. Assessment of workplace environment include study of toxicology, industrial process, environmental sampling, chemical and physical components of air, evaluation of ventilation system, noise control, protection from radiation, occupational hazard, and effect on health. Worksite analysis is the essential procedure to determine what job or workstation is the potential source of health-related problem (**Table 1**).

OCCUPATIONAL AND OTHER WORK-RELATED DISEASE

Understating between work and health is essential. Interaction between man, environment, and work give rise to various types of stress and hazard that may be present in different type of occupation including industries, agriculture, etc. Occupational diseases are spectrum of work-related disease where causative factors related to health at the work place fully identified, measured, and controlled. Work-related disease may have weak inconsistent relationship to working conditions and their strength and magnitude may vary. Occupational disease can be defined as adverse health conditions of the human beings, severity of which depends on exposure of the factors on the workplace. Factors may be as follows:

- *Physical*: Heat, noise, and radiation
- *Chemical*: Solvent, pesticide, heavy metal, and dust
- *Biological*: Tuberculosis, hepatitis B virus, and HIV
- *Ergonomics*: Poorly designed tools at work area and repetitive motion
- *Psychological stressors*: Excess workload and inadequate personal support
- *Mechanical*: Responsible for injuries and accident rather than occupational disease.

Occupational diseases may be overlooked by physician due to its specific characteristics. Most occupational diseases have similar clinical and pathologic features as nonoccupational disease (asthma due to toluene diisocyanate may not be clinically differentiated from asthma due to other cause). Occupational disease may occur after termination of exposure (asbestos-related mesothelioma occurs 30–40 years after the exposure). Clinical manifestations of occupational disease are dose and exposure time-dependent and occupational and nonoccupational factors both act in combination to produce the disease. Work-related disease are multifactorial and often more common than occupational disease, therefore they need special attention by health service infrastructure which incorporates the OH services. Work-related diseases which need special attention are behavioral

and psychosomatic disorder, hypertension, coronary artery disease, peptic ulcer, nonspecific respiratory disease, and locomotor disorders.

EARLY DETECTION OF OCCUPATIONAL DISEASE

Early detection of pathological changes is necessary to minimize the damage caused by occupational disease. Certain occupational disease presents as early clinical, functional, biochemical, physiological, and morphological changes and are reversible if detected and managed early. Periodic examination is important in early detection of occupational disease. Periodic examination should include simple screening test, positive cases should then undergo comprehensive examination to confirm or exclude the diagnosis of occupational disease. Early detection of occupational disease caused by biological agents: Pulmonary tuberculosis can be detected by X-ray; hepatitis B and C, HIV, and brucellosis can be detected by serologic examination. Early detection of occupational disease caused by physical factors is summarized in **Table 2**. Early detection of occupational disease caused by heavy metals is summarized in **Table 3**. Early detection of exposure of organic solvent is summarized in **Table 4**.

OCCUPATIONAL ERGONOMICS

Ergonomics is the understanding of complex relationship between human-machine and environment. Ergonomics also includes study of physical and psychological aspect of work environment (facility, equipment, and tools) in relation with the workers. The fundamental principle of ergonomics is that all type of work activities gives some kind of physical or mental stress to workers. To keep work performance satisfactory, this stress level should be kept within reasonable limit and worker's health and well-being should be monitored. The aim of ergonomics is to optimize comfort, health, safety, and efficiency of the workers. Benefits to employers can be measured in terms of increased efficiency and productivity reduction in work time loss in illness or injury and decreased insurance cost. Ergonomics has four major components: (*1) Human factor engineering, (2) Work physiology, (3) Occupational biomechanics, and (4) Anthropometry.*

Human factor engineering also called engineering psychology related to information processing aspect of the work and objective are to design procedures, equipment, and work environment to minimize the likelihood of accidents caused by human error. *Work physiology* is subdiscipline of ergonomics which concern with stress due to metabolic conversion of biomechanical energy source, glucose to mechanical work. Workers will feel fatigue if stress is excessive. Jobs which require highly repetitive and forceful exertion, injury may occur to musculoskeletal tissues and peripheral nerves. *Biomechanics* is subdivision of ergonomics related to mechanical properties of the human tissue, concern with resistance of the human tissue to the stress. Occupational biomechanics especially focus on prevention of stress of lower back and upper extremities. *Anthropometry* is concern with matching tools and workspace to the dimensions of the human body (workers). Mismatch in size between worker and workplace equipment or machinery increases the physical

TABLE 2: Early detection of occupational disease caused by physical factors.

Heat	Irritability, discomfort, lassitude, lack of concentration, low work performance, heat rash, heat exhaustion, and heat stroke
Noise	Noise-induced hearing loss can be detected by audiometry
Vibration	Vibration causes vascular disorders of arms and changes in small bones of the wrist. Vascular changes difficult to detect early but X-ray can be helpful in detecting rarefaction of lunate bone
Atmospheric pressure	Aseptic bone necrosis around knee, hip, and shoulder after exposure to increased atmospheric pressure can be detected by X-ray
Infrared radiation	Cataract can cause progressive failure of vision and can be detected by slit-lamp examination
Ionizing radiation	Ionizing radiation exposure can also cause cataract. Bone marrow can be affected so periodic complete hemogram can be done and leukocytes must be evaluated

TABLE 3: Early detection of occupational disease caused by heavy metals.

Lead	• *Acute effects*: Abdominal pain, encephalopathy, hemolysis, and acute renal failure • *Chronic effects*: fatigue, arthralgia, myalgia, anemia, gout, and neuropathy • *Lead concentration in blood can be determined*: Lead poisoning >80 µg/dL
Mercury	*Acute respiratory distress, gingivitis, tremor, proteinuria, renal failure, ataxia, spasticity, paresthesia, and visual and auditory disturbance*: Early detection of exposure to mercury is carried out by estimation of mercury in urine (<20 µg/L in nonexposed individuals)
Manganese	*Fever, chills, dyspnea (metal fume fever), pneumonia, Parkinson-like syndrome, and behavioral syndrome*: Diagnosing the disease on the basis of neuropsychiatric clinical staging is helpful not the estimation of manganese in body fluids
Arsenic	• *Acute*: Nausea, vomiting, diarrhea, intravascular hemolysis, jaundice, and oliguria • *Chronic*: Hyperkeratosis, hyperpigmentation, and cardiac and peripheral vascular disease • Chronic exposure of arsenic can be estimated by measurement of arsenic in urine (in nonexposed normal individuals <30 µg/L). Estimation of arsenic in hair or in nails also good index of chronic arsenic exposure

stress in workers. This mismatch makes the worker to adjust, need to bend over for work, having to work with one or both arm and should held high for longer period of time, and having to sit over bench which is too high or too low.

STRESS AND ADVERSE PSYCHOLOGICAL FACTORS AT WORK

Stress is the imbalance between demand and response capabilities and failure to achieve demand is important consequences. Health, health services, and community are influenced by psychological factors. Common workplace stressors and their prevention and control are summarized in **Table 5**.

OCCUPATIONAL SAFETY AND ACCIDENT PREVENTION

Occupational accidents occur at the workplace, which may cause damage to machinery, tools, and people (bodily injury or death). Occupational safety measure to be implemented with the aim to avoid any destruction of health and other

TABLE 4: Early detection of exposure of organic solvent.

Organic solvent	*Clinical features*	*Method of evaluation of exposure*
Benzene	• *Acute*: Anesthesia, nausea, vomiting, headache, sleepiness, fatigue, slurred speech, disequilibrium, and depression • *Chronic*: Bone marrow, depression, and aplastic anemia	• Periodic hemogram may detect early hemopoietic abnormalities • Benzene in blood • Benzene, trans trans-muconic acid, and phenylmercapturic acid in urine
Methylbenzene (toluene)	• Isolated toluene exposure is rare usually with benzene • Conjunctival irritation and ulceration cardiac arrhythmia • Liver and kidney dysfunction and bone marrow depression in chronic exposure	Hippuric acid in urine collected at the end of work shift (hippuric acid is not a metabolite of toluene)
Xylene	• Mucus membrane irritation • Chronic exposure may cause aplastic anemia	Methylhippuric acid in urine
Aminobenzene (aniline)	Mild skin irritant, cyanosis in moderate exposure, anoxia and death in severe exposure	• Methemoglobin in blood • Para-aminophenol in urine
Carbon tetrachloride	Nausea, vomiting, drowsiness, dizziness, and chronic exposure causes scaly dermatitis and liver and renal dysfunction	Carbon tetrachloride in exhaled air, blood concentration level has limited value
Polychlorinated biphenyls	• Skin rash, eye irritation, nausea, and vomiting • Chronic symptoms include anorexia, weight loss, and liver dysfunction	Hemogram
Methylene chloride (dichloromethane)	*Skin and mucous membrane irritant*: Acute intoxication after inhalation (stupor, tingling, and numbness of limbs), dry scaly dermatitis, and cardiac dysfunction due to carboxyhemoglobin	Carboxyhemoglobin level in blood and carbon monoxide level in exhale air

TABLE 5: Common workplace stressors and their prevention and control.

Common workplace stressors	• *Organizational*: Change, inadequate communication, interpersonal conflict, and conflict with organizational goals • *Career development*: Lack of promotional opportunities and new responsibilities beyond capabilities • *Role*: Role conflict, role ambiguity, inadequate resource, and authority to accomplish the job • *Task*: Quantitative and qualitative overload • *Work overload*: Poor aesthetics, physical exposure, ergonomics problem, noise, odor, and safety hazards
Prevention and control of stress	• *Treat individual*: Medical treatment of hypertension, backache, and depression • *Employee assisting program*: Smoking, alcohol, and drugs • *Reduce individual vulnerabilities*: Individual or group counseling • *Training program*: Relaxation, medication, and biofeedback • *General support*: Exercise program and recreational activities • *Organizational*: Attitude survey, development of flexible and responsive management, improve internal communication, supervisor training, and management development

TABLE 6: Examples of overt and cumulative trauma affecting occupational group and prevention.

Causes	*Injury/disease*	*Affected occupation*
Overt trauma		
Mechanical energy	Laceration	Sheet metal workers, press operator, and fabric cutters
	Fracture	Material handler's, miner, and construction workers
	Contusion	Workers exposed to low energy impact and material handlers
	Amputation	Press operator and machine operators
	Crush injuries	Material handler's, press operator, and construction workers
	Eye injury	Miners, grinders, and saw mill operator
	Strain/sprain	Material handlers and construction workers
Thermal energy	Burns	Foundry smelter and glass worker welders
	Heat strain	Firefighter smelter and steel workers
	Cold strain	Utility workers
Chemical energy	Burn	Hazardous waste worker and process workers
	Asphyxiation	Firefighter, hazardous waste worker, and confined space workers
Electric energy	Electrocution, shock, and burn	Utility workers, construction workers, and electricians
Nuclear energy	Radiation burn and illness	Hospital workers, industrial radiographers, and nuclear workers
Cumulative trauma		
Heavy lifting and prolonged awkward position	Back pain	Material handlers, nurses, truck drivers, and sewing machine operators
Vibrations	Raynaud's phenomenon	Lumberjacks, grinding machine operator, and jackhammer operators
Control and prevention of occupational accident		
• Contain hazard from machine by enclosing and guarding them • Train operating personnel • Prescribe personal protective agent to worker to safeguard from hazard • Provide advisory services on safety and health problem • Develop centralized program to control accident and hazard • Develop and apply safety standard • Coordination between engineering, industrial hygiene, and medical purchasing department to ensure purchase of safe tools, equipment, and supplies • Collect and analyze data on illness and injuries • Ensure education and training of employee in specific health and safety principles and technique		

resources, prevent insufficiency at workplace due to accident, prevent social harm due to accident, and promote accident prevention to raise the morale of workers. Common types of occupational accidents are falls or struck by material, striking against objects or trap between the objects, strenuous movement, exposure to extreme temperature, electric current, and radiations. Occupational accidents give rise to various types of injuries, wound, fracture, dislocation, burn, poisoning, and diseases. Various parts of the body such as head, neck, thorax, abdomen, and upper or lower extremities can be affected by occupational accident. Few examples of overt and cumulative trauma affecting occupational group and their prevention are summarized in **Table 6**.

EPIDEMIOLOGY AND BIOSTATISTICS IN OCCUPATIONAL HEALTH

Occupational health is considered as components of public health. Epidemiology and statistics are the key disciplines of public health and population-based studies are an integral part of OH practice. Epidemiology is the study of the distribution and determinants of the health problem in the population and application of the study to control the health problem. Occupational epidemiology is related to study of occupational disease and their determinants. Important questions during investigations are who is at risk, where is the risk, and when and how? Biostatistics associated with description, summarization, and interpretation of data also in development of procedure. Epidemiologic study measures risk of disease in human population. Three types of epidemiologic study usually carried out: (1) Descriptive, (2) Analytical, and (3) Interventional (rarely done). Cohort study is commonly performed in occupational epidemiology.

RECORD KEEPING

Keeping worker's health record and reporting is important in OH. Coding system should be used while maintaining the health record. Record keeping is important even in small OH services. In an OH records can be used for documenting

exposure to hazards, employee health data for job placement, documenting employee health overtime, and fulfillment of regulatory requirements. There are seven types of basic health record on workers' health: (1) health and safety inspection, (2) environmental monitoring, (3) health monitoring, (4) first aid provided in workplace, (5) accident investigations, (6) sickness certificates, and (7) personal health records. Record keeping should be in simplest, consistent, convenient, efficient, and economical manner but with controlled access. Computer storage permits automatic and rapid retrieval of data in any combination and desired sequence. It is recommended to secure the record for 30 years and in some countries mandated by law as well.

OCCUPATIONAL HEALTH FOR WOMEN

Women workforce increasing day by day all over the world, women work very hard not only as housewives and mother but also in different sectors. Working women are in increased risk for fatigue, malnutrition, stress, and exposed to various types of hazards at the workplace. Industrial expansion in many countries happens without sufficient protective measures for female workers. Also, women are under stress since their work is considered secondary importance by management and medical facilities are also inadequate. Stress-related issues present in nearly all jobs held by women, mostly are low-paying job and even create more stress for single mother and home obligation for children. Women are at more risk of chemical agent, toxic substance such as organic solvent are more likely to retain in women bodies due to high fat content and may causes menstrual disturbance and spontaneous abortion. Women working in agriculture industries exposed to pesticide fertilizers and at risk of infertility and women working with textile mill exposed to dust which causes byssinosis. Women working in textile industries are exposed to noise vibration, heat, and stress which may lead to low birthweight babies. Women working in agriculture sector exposed to snake bite, tetanus, and worm infestation. Nurses are exposed to tuberculosis, hepatitis B and C, rubella, and other biological agents. Women workforce more likely to face ergonomic problem because most of the industrial and agricultural process and machine are designed for male bodily dimension and female workers find difficulty to operate them. To ensure safety and maintain total health in working women OH services should be established at all work places. Points to be implemented in OH care programs for working women are: (1) special health education, (2) regulations to safeguard working women, (3) environmental monitoring, (4) preplacement medical examination, (5) periodic medical examination, (6) equipment design, (7) emphasis on underserved working women, (8) research and survey, (9) and while planning the primary healthcare (PHC) services for working women address issues related to them maternity protection, family planning, and counseling.

SUMMARY

Occupational health has progressed from monodisciplinary, risk-oriented activity to multidisciplinary and comprehensive approach that works towards individual's physical, mental, social well-being, general health, and personal development. OH is multidisciplinary activities help in preventing and controlling the occupational diseases by eliminating occupational factors. OH activities enable workers to conduct socially and economically productive lives to contribute positively to sustainable development.

MULTIPLE CHOICE QUESTIONS

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SHORT ANSWER QUESTIONS

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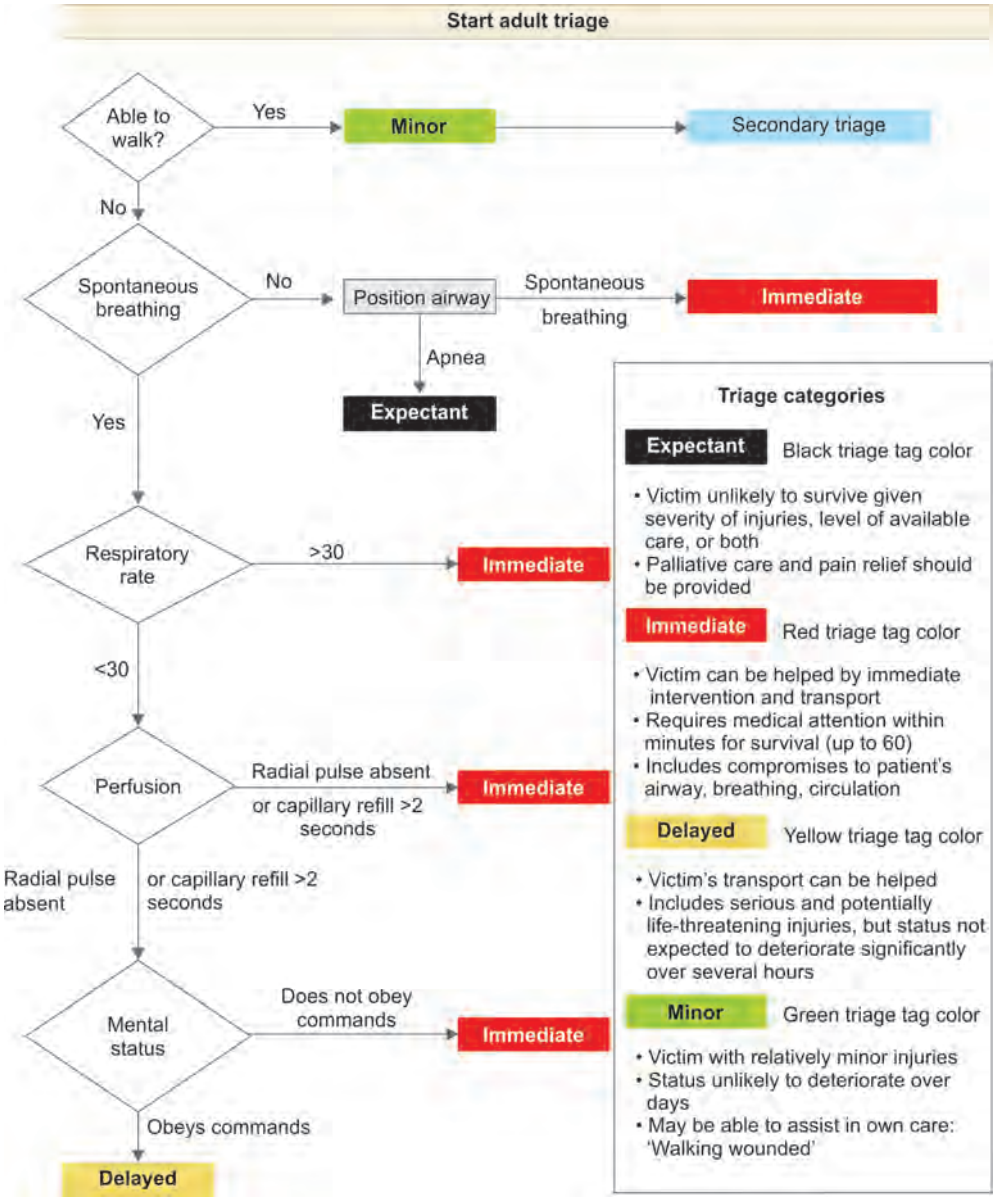
Z drugs 1437
Zaleplon 1437
Zanamivir 1233
Zargar classification 1479
Z-drugs 1431
Ziehl–Neelsen staining 1337
Zika virus 629, 1286
Zinc 57, 677
  sulphate 1180
  supplementation 651, 1180
Zipper injury 775
Zipper removal 775*f*
Zoledronic acid 973
Zolpidem 1437
Zona
  fasciculata 893, 894
  glomerulosa 893, 894
  reticularis 893
Zoonosis 1275
Zoonotic dermatologic infection 1311
Zoonotic disease 1295, 1313
Zoonotic encephalitis 1310
Zoonotic infections 1307, 1311
  risk factors for 1307*t*
Zoonotic meningitis 1310
Zoonotic pneumonias 1311*t*
Zoonotic respiratory infection 1310
Zoonotic viruses 1312
Zopiclone 1437
Zygoma 1666

PLATE 1

FIG. 2: Personal protective equipment levels. ***(Chapter 29)***



(START: simple triage and rapid treatment)

FLOWCHART 1: START adult triage algorithm. ***(Chapter 29)***

PLATE 2

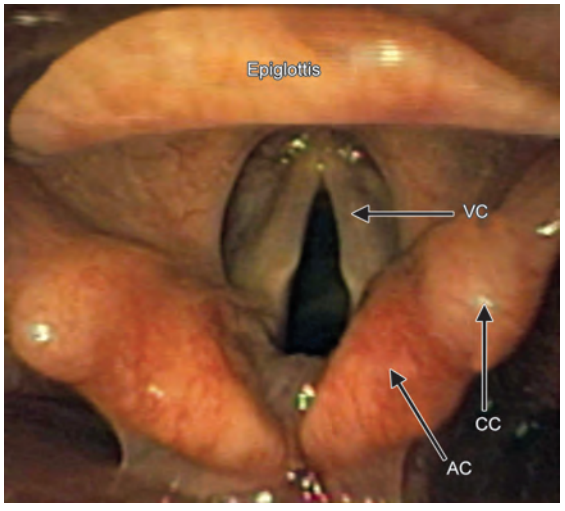
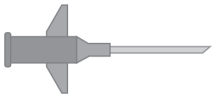
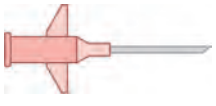
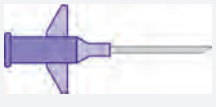
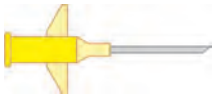


FIG. 7: Laryngoscopic view—anatomy of the laryngeal inlet revealed at direct laryngoscopy. Beneath the epiglottis (E), a view is sought of the whitish vocal cords (VC) in their triangular orientation. The rounded paired posterior (corniculate) cartilages (CC) and arytenoid cartilages (AC) are also shown. ***(Chapter 32)***

FIG. 5: Venturi device. ***(Chapter 36)***

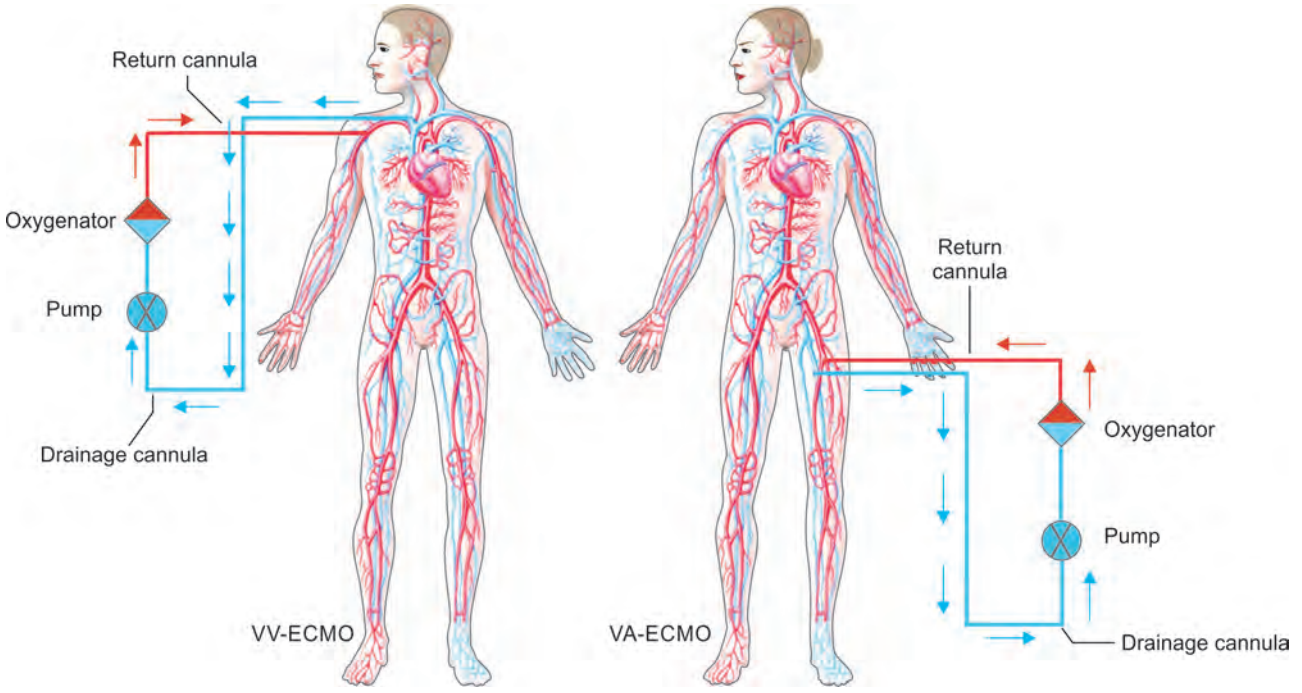
(Chapter 42)

TABLE 3: Selection of peripheral cannula as per prescribed therapy.

Color	*Gauge size*	*External diameter (mm)*	*Length (mm)*	*Water flow rate (mL/min)*	*Recommended uses*
Orange	14G	2.1 mm	45 mm	~240 mL/min	Trauma, Rapid blood transfusion, Surgery[1]
 Gray	16G	1.8 mm	45 mm	~180 mL/min	Rapid fluid replacement, Trauma, Rapid blood transfusion[1]
Green	18G	1.3 mm	32 mm	~90 mL/min	Rapid fluid replacement, Trauma, Rapid blood transfusion[1]
 Pink	20G	1.1 mm	32 mm	~60 mL/min	Most infusions, Rapid fluid replacement, Trauma, Routine blood transfusion[1]
 Blue	22G	0.9 mm	25 mm	~36 mL/min	Most infusions neonate, pediatric, older adults, Routine blood transfusion[1]
 Yellow	24G	0.7 mm	19 mm	~20 mL/min	Most infusions neonate, pediatric, older adults, Routine blood transfusion, Neonate or Pediatric blood transfusion[1]
Purple	26G	0.6 mm	19 mm	~13 mL/min	Pediatrics, Neonate[1]

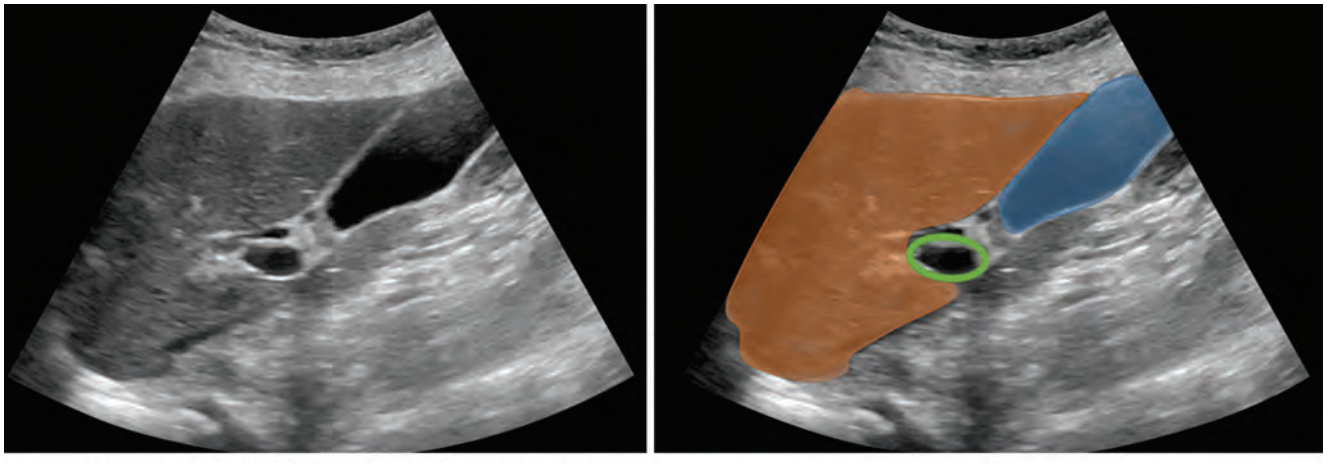
Source: Infusion Therapy Standards of Practice Jan/Feb 20161 https://www.bd.com/infusion/products/ivcatheters/iagbc/videos/pdfs/iagbc_wp3.pdf

PLATE 3



(VA-ECMO: venoarterial extracorporeal membrane oxygenation; VV-ECMO: venovenous extracorporeal membrane oxygenation)

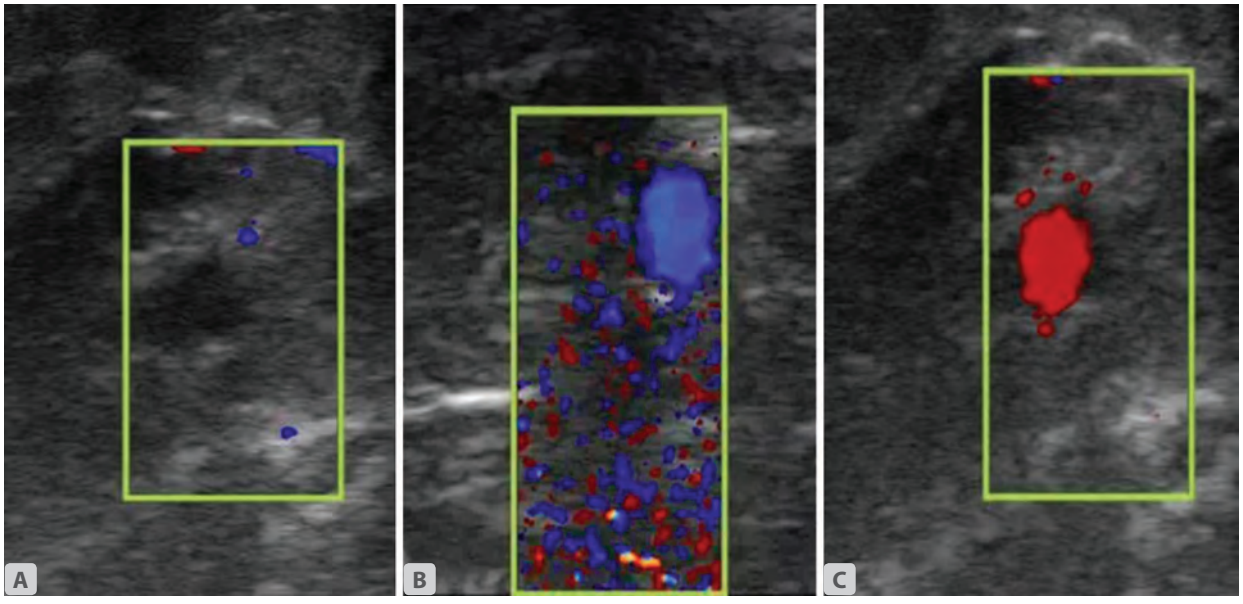
FIG. 1: Typical schematic illustration of VV-ECMO and VA-ECMO supports. ***(Chapter 51)***



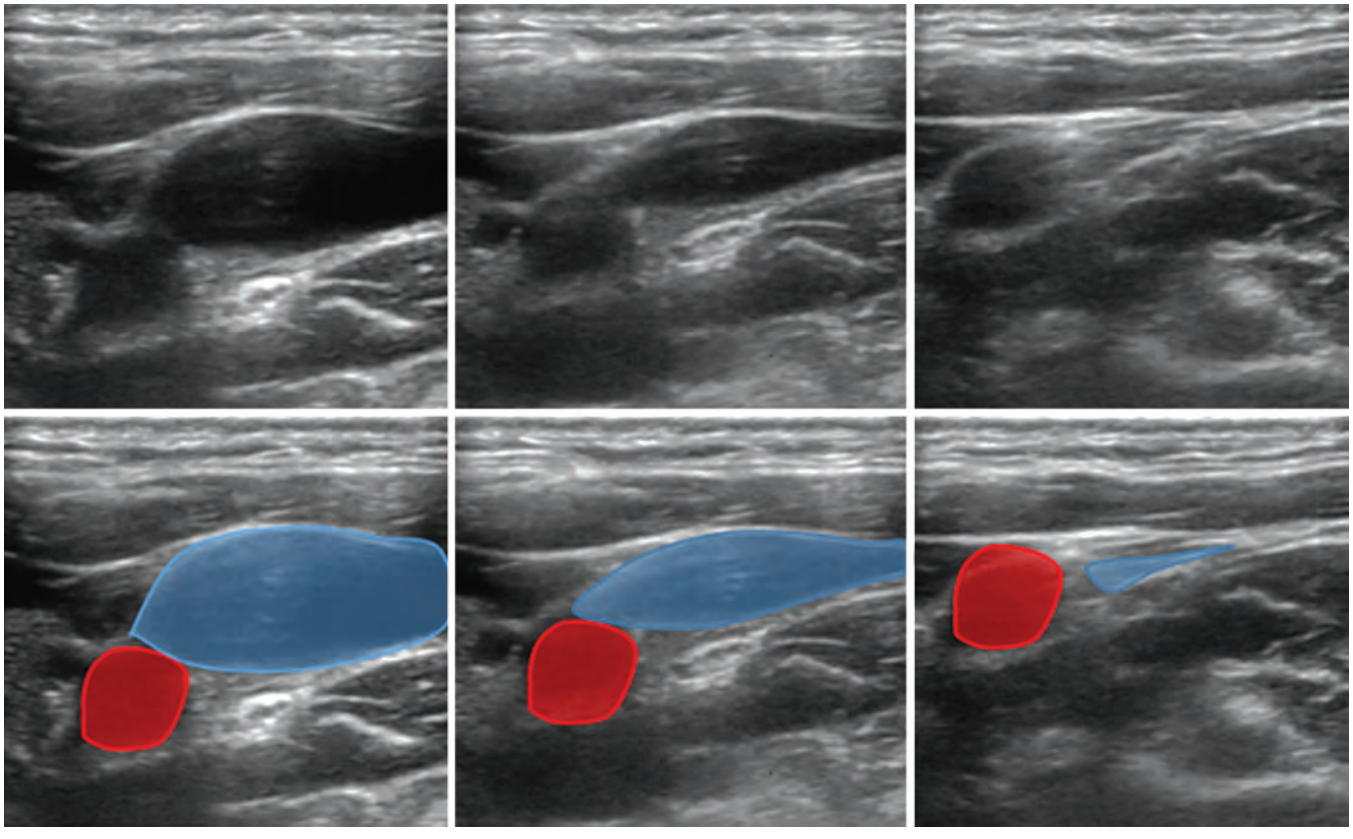
Blue: The gallbladder in longitudinal view is an anechoic structure.
Green: The walls of the portal vein represent a hyperechoic structure.
Orange: The liver parenchyma represents a hypoechoic structure.

FIG. 1: Varying echogenicity of structures seen on ultrasound. ***(Chapter 55)***

PLATE 4



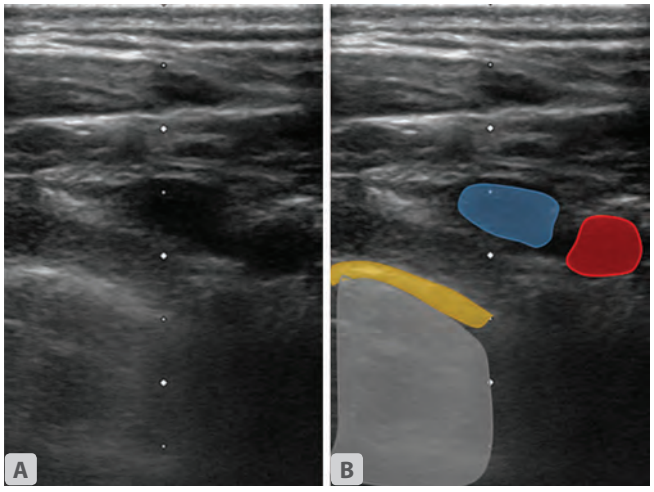
FIGS. 3A TO C: Use of color Doppler to identify vascular flow; (A) A nonvascular structure with no flow seen on Doppler; (B) A vascular structure with flow away from the probe consistent with a vein; (C) A vascular structure with pulsatile flow toward the probe consistent with an artery. ***(Chapter 55)***



(Blue: internal jugular vein; Red: carotid artery. Internal jugular and carotid artery shown from left to right with progressive compressibility of the internal jugular vein)

FIG. 7: Sonographic anatomy of internal jugular vein and carotid artery. ***(Chapter 55)***

PLATE 5



FIGS. 9A AND B: Transverse infraclavicular ultrasound view of the subclavian vessels and lung. ***(Chapter 55)***

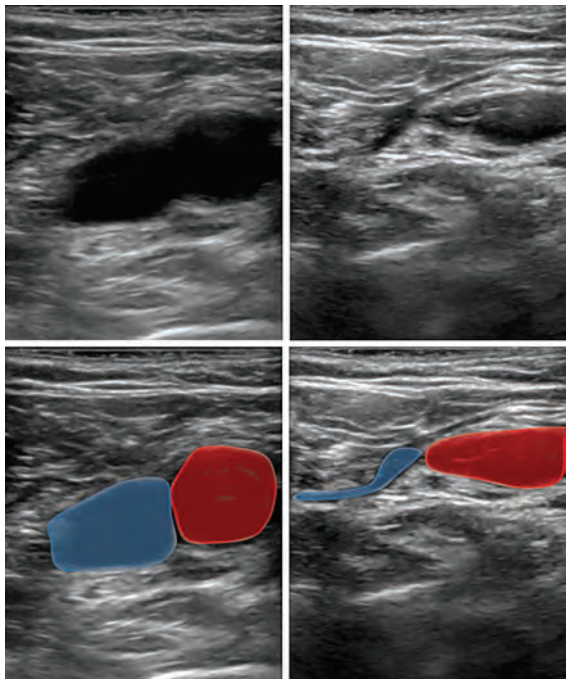
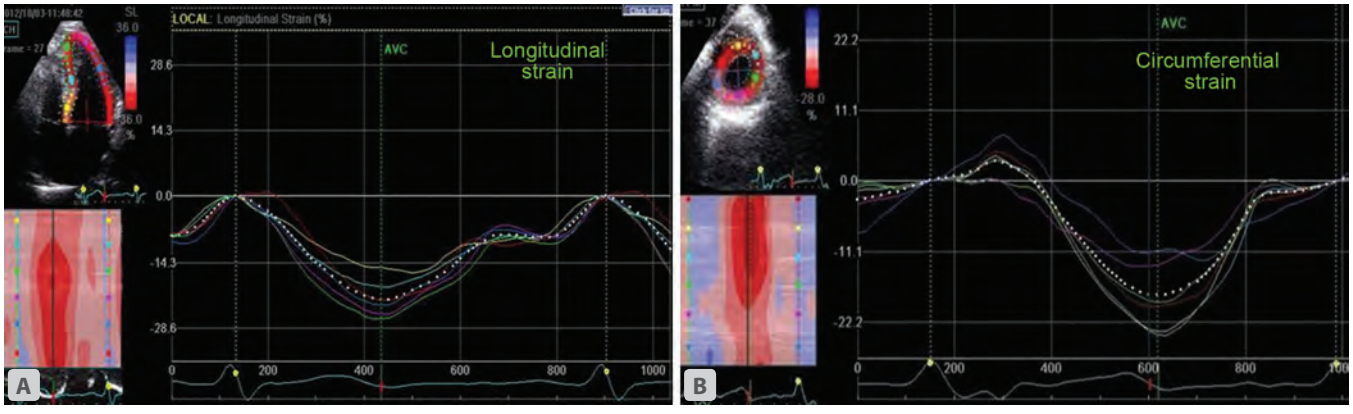


FIG. 11: Ultrasound view of a femoral vasculature with a patent femoral vein. ***(Chapter 55)***



FIGS. 2A AND B: Speckle tracking echocardiography-based measurement of left ventricular longitudinal and circumferential strain. ***(Chapter 63)***

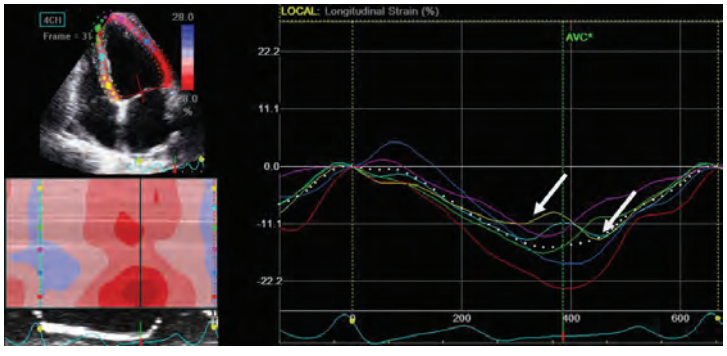
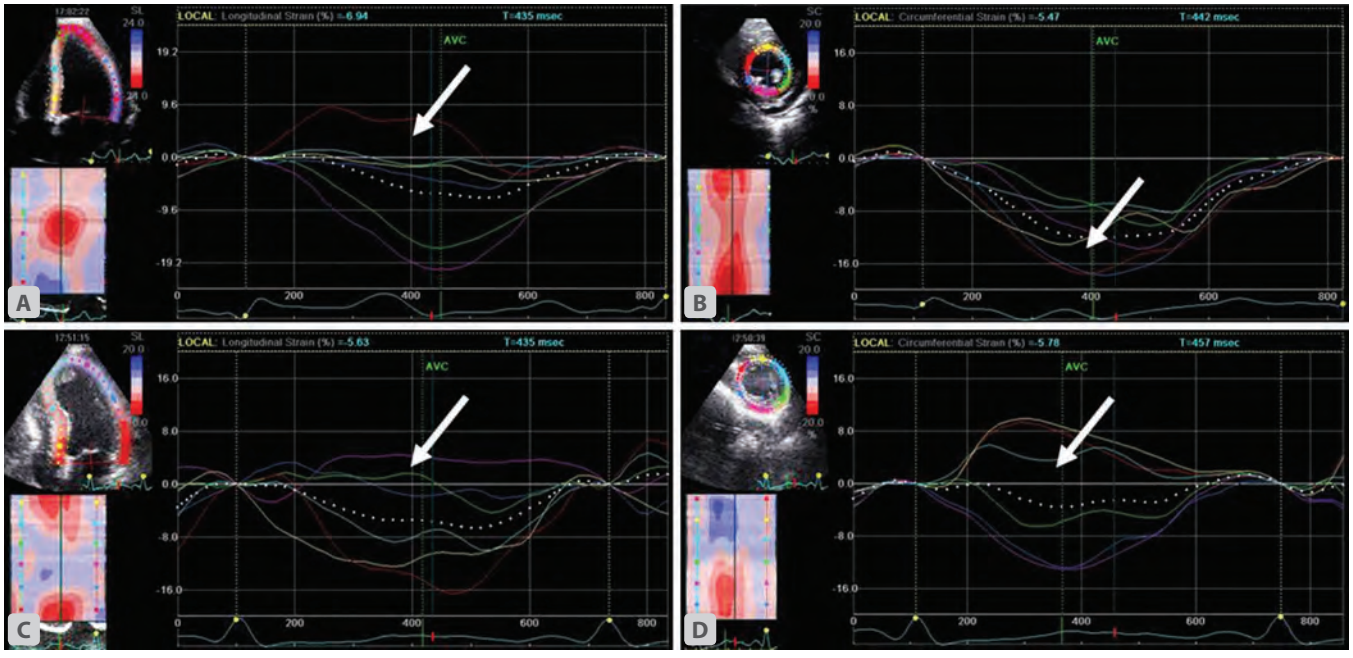
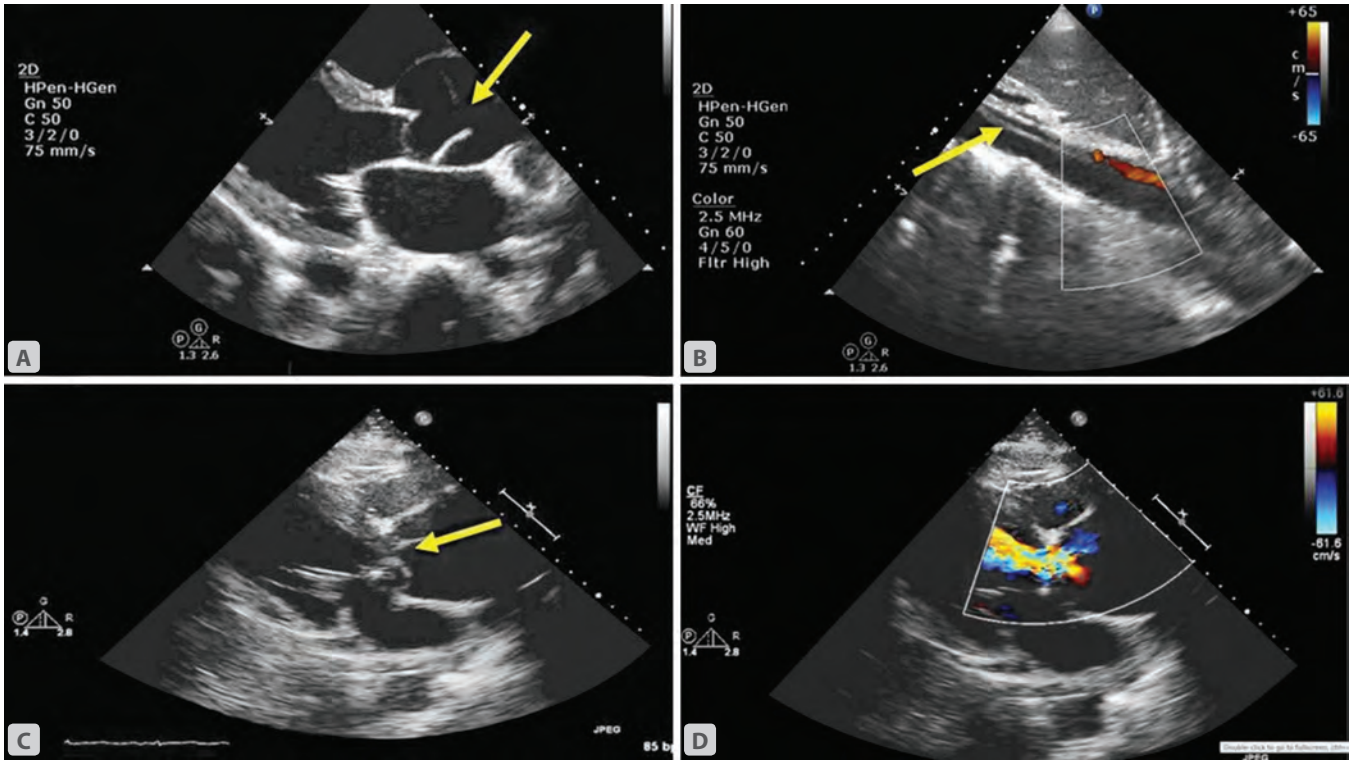


FIG. 4: Reduced systolic longitudinal strain with post-systolic shortening (arrows) in basal septum (yellow trace). ***(Chapter 63)***

PLATE 6

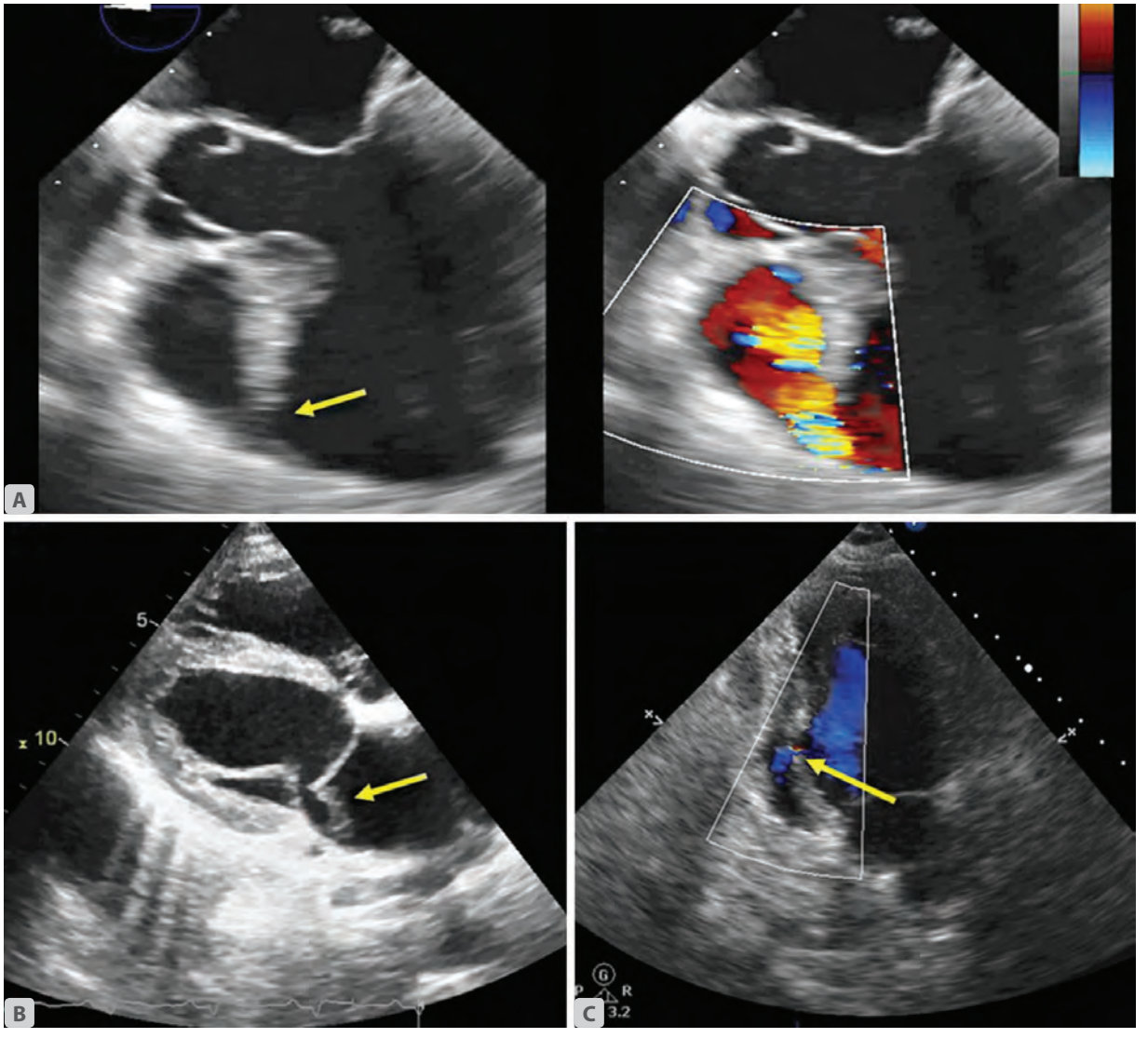


FIGS. 5A TO D: Differential involvement of left ventricular longitudinal and circumferential strain in patients with subendocardial and transmural infarcts. (A and B) Longitudinal strain is impaired (A) but circumferential strain is preserved (B) in basal segments in a patient with subendocardial infarct; (C and D) Both longitudinal and circumferential strains are impaired in apical segments in a patient with transmural infarct. ***(Chapter 63)***



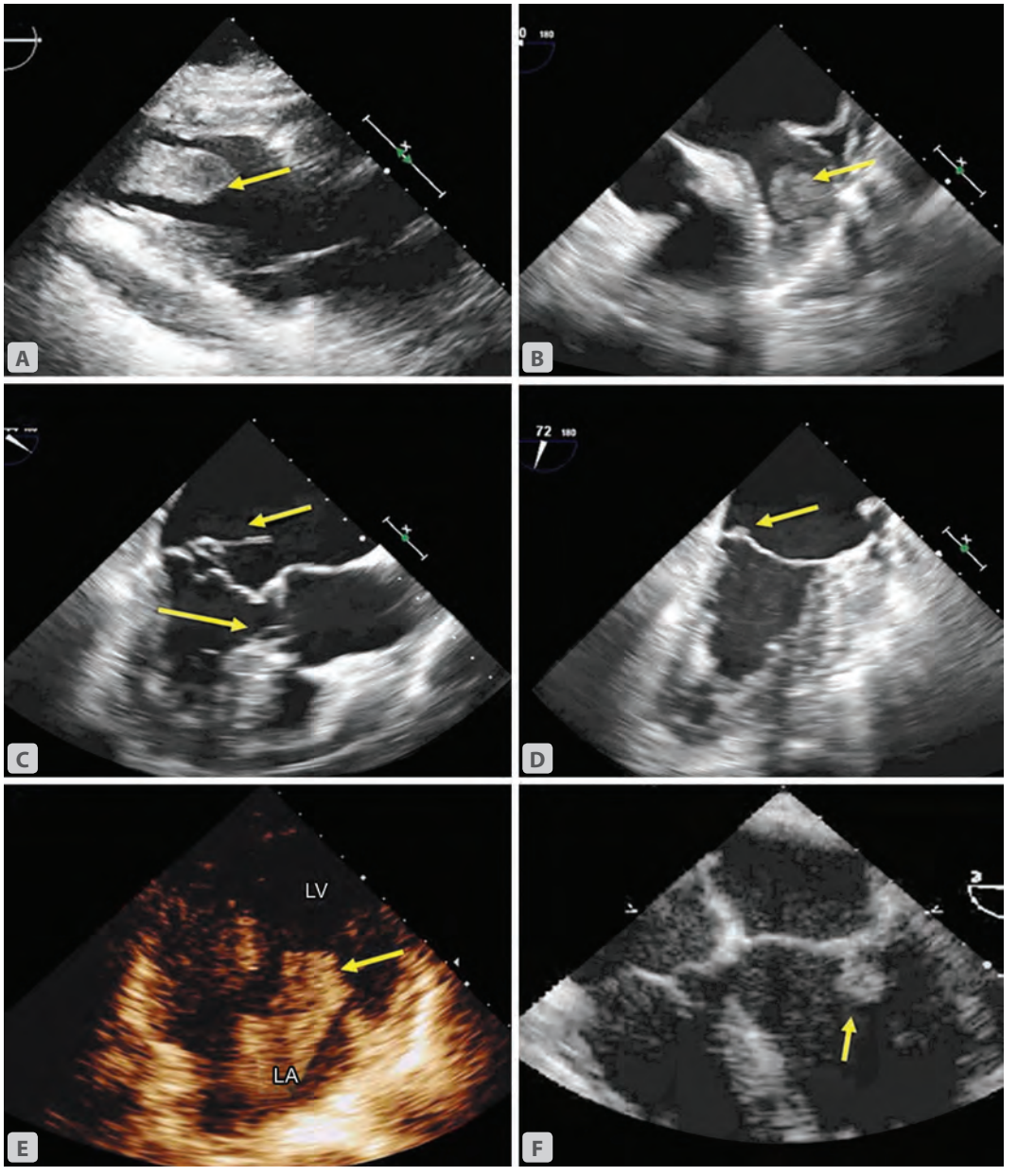
FIGS. 6A TO D: Two examples of acute aortic dissection. (A) Intimal flap (arrow) is seen in the aortic root; (B) In the same patient, the dissection flap (arrow) is seen extending into the abdominal aorta also; (C and D) Intimal flap (C, arrow) in another patient is prolapsing through the aortic valve causing severe aortic regurgitation. ***(Chapter 63)***

PLATE 7



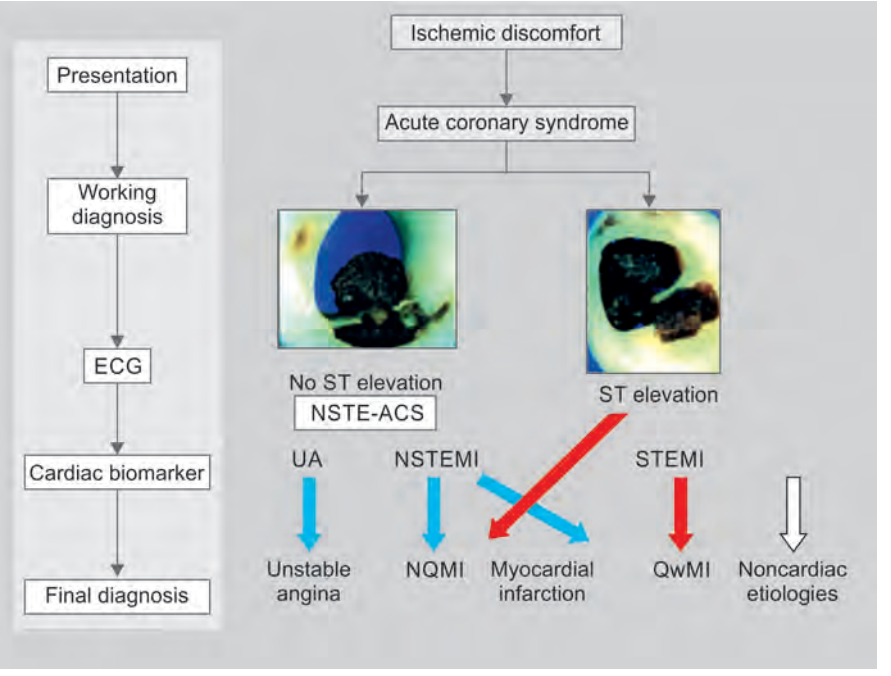
FIGS. 9A TO C: *Examples of mechanical complications of myocardial infarction.* (A) There is apical ventricular septal rupture (arrow) with left to right shunt through the defect; (B) One of the *papillary muscles has got ruptured* and is seen attached to the anterior mitral leaflet and prolapsing into the left atrium. The anterior mitral leaflet itself is flail; (C) Contained *rupture of the inferior wall*. Blood flows through the defect (arrow) into a small pseudoaneurysm. ***(Chapter 63)***

PLATE 8



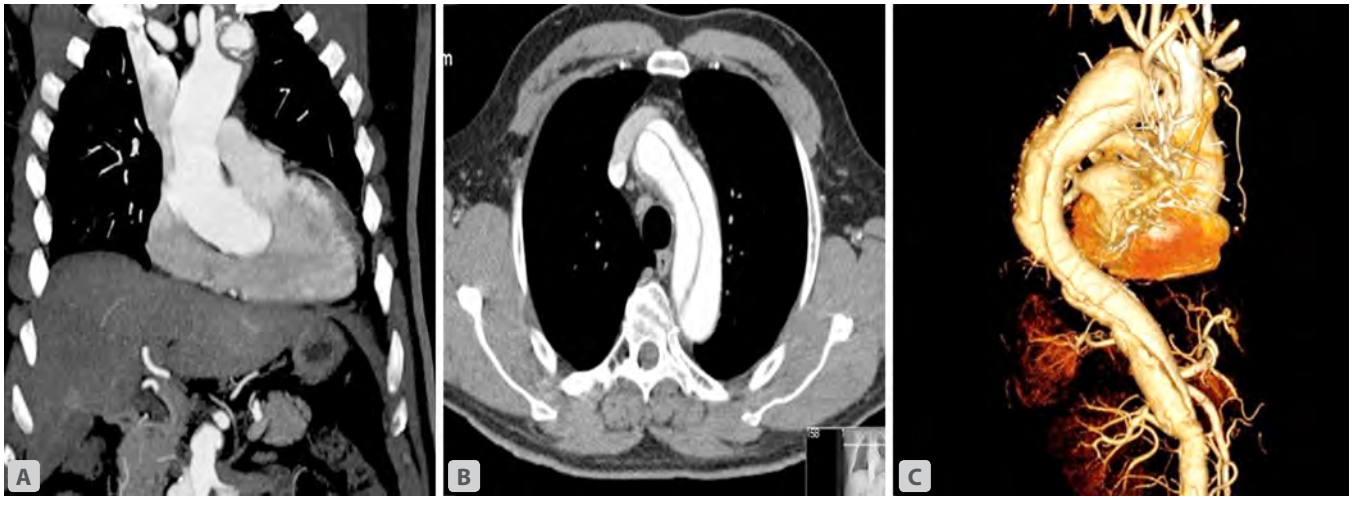
FIGS. 10A TO F: *Common causes of cardioembolic stroke.* (A) Large left ventricular apical clot (arrow) in a patient with anterior wall myocardial infarction; (B) Left atrial appendage clot (arrow); (C) Vegetations (arrows) attached to both mitral and aortic valve leaflets; (D) Sessile vegetation (arrow) on the atrial surface of the mitral leaflet in a patient with non-bacterial thrombotic endocarditis; (E) Large left atrial myxoma (arrow) prolapsing into the left ventricular cavity through the mitral orifice; and (F) Papillary fibroelastoma (arrow) attached to the mitral leaflet. ***(Chapter 63)***

PLATE 9



(ACS: acute coronary syndrome; NSTE-ACS: non-ST elevation ACS: NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina)

FIG. 2: Initial evaluation of an individual presenting with symptoms suggestive of acute coronary syndrome (ACS): ascertaining the type of ACS. ***(Chapter 65)***



FIGS. 5A TO C: (A) Aortic root dilatation; (B) CT angiographic image showing dissection flap in the arch of aorta; (C) CT angiogram in aortic dissection. ***(Chapter 77)***

PLATE 10

FIG. 1: Double-lumen endobronchial tube—blue colored part is the bronchial tube and transparent one is the tracheal tube. ***(Chapter 82)***

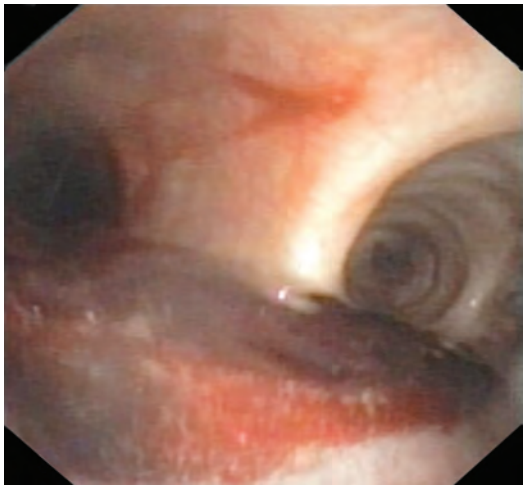
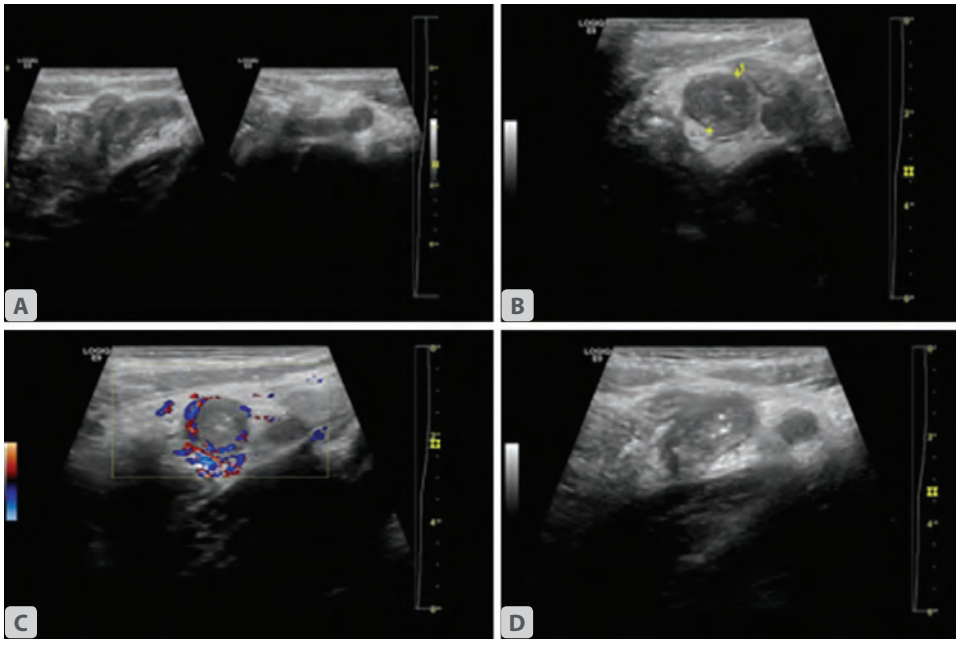


FIG. 5: Bronchoscopy showing bleeding from left main bronchus and spilling into right main bronchus. ***(Chapter 82)***

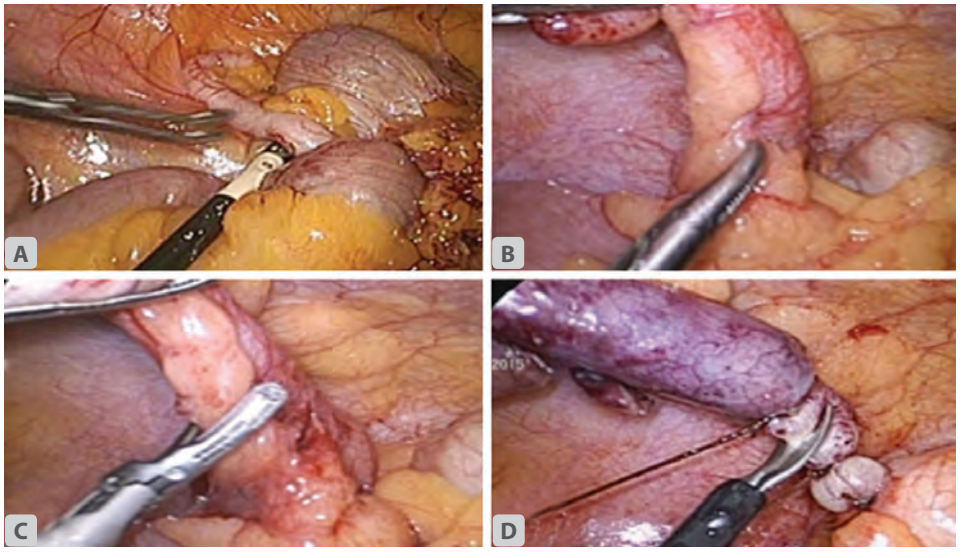
FIG. 1: Grade 4 clubbing of all nails of the hands. ***(Chapter 83)***

FIG. 2: Peripheral cyanosis in one of the hands. ***(Chapter 83)***

PLATE 11

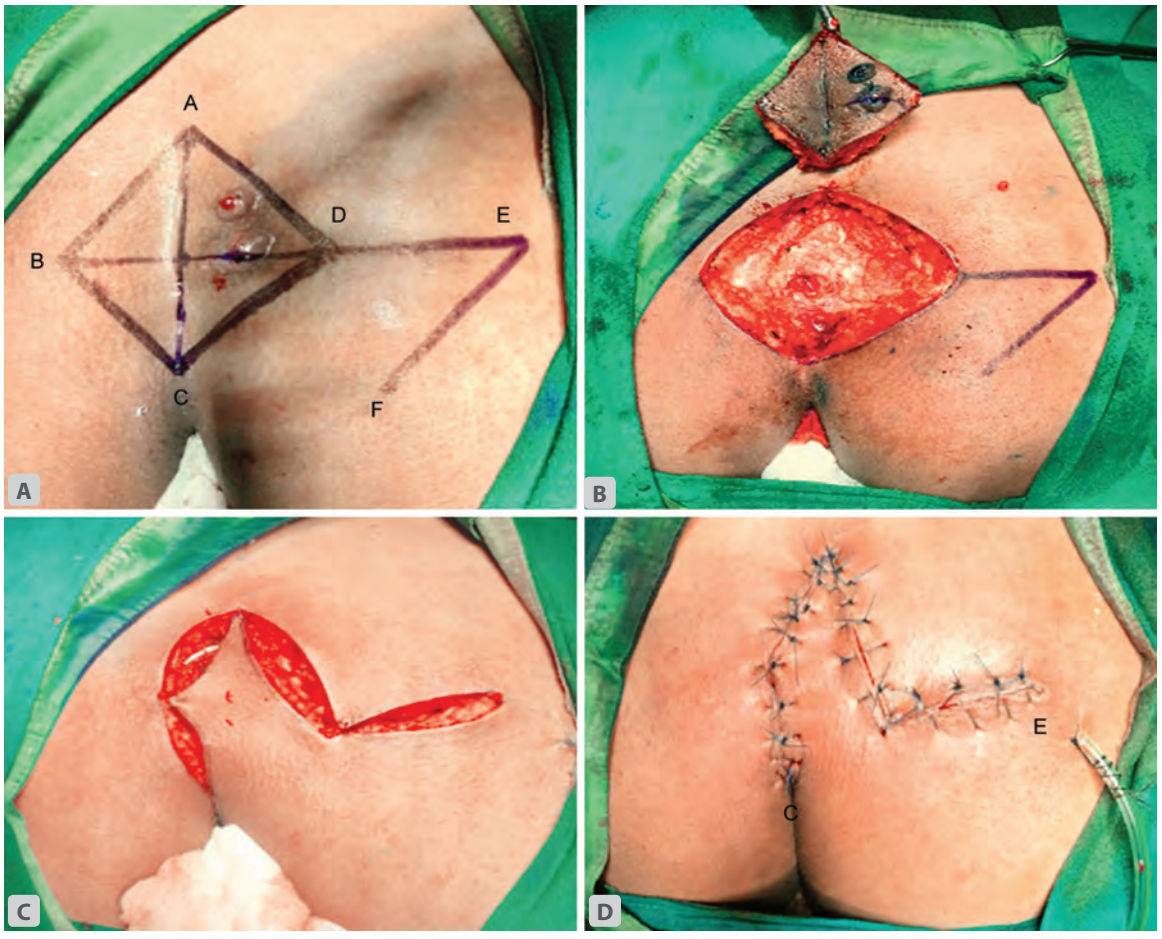


FIGS. 2A TO D: Ultrasonography findings of acute appendicitis. (A) Thickening of the appendiceal wall and increased blood flow (ring of fire appearance); (B) Loss of wall compressibility; (C) Increased echogenicity of the surrounding fat; (D) Loculated pericecal fluid. ***(Chapter 103)***



FIGS. 4A TO D: Laparoscopic appendectomy. (A) Localization; (B) Dissection of mesoappendix; (C) Harmonizing mesoappendix; (D) Endo-loop ligation and division of appendix. ***(Chapter 103)***

PLATE 12



FIGS. 4A TO D: (A) Rhomboid excision with Limberg flap. (B) Rhomboid area to be excised and flap to be taken is marked. (C) Rhomboid excision of diseased tissue is done. (D) Flap created and fixed at points A, B, C, D suction drain in situ. ***(Chapter 104)***

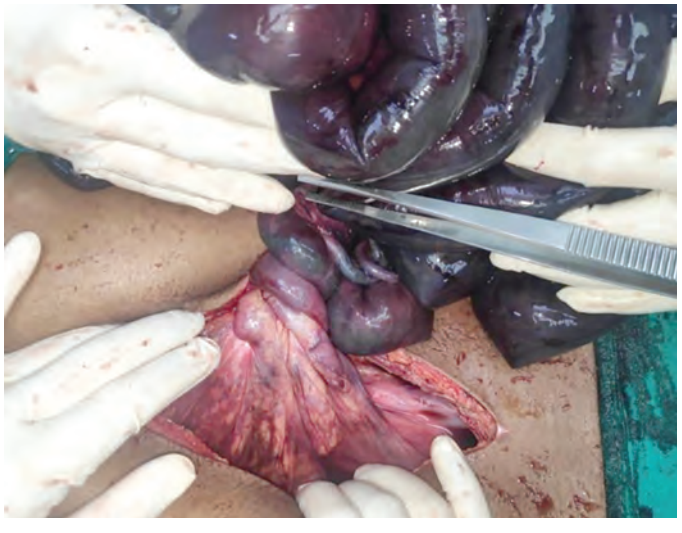


FIG. 4: Surgical resection of gangrenous ischemic bowel. ***(Chapter 105)***

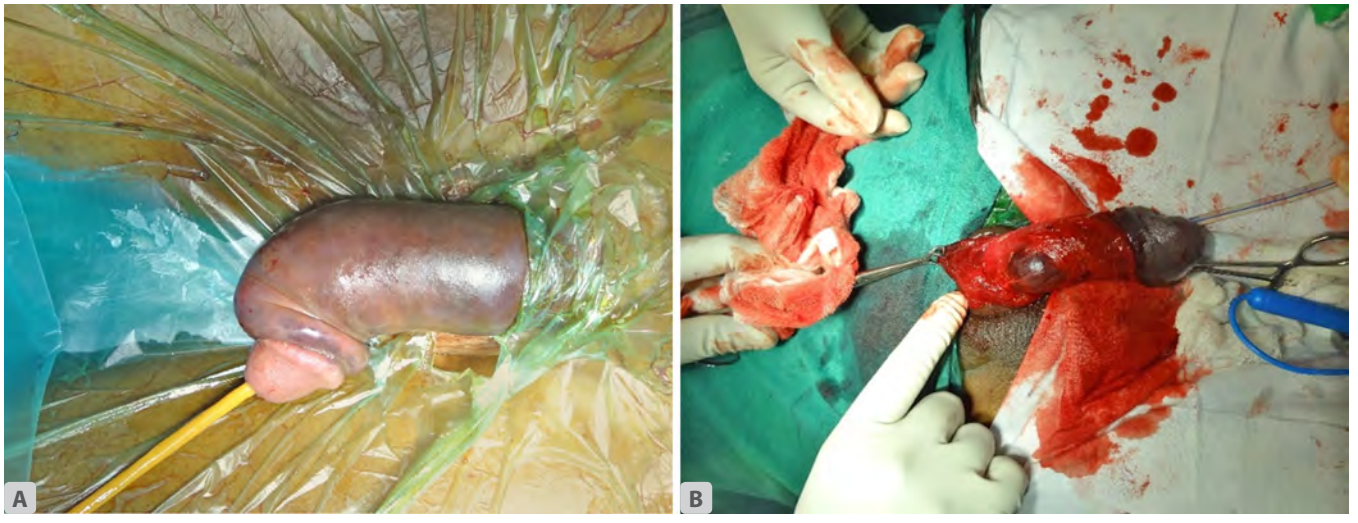
Courtesy: Dr Ashok Puranik.

FIG. 3: Phimosis in a child. ***(Chapter 113)***

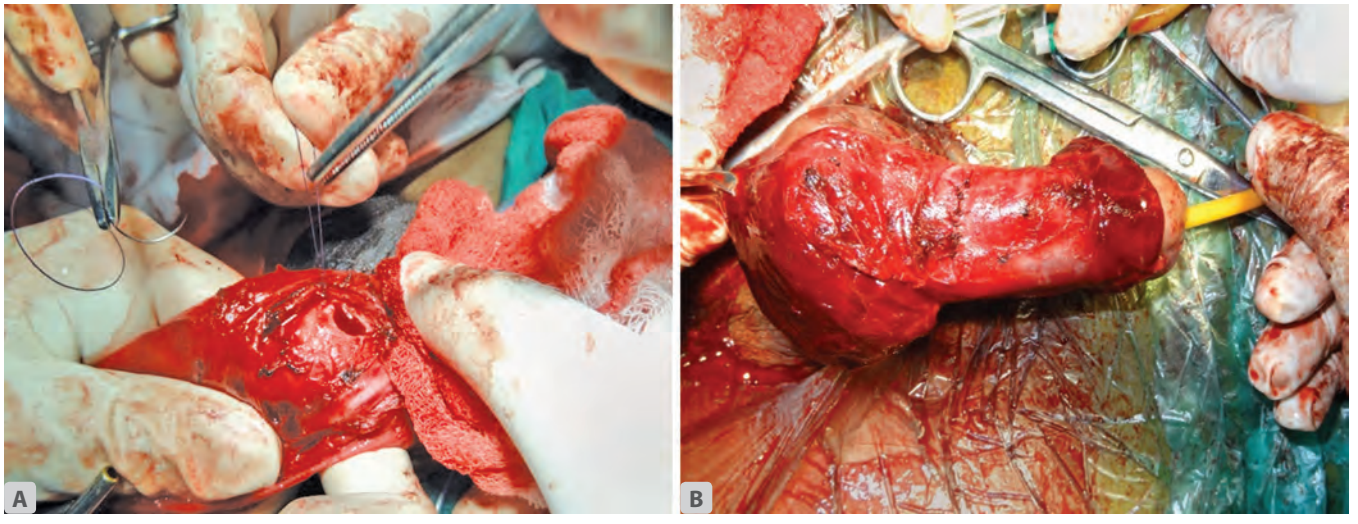
PLATE 13

FIG. 4: Phimosis in an adult. ***(Chapter 113)***

FIG. 5: Paraphimosis in a child. ***(Chapter 113)***



FIGS. 6A AND B: Examination of penile fracture. (A) Eggplant appearance of penile fracture; (B) Hematoma on ventrolateral aspect. ***(Chapter 113)***



FIGS. 7A AND B: Surgical correction of penile fracture. (A) Closure of tunica tear in process; (B) After completion of closure. ***(Chapter 113)***

PLATE 14

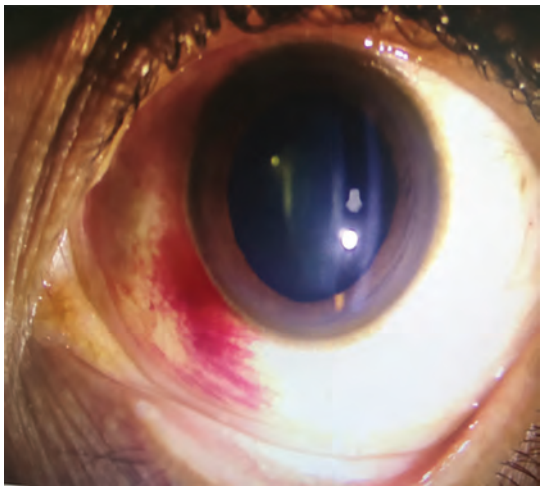


FIG. 1: Subconjunctival hemorrhage. ***(Chapter 133)***

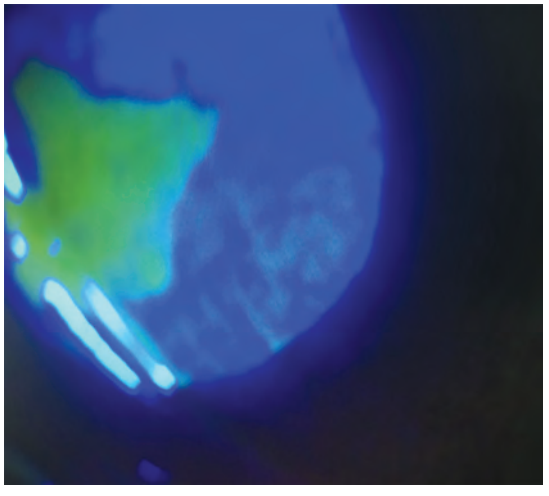


FIG. 2: Corneal abrasion. ***(Chapter 133)***

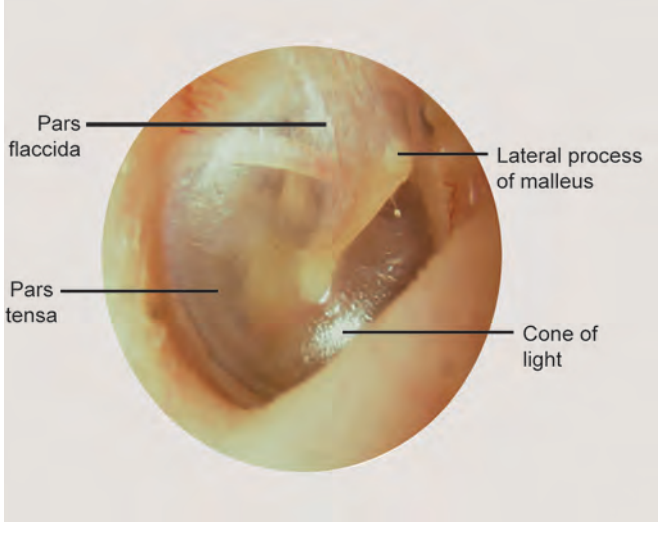


FIG. 2: Normal ear on otoscopic examination. ***(Chapter 134)***

FIG. 3: External ear appearance in otitis externa. ***(Chapter 134)***

FIG. 4: External auditory canal erythema and edema. ***(Chapter 134)***

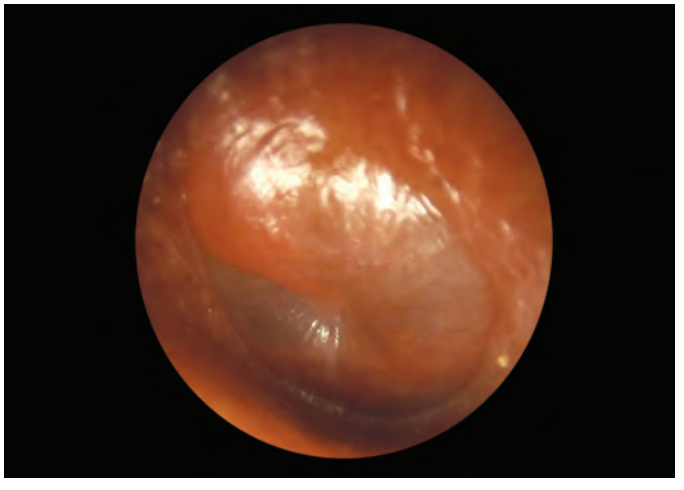


FIG. 5: Otoscopic appearance of external auditory canal and tympanic membrane in otitis media. ***(Chapter 134)***

PLATE 15

FIG. 6: Postauricular erythema and swelling in acute mastoiditis. ***(Chapter 134)***

FIG. 5: Nasal cavity examination. ***(Chapter 135)***

FIG. 7: Otoscopic appearance of tympanic membrane in a bullous myringitis. ***(Chapter 134)***

FIG. 9: Nasal septal hematoma. ***(Chapter 135)***

FIG. 8: Perforated tympanic membrane. ***(Chapter 134)***

FIG. 1: Redness and edema of the oropharynx and petechiae on the soft palate. ***(Chapter 137)***

PLATE 16

FIG. 3: Redness and edema of epiglottis. ***(Chapter 137)***

FIG. 10: Exudative pharyngitis in the throat with mononucleosis. ***(Chapter 137)***

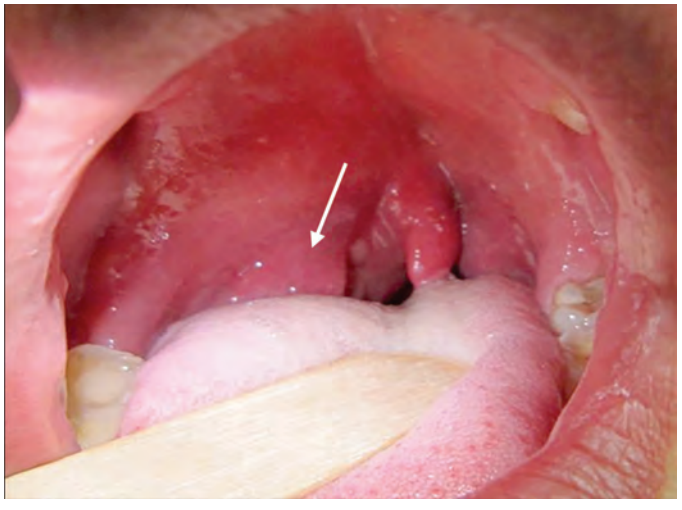


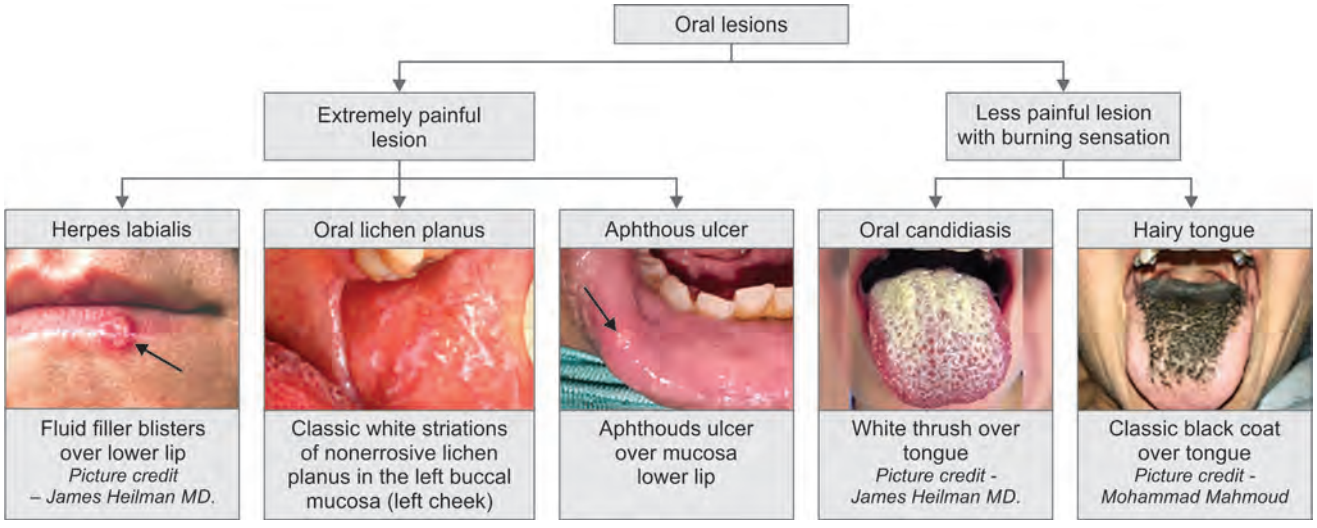
FIG. 5: A right-sided peritonsillar abscess with deviation of uvula to left side. ***(Chapter 137)***

FIG. 12: Hyperplastic candidiasis. ***(Chapter 137)***
Courtesy: Devinder Singh, DNB gastroenterology

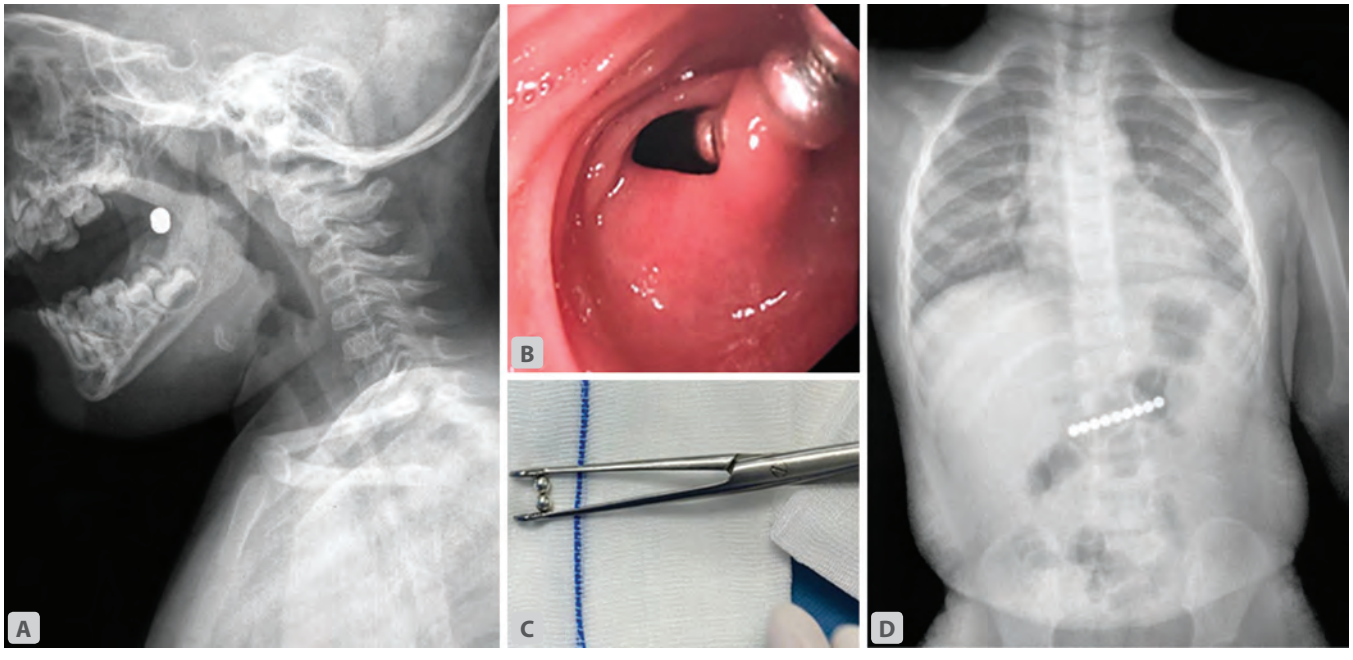
FIG. 6: Swelling of submandibular glands along with swelling of neck and surrounding tissue. ***(Chapter 137)***

FIG. 14: Vesicles/blisters around the lips. ***(Chapter 137)***

PLATE 17


Oral lesions
Extremely painful lesion
Less painful lesion with burning sensation
Herpes labialis
Oral lichen planus
Aphthous ulcer
Oral candidiasis
Hairy tongue
Fluid filler blisters over lower lip
Picture credit – James Heilman MD.
Classic white striations of nonerrosive lichen planus in the left buccal mucosa (left cheek)
Aphthouds ulcer over mucosa lower lip
White thrush over tongue
Picture credit - James Heilman MD.
Classic black coat over tongue
Picture credit - Mohammad Mahmoud

FLOWCHART 4: Evaluation of oral lesions. ***(Chapter 137)***



FIGS. 11A TO D: Child who presented after pain and dysarthria after being found playing with magnets. (A) Lateral X-ray revealed two circular and superimposed densities within the oral cavity. (B): Bronchoscopy revealed the patient's uvula to be entrapped between two magnets. (C) Removed spherical magnets. (D) X-ray of the chest and abdomen revealed multiple secondary ingested foreign bodies within the abdomen forming a sequential chain within the intestine. ***(Chapter 138)***

PLATE 18

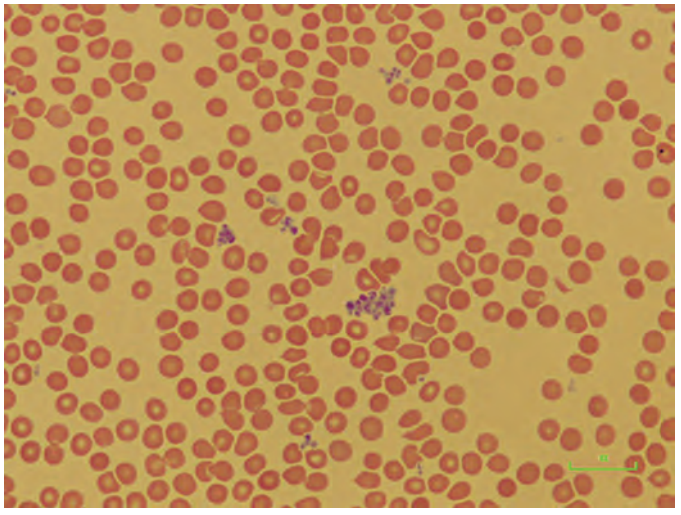


FIG. 1: Platelet clumping. Not an emergency but can give an erroneously low platelet count. ***(Chapter 140)***

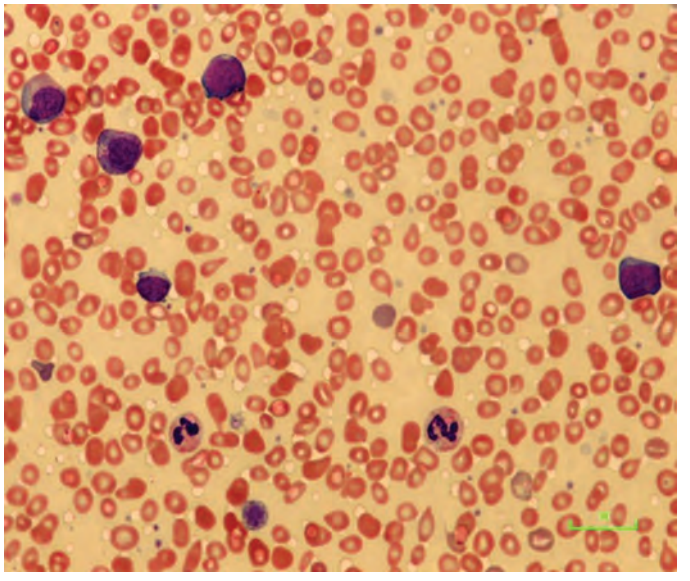
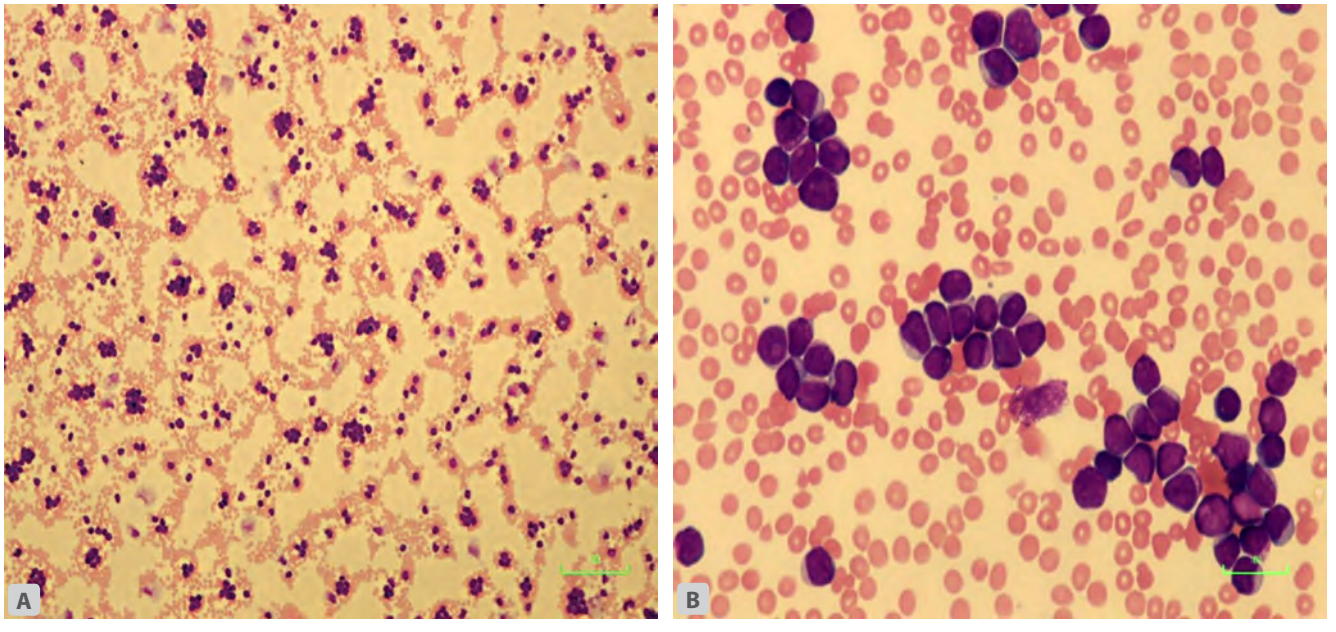


FIG. 1: Slide of acute myeloid leukemia, myelocytes, myeloid blast, dysplastic giant platelets, and polychromasia. ***(Chapter 141)***



FIGS. 2A AND B: (A) Slide shows hyperleukocytosis in a patient with acute myeloid leukemia (AML). (B) Slide shows myeloid blasts seen in the AML with hyperleukocytosis. Myeloid blasts contain granules, best seen in the highlighted cells. ***(Chapter 141)***

PLATE 19

(Chapter 148)

TABLE 1: Primary skin lesions.

S. No.	*Type of lesion*	*Description*	*Example*
1.	Macule	A circumscribed area of skin or mucous membrane different in color or texture from its neighboring tissue, measuring <1 cm in diameter.	
2.	Patch	A circumscribed area of skin or mucous membrane different in color or texture from its neighboring tissue, measuring >1 cm in diameter.	
S. No.	*Type of lesion*	*Description*	*Example*
3.	Papule	A small solid, elevation of the skin <1 cm in diameter.	

Continued

PLATE 20

Continued

4.	Plaque	A solid elevated area of skin >1 cm in diameter, where the horizontal dimensions are more than vertical.	
5.	Nodule	A solid elevated area of skin >1 cm in diameter, which can be observed as an elevation or can be palpated.	
6.	Vesicle	A circumscribed elevated area of skin <1 cm in diameter, containing fluid other than pus.	
S. No.	***Type of lesion***	***Description***	***Example***
7.	Bulla	A circumscribed elevated lesion of >1 cm in diameter containing free fluid other than pus.	

Continued

PLATE 21

Continued

8.	Pustule	A circumscribed area of the skin of any size containing visible purulent exudate.	
9.	Cyst	A closed cavity or sac with an epithelial, endothelial, or membranous lining, containing fluid or semisolid material.	
10.	Wheal	An elevated, evanescent compressible area due to dermal edema. It is pale and often surrounded by a dermal flare.	

PLATE 22

(Chapter 148)

TABLE 2: Secondary skin lesion.

S. No.	*Type of lesion*	*Description*	*Example*
1.	Erosion	Loss of whole or part of the epidermis, but with the dermis left intact, and which heals without scarring.	
2.	Ulcer	A breach in continuity of the epidermis and at least a part of dermis, associated with necrosis of tissue and which heals with scarring.	
3.	Excoriation	Loss of substance of skin produced by scratching (linear erosions).	
4.	Scale	Visible exfoliation of skin.	

Continued

PLATE 23

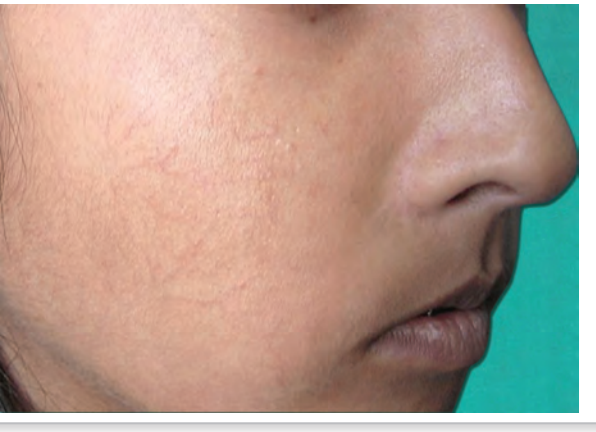
Continued

S. No.	Type of lesion	Description	Example
5.	Crust	Accumulation of dried up exudate, secretion, or hemorrhage on the skin surface as a result of its disruption.	
6.	Scar	A visible alteration in the appearance of the skin due to fibrous tissue replacing normal tissues destroyed by disease or injury.	
7.	Lichenification	Thickening of the skin with exaggeration of its normal marking often as a result of chronic scratching or rubbing.	
8.	Sclerosis	Circumscribed or diffuse hardening of skin usually due to fibrosis.	

PLATE 24

(Chapter 148)

TABLE 3: Special lesions.

Special lesions		
Burrow	A passage or a tunnel in the skin that houses a parasite, e.g., scabies.	
Comedones	A plug of keratin or a sebum in a dilated pilosebaceous orifice, e.g., acne vulgaris.	
Purpura	Discoloration of skin due to extravasation of blood. • If >2 cm in diameter—ecchymosis • If <2 cm (pin point)—petechiae • If linear, it is called vibex	
Telangiectasias	Permanent dilatation of capillaries.	

Continued

PLATE 25

Continued

Special lesions		
Fissure	A small linear gap or slit in the skin surface.	
Sinus	A closed cavity or channel that permits the escape of pus or fluid.	
Milium	A tiny white superficial cyst with an epidermal lining containing keratin.	

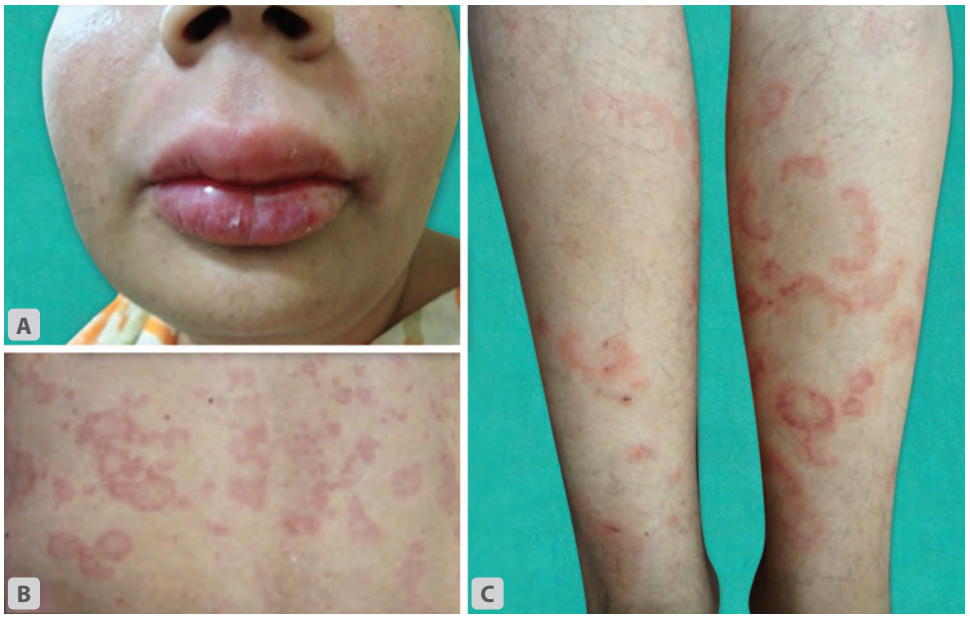
PLATE 26

FIGS. 1A TO C: (A and B) Epidermal involvement in Stevens–Johnson syndrome (SJS); (C) Toxic epidermal necrolysis (TEN). ***(Chapter 149)***

FIG. 2: Pyoderma gangrenosum. ***(Chapter 149)***

FIGS. 3A AND B: Necrotizing fasciitis. ***(Chapter 149)***

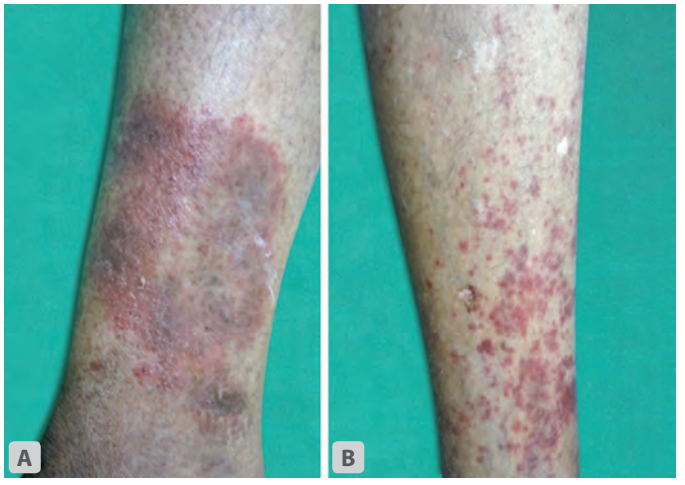
PLATE 27



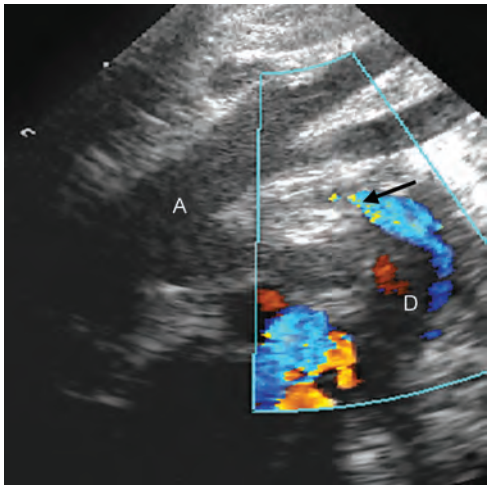
FIGS. 4A TO C: (A) Angioedema; (B and C) Urticaria. ***(Chapter 149)***

FIGS. 5A AND B: (A) Pemphigus vulgaris; (B) Pemphigus fallacious. ***(Chapter 149)***

PLATE 28



FIGS. 6A AND B: Vasculitis. ***(Chapter 149)***



(AAO: ascending aorta, DAO: descending aorta)

FIG. 3: Echocardiography with color flow mapping of a neonate with aortic arch interruption, restrictive PDA and LV dysfunction. Suprasternal long axis view showing arch interruption, small PDA (black arrow) filling descending aorta. ***(Chapter 170)***

FIGS. 7A TO D: Psoriasis. ***(Chapter 149)***

PLATE 29

FIGS. 1A AND B: Pediatric oral and dental trauma. (A) 12 years of age female that fell while riding her bike and sustained oral/dental injuries. (B) 3 years of age male that fell onto a concrete sidewalk and sustained a dental injury. ***(Chapter 173)***

FIG. 3: Frenulum laceration. 18-month-old male that fell and sustained frenulum laceration. No intervention was required and he was discharged to home. ***(Chapter 173)***

FIGS. 4A AND B: Tongue laceration. (A) 8 years of age male who sustained tongue laceration while jumping on a trampoline. (B) Laceration repaired with horizontal mattress sutures in the ED with procedural sedation. ***(Chapter 173)***

PLATE 30

FIG. 1: Miliaria rubra. ***(Chapter 174)***

FIG. 2: Neonatal acne. ***(Chapter 174)***

FIG. 3: Transient pustular melanosis. ***(Chapter 174)***

FIG. 4: Infantile acropustulosis. ***(Chapter 174)***

FIG. 5: Erythema toxicum. ***(Chapter 174)***

FIG. 6: Seborrheic dermatitis. ***(Chapter 174)***

PLATE 31

FIG. 7: Oral candidiasis. ***(Chapter 174)***

FIG. 8: Irritant diaper dermatitis. ***(Chapter 174)***

FIG. 9: *Candida* diaper rash. ***(Chapter 174)***

FIG. 10: Drool rash. ***(Chapter 174)***

PLATE 32

FIGS. 11A TO E: Infantile scabies. ***(Chapter 174)***

FIG. 12: Infantile eczema. ***(Chapter 174)***

FIG. 13. Mongolian spot. ***(Chapter 174)***

PLATE 33

FIG. 14: Neurofibromatosis with axillary freckling (Crowe sign). ***(Chapter 174)***

FIG. 17. Cutis marmorata. ***(Chapter 174)***

FIG. 15: Darier sign for urticaria pigmentosa. ***(Chapter 174)***

FIG. 18: Harlequin color change. ***(Chapter 174)***

FIG. 16: Incontinentia pigmenti. ***(Chapter 174)***

FIG. 19: Nevus flammeus. ***(Chapter 174)***

PLATE 34

FIG. 20: Strawberry hemangioma. ***(Chapter 174)***

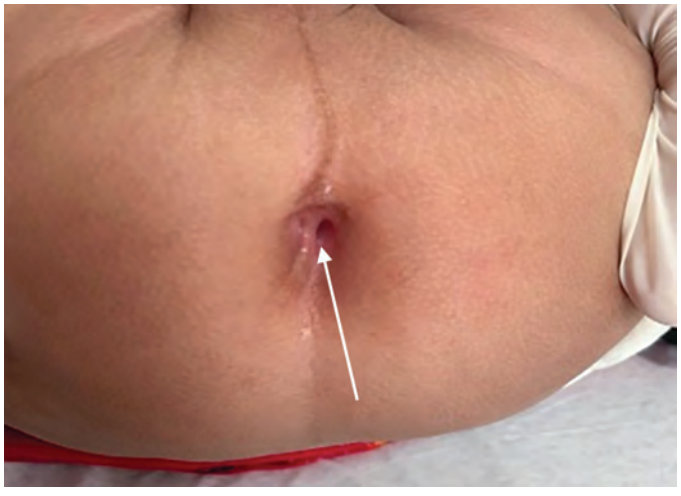
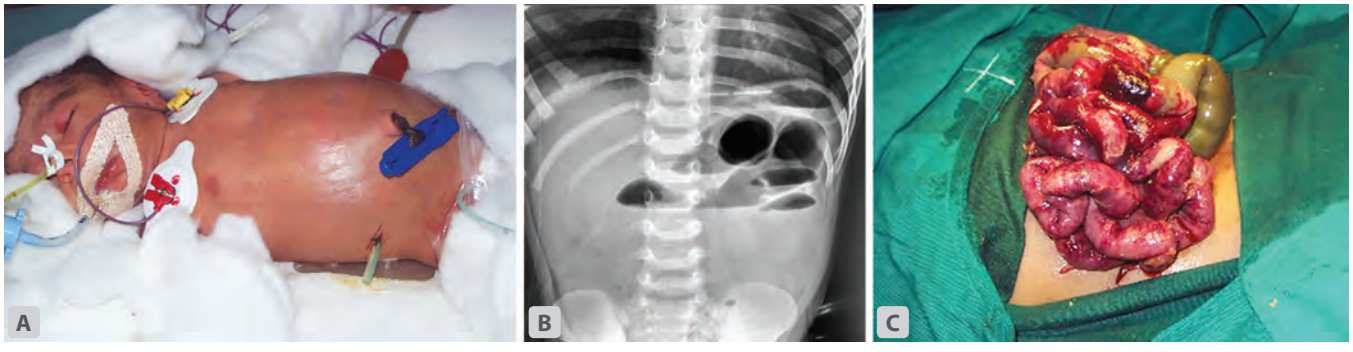
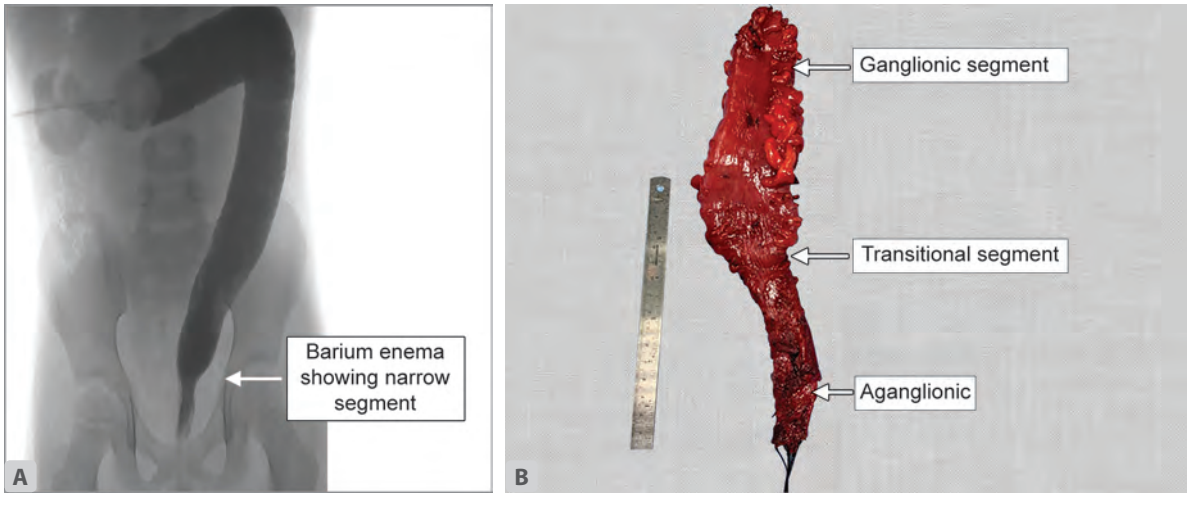


FIG. 3: Anal dimple—anorectal malformation (ARM). ***(Chapter 176)***

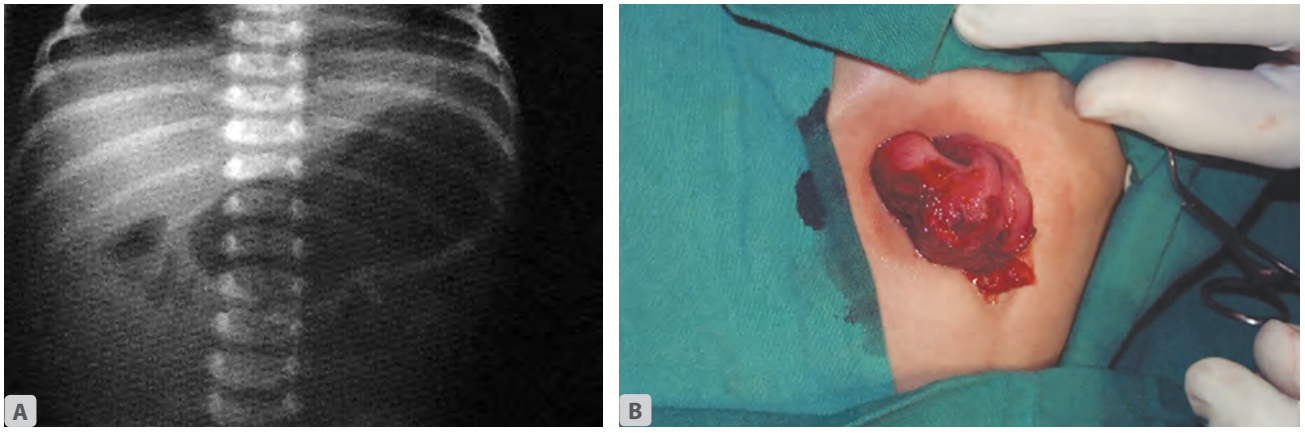


FIGS. 1A TO C: (A) Clinical picture of neonatal necrotizing enterocolitis (NNEC); (B) X-ray abdomen showing multiple air fluid levels; (C) intestinal gangrene ***(Chapter 176)***

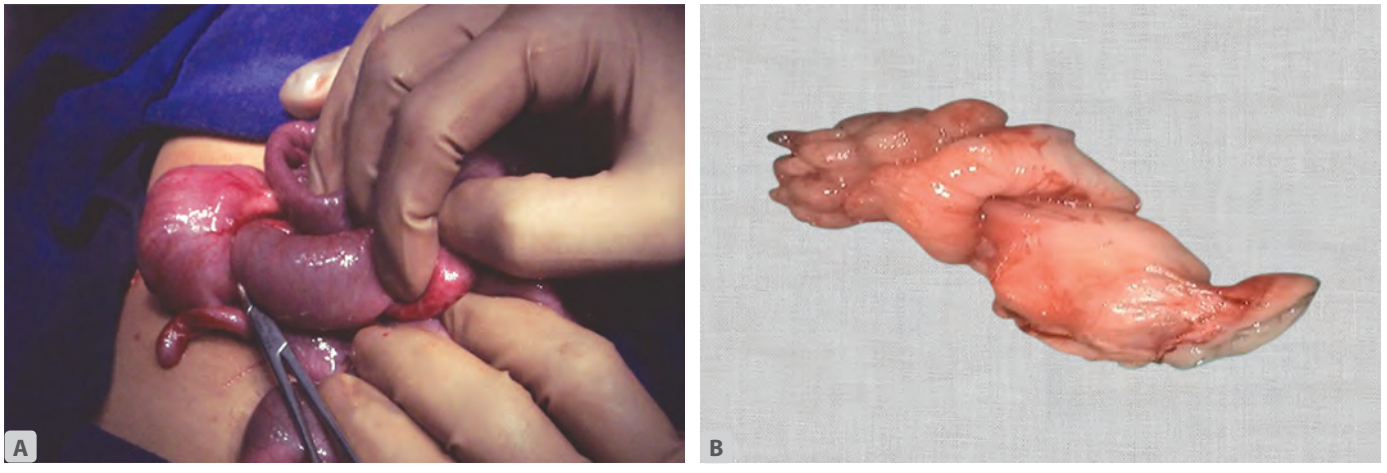


FIGS. 4A AND B: (A) Barium study in Hirschsprung's disease; (B) intraoperative Hirschsprung's specimen. ***(Chapter 176)***

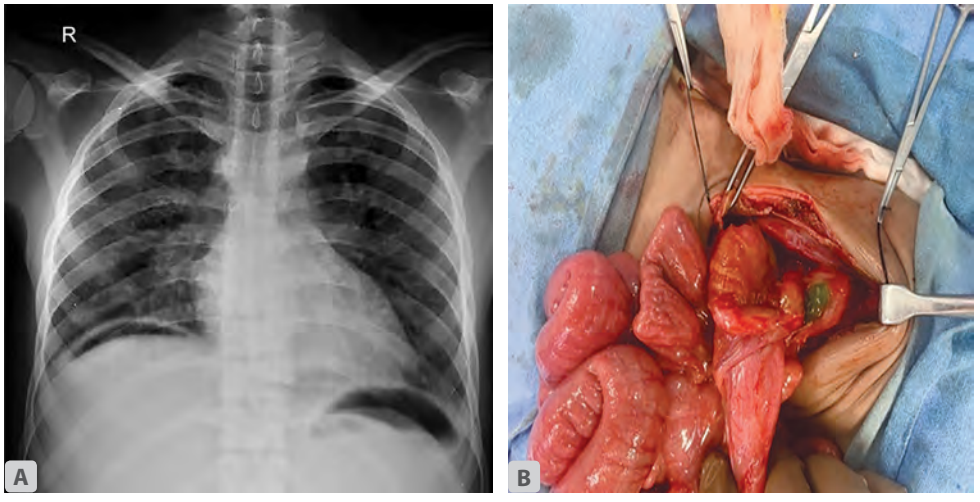
PLATE 35



FIGS. 5A AND B: (A) X-ray pyloric stenosis; **(**B**)** intraoperative specimen pyloric stenosis. ***(Chapter 176)***

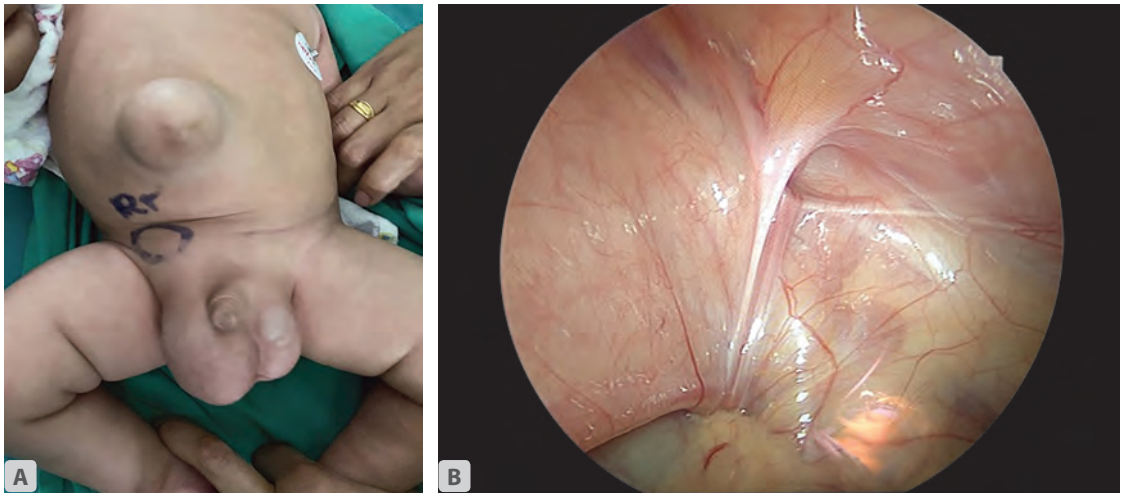


FIGS. 6A AND B: (A) Intussusception; (B) resected specimen. ***(Chapter 176)***



FIGS. 7A AND B: (A) X-ray showing air under the diaphragm; (B) Intestinal perforation. ***(Chapter 176)***

PLATE 36



FIGS. 8A AND B: (A) Irreducible swelling right inguinal and umbilical hernia; (B) laparoscopic correction. ***(Chapter 176)***

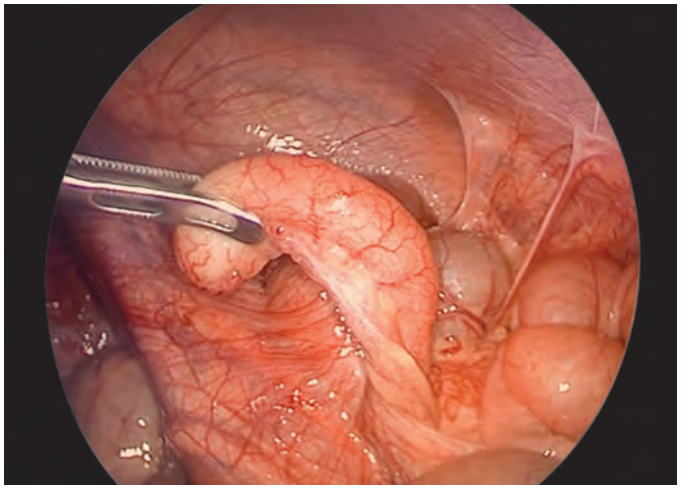
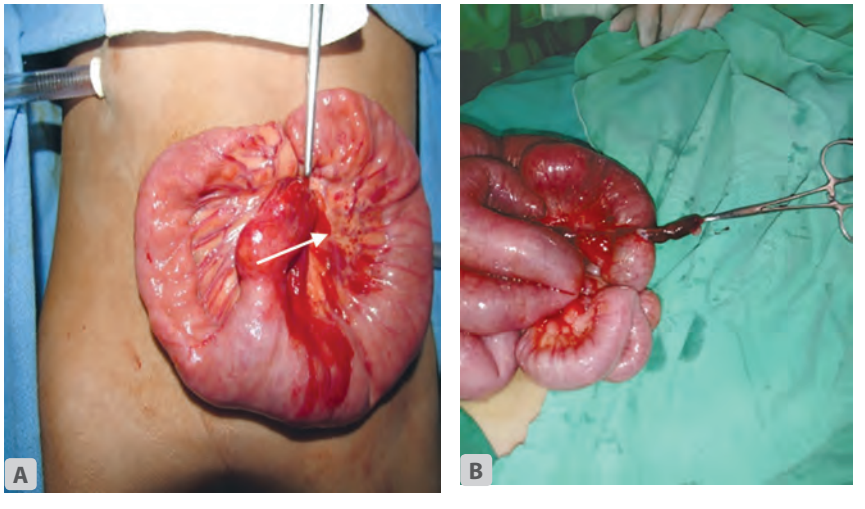


FIG. 10: Appendix (laparoscopic view). ***(Chapter 176)***



FIGS. 11A AND B: (A) Meckel's diverticulum; (B) Meckel's gangrenous. ***(Chapter 176)***

PLATE 37

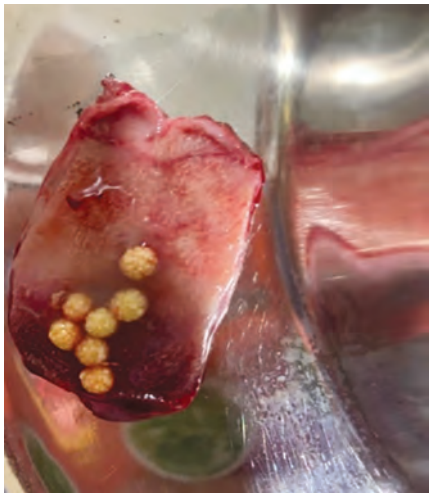


FIG. 12: Gallstones. ***(Chapter 176)***

FIG. 4: *Physostigma venenosum*—calabar bean. ***(Chapter 200)***

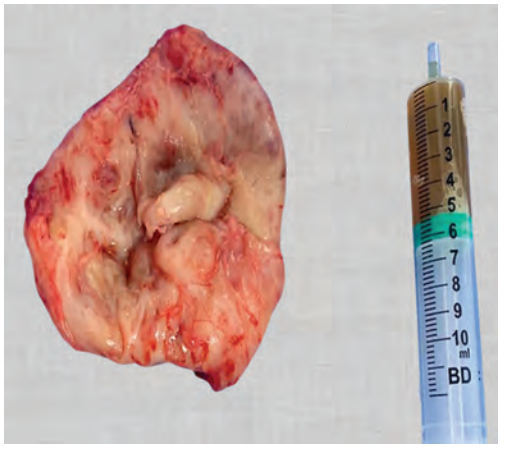


FIG. 14: Mesenteric cyst. ***(Chapter 176)***

FIG. 1: *Thevetia peruviana* (yellow oleander). ***(Chapter 215)***
Courtesy: Avighna Richhariya.

FIG. 3: Greenish frothy fluid oozing out of mouth and nose—dichlorvos poisoning. ***(Chapter 200)***
Courtesy: Dr Swapnil Agarwal.

FIG. 2: *Nerium odorum* (pink oleander). ***(Chapter 215)***
Courtesy: Avighna Richhariya.

PLATE 38

FIG. 2: Septal hematoma. ***(Chapter 222)***

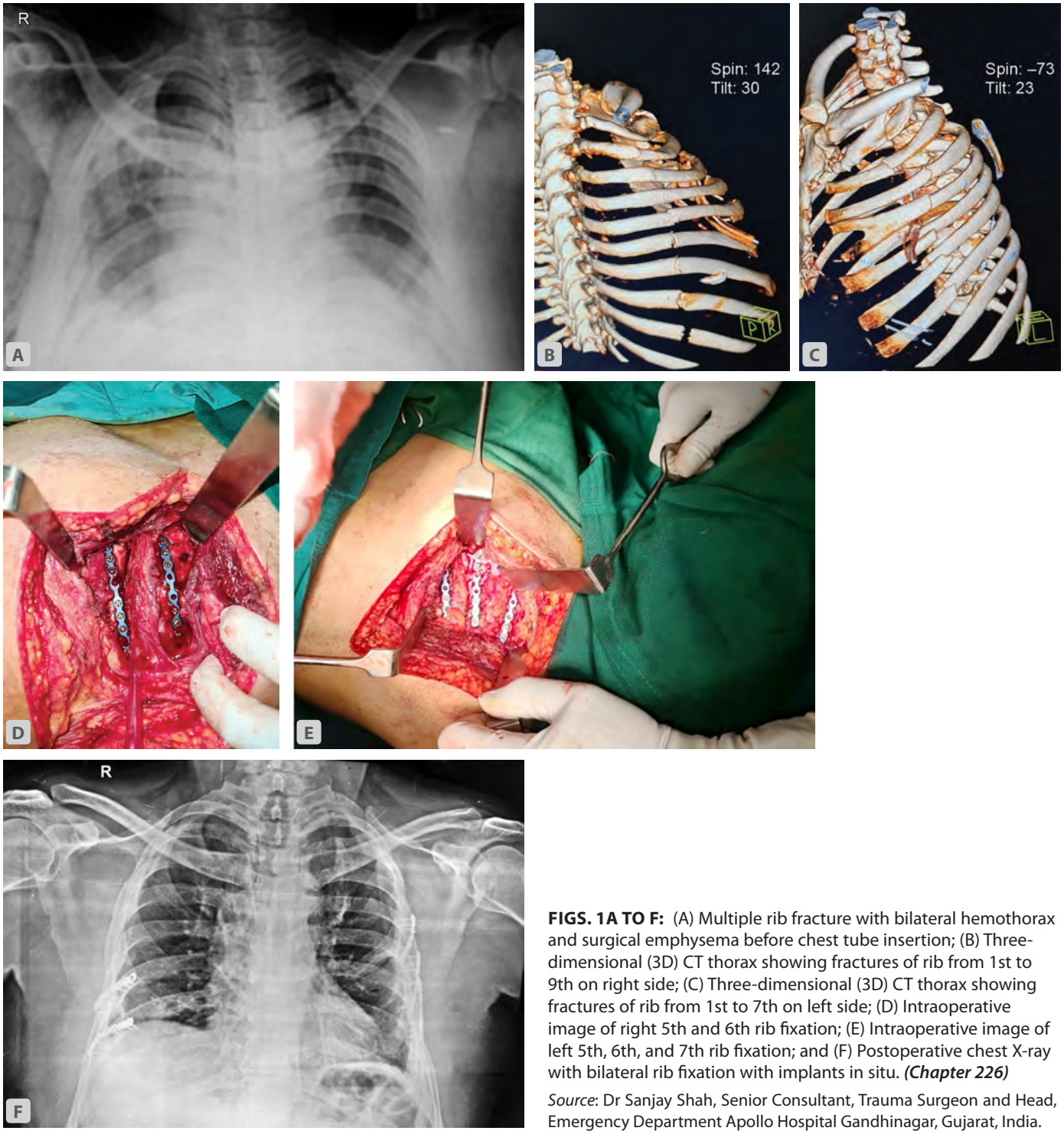
FIG. 4: Hemotympanum. ***(Chapter 222)***

FIG. 13: Laceration of the eyelid. ***(Chapter 222)***

FIG. 12: Periorbital edema. ***(Chapter 222)***

FIG. 14: Laceration of the tongue. ***(Chapter 222)***

PLATE 39

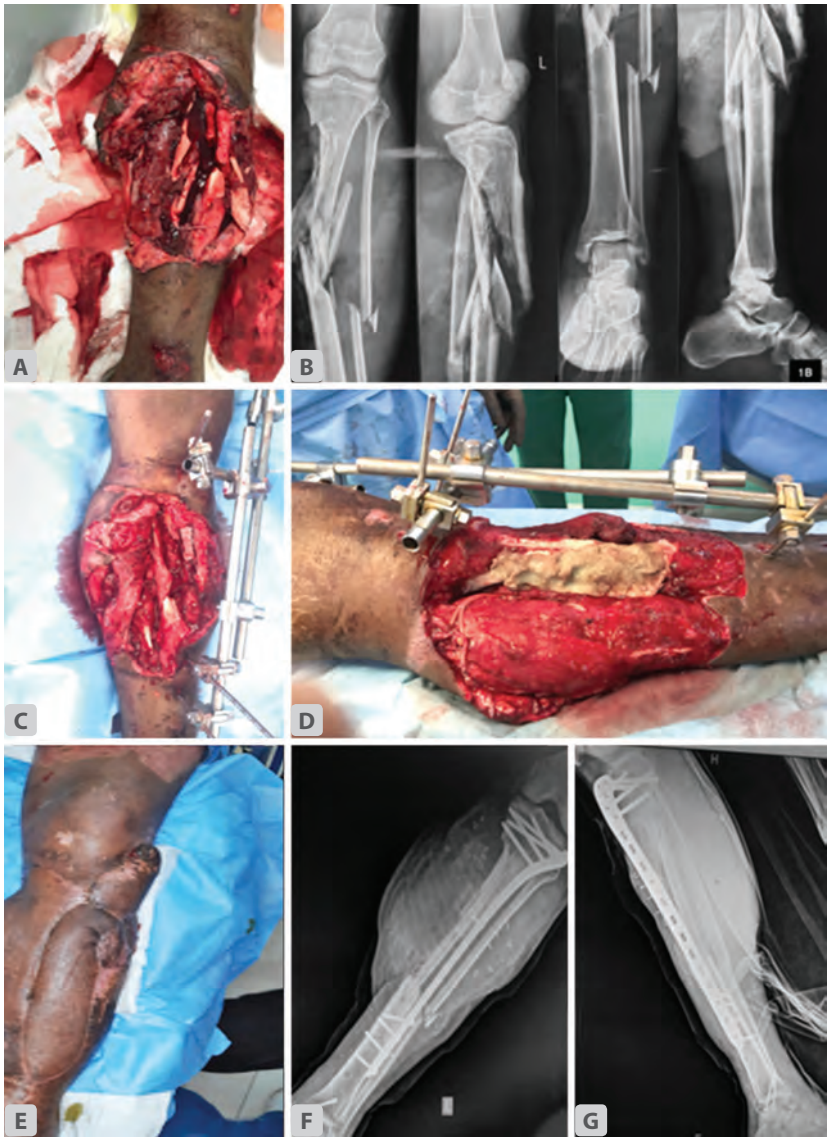


FIGS. 1A TO F: (A) Multiple rib fracture with bilateral hemothorax and surgical emphysema before chest tube insertion; (B) Three-dimensional (3D) CT thorax showing fractures of rib from 1st to 9th on right side; (C) Three-dimensional (3D) CT thorax showing fractures of rib from 1st to 7th on left side; (D) Intraoperative image of right 5th and 6th rib fixation; (E) Intraoperative image of left 5th, 6th, and 7th rib fixation; and (F) Postoperative chest X-ray with bilateral rib fixation with implants in situ. ***(Chapter 226)***

Source: Dr Sanjay Shah, Senior Consultant, Trauma Surgeon and Head, Emergency Department Apollo Hospital Gandhinagar, Gujarat, India.

PLATE 40

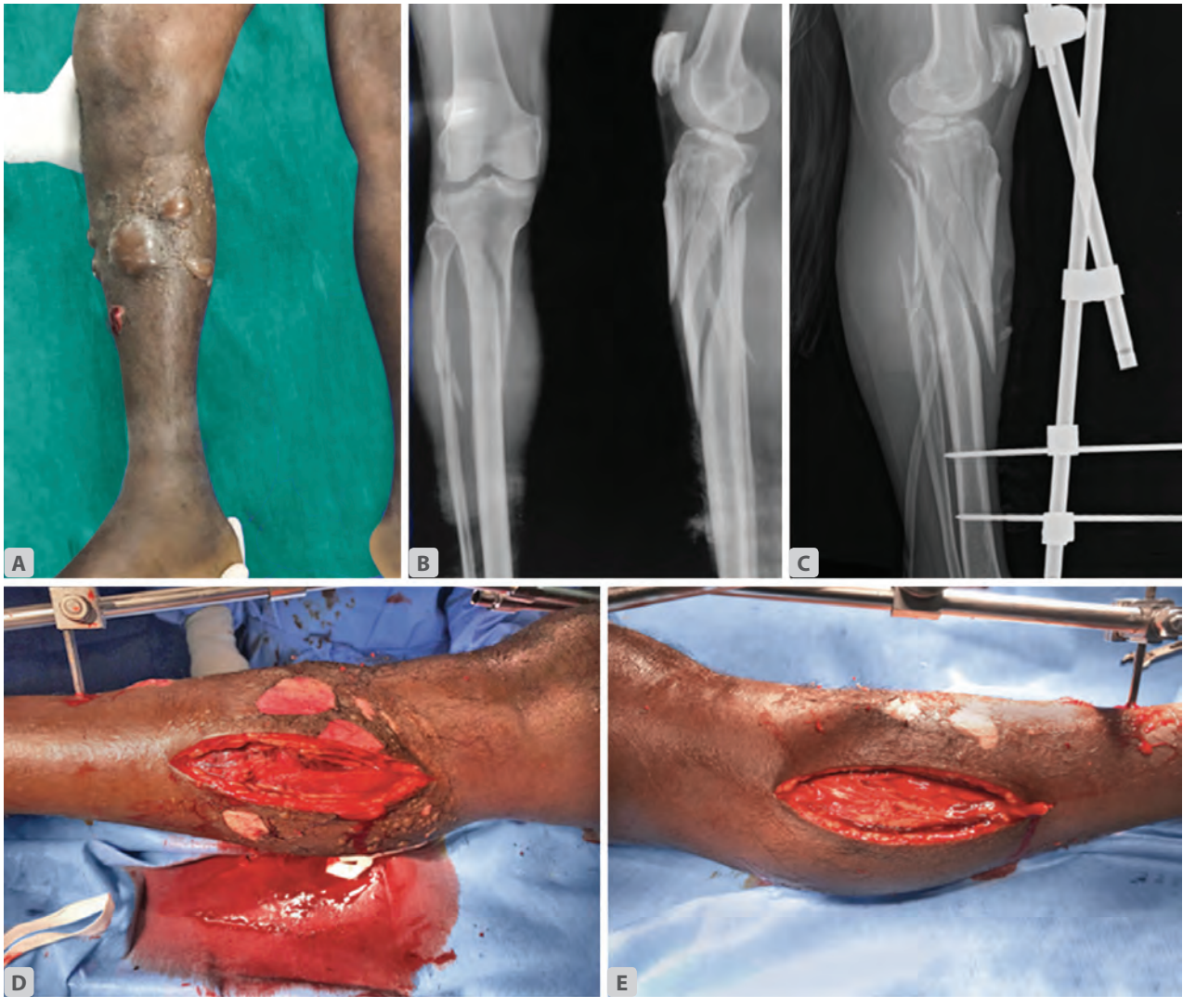
FIG. 1: Visible external injury in abdominal trauma. ***(Chapter 227)***



FIGS. 1A TO G: (A and B) Severely mangled extremity with comminuted fracture; (C) Clinical picture after thorough debridement and knee spanning external fixator; (D) Bone loss spaced with antibiotic bone cement; (E) Post soft-tissue reconstruction; (F and G) X-rays showing good incorporation of the vascularized fibular graft. Compartment pressure measurement should be done in the case of comatose patients. ***(Chapter 229)***

Courtesy: Dr Kesavam.

PLATE 41



FIGS. 2A TO E: (A and B) Right proximal tibial fracture with impending compartment syndrome; (C to E) Application of spanning external fixator, two incision lower limb compartment release. ***(Chapter 229)***

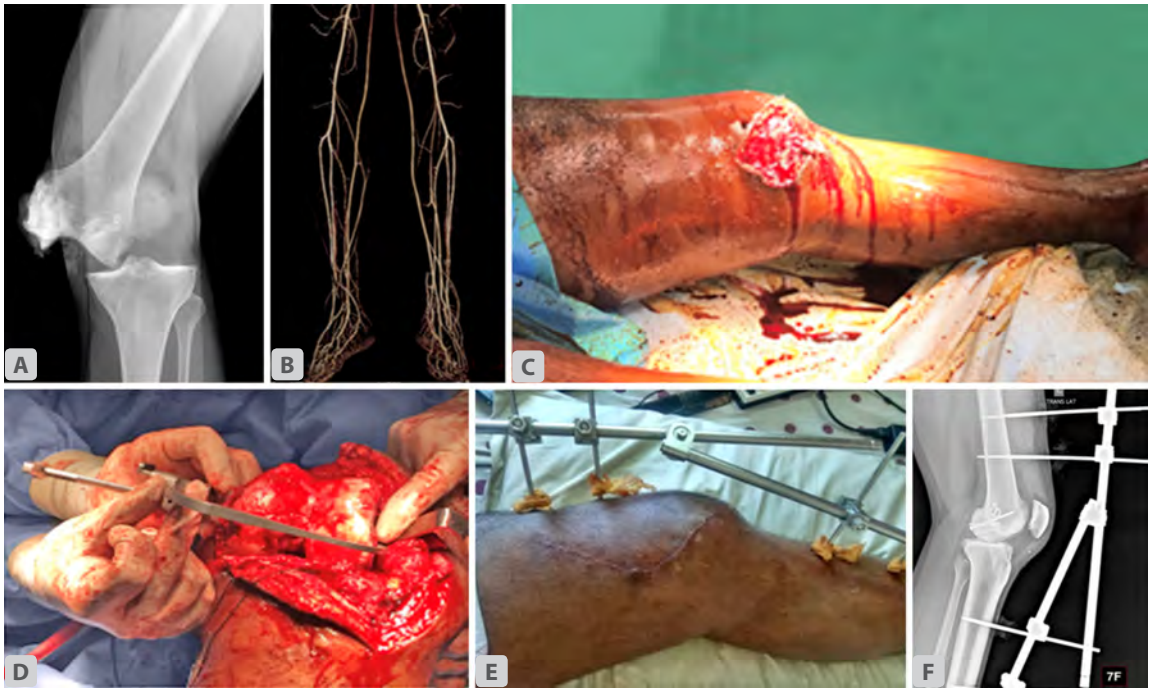
Courtesy: Dr Kesavam.

PLATE 42

FIGS. 3A TO F: (A) Left arm-twisting injury while trying to bend the iron rod in the machine. Note the broken arm encircled around the iron rod. (B) After a thorough wash. (C) Dressed and splinted in extension. (D to F) X-rays are taken at the bedside after proper splinting. ***(Chapter 229)***

Courtesy: Dr Kesavan and Dr Selvaseetharaman.

PLATE 43



FIGS. 7A TO F: (A) X-ray showing medial knee dislocation. Also note the button over the lateral femoral condyle. (B) Normal lower limb arteriogram. (C and D) Intraoperative picture showing the open wound. The wound extended for fracture fixation and ligament reconstruction. Also, knee spanning external fixation is placed to secure the reduction. (E) Healed wound with ex fix in situ. (F) Post ligamentous reconstruction X-ray lateral view showing ex fix in place. ***(Chapter 229)***

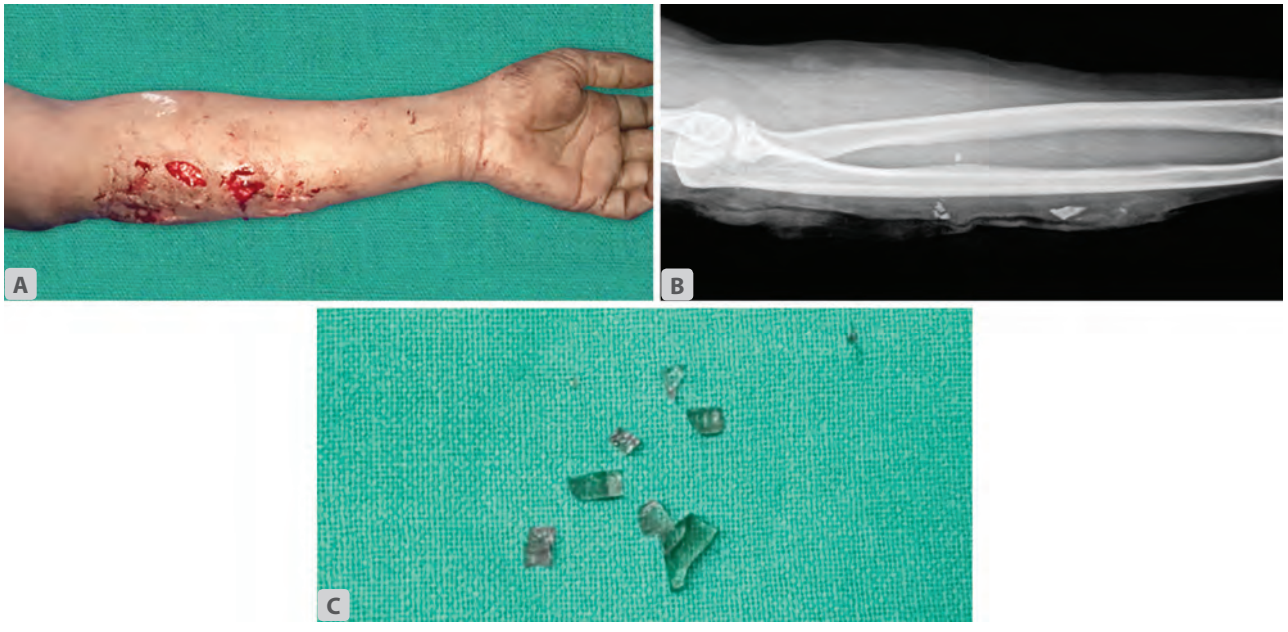
Courtesy: Dr Ajith Yadav.

FIG. 1: Clean lacerated wound on the forehead. ***(Chapter 236)***

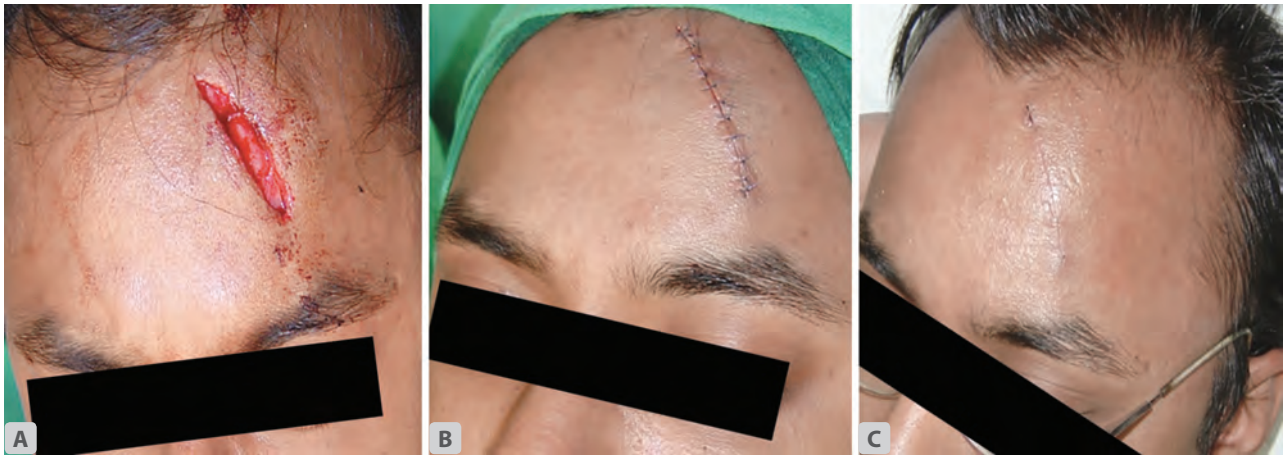
FIG. 2: Complicated laceration of the face. ***(Chapter 236)***

PLATE 44

FIG. 3: Post-traumatic tattooing due to inadequate removal of foreign bodies. ***(Chapter 236)***



FIGS. 4A TO C: (A) Patient involved in road traffic accident with multiple cut injuries to the forearm with retained glass pieces; (B) X-ray showing multiple radiopaque shadows suggestive of retained glass particles; (C) Multiple glass pieces removed from the wound. ***(Chapter 236)***



FIGS. 5A TO C: (A) Clean lacerated wound of the forehead; (B) Primary closure of the wound; (C) Postoperative results after 4 weeks ***(Chapter 236)***

PLATE 45

FIGS. 1A TO C: Dry cooling for transfer of the amputated part. (A) Finger in a clean plastic bag; (B) Ice in a separate plastic bag; (C) Bag with a finger placed such that the finger does not have direct contact with the ice. ***(Chapter 237)***

FIGS. 2A AND B: (A) Clean lacerated wound of the right eyebrow (no need to shave the hair); (B) Good eyebrow alignment after 1 week. ***(Chapter 237)***

FIGS. 3A AND B: (A) Clean lacerated wound of the forehead and eyebrow; (B) A single stitch taken to align the eyebrow prior to a primary repair of the remaining wound. ***(Chapter 237)***

PLATE 46

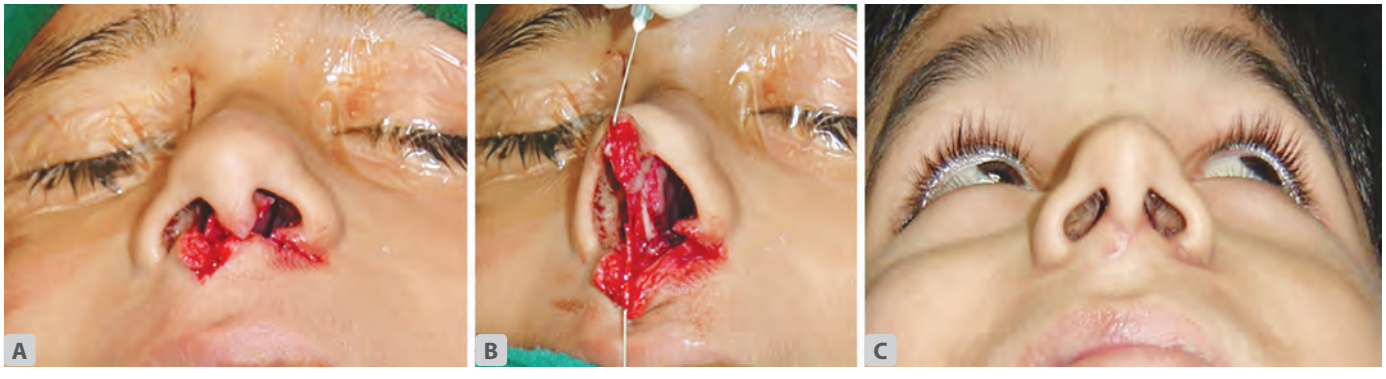
FIGS. 4A AND B: (A) Complex periorbital laceration involving the eyebrow, lid, and lateral canthus; (B) Results after 6 months—careful anatomical alignment maintained during the repair. ***(Chapter 237)***

FIGS. 5A AND B: (A) Complex periorbital injury showing disruption of the medial canthus with nasolacrimal duct injury and facial skin avulsion following a road traffic accident; (B) Late postoperative (6 months) results of a primary repair and fixation of underlying fractures. ***(Chapter 237)***

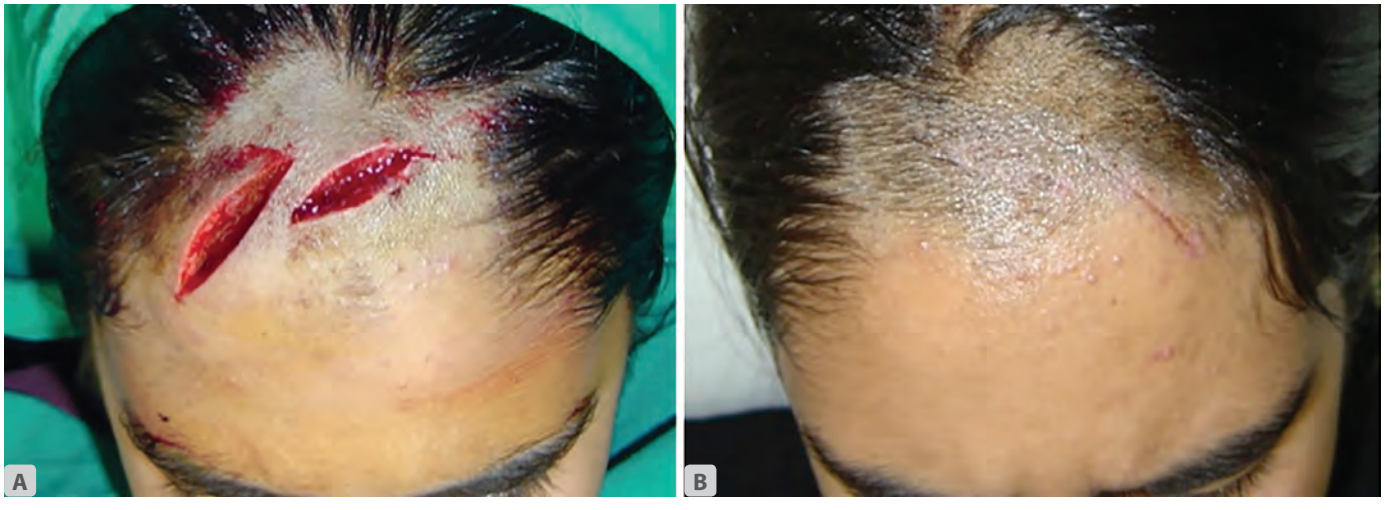
FIG. 6: Poorly stitched oblique cheek laceration with parotid duct injury. The wound was re-explored and the parotid duct repaired. ***(Chapter 237)***

PLATE 47

FIGS. 7A AND B: (A) Complex ear laceration with exposed cartilage; (B) Well-aligned repair with good healing on postoperative day 7. ***(Chapter 237)***



FIGS. 8A TO C: (A) Complicated nasal injury following a fall on a sharp object; (B) Identifying the injured structures—septal cartilage, columella, upper lip, and nasal floor; (C) Postoperative (day 30) picture showing good anatomical alignment. ***(Chapter 237)***



FIGS. 9A AND B: (A) Patient referred from a primary health center with shaved scalp hair (avoid shaving unless grossly contaminated); (B) Wound on postoperative day 10. ***(Chapter 237)***

PLATE 48

FIGS. 10A AND B: (A) Scalp avulsion following a road traffic accident—needed removal of the avulsed skin flap and split skin graft; (B) Postoperative results on day 15. ***(Chapter 237)***

FIGS. 11A AND B: (A) Upper lip clean laceration involving the vermilion border—repaired with careful white roll alignment of the vermillion border; (B) Postoperative day 10 results. ***(Chapter 237)***

FIGS. 12A AND B: (A) Complex lip laceration following a road traffic accident showing a through-and-through avulsion of the lower lip with other facial injuries. A three-layer repair (mucosa, muscle, and skin); (B) Results on postoperative day 30. ***(Chapter 237)***

PLATE 49

FIGS. 13A AND B: (A) Deep through-and-through laceration of the tongue that was repaired by a layered closure with a 5-0 Vicryl; (B) Intraoperative results. ***(Chapter 237)***

FIGS. 14A TO D: (A) Patient reported with a facial nerve palsy following facial laceration repair at a primary care unit; (B) Operative picture showing the exploration of the wound and identification of the facial nerve injury; (C) Gradual recovery of the repaired facial; (D) Complete recovery. ***(Chapter 237)***

FIG. 15: Soft-tissue deficit of the upper lip following a human bite, which will require an expert plastic surgical repair. ***(Chapter 237)***

FIG. 16: Human bite on the nose with subtotal nasal loss which will require a complex plastic surgical repair. ***(Chapter 237)***

PLATE 50

FIGS. 17A TO C: (A) Pet dog bite with a through-and-through disruption of the upper and lower lips (front view); (B) Pet dog bite with a through-and-through disruption of the upper and lower lips (lateral view); (C) Results at postoperative day 30. ***(Chapter 237)***

FIGS. 18A AND B: (A) Table fan injury with devascularized left thumb, requiring neurovascular and tendon repair; (B) Postoperative month 3 results. ***(Chapter 237)***

FIGS. 2A AND B: (A) Partial thickness with partial thickness superficial burn noted on abdomen and bilateral thighs having partial-thickness superficial burns; (B) Flame burns: Upper extremity circumferential burns, causing a tourniquet effect on the distal forearm and hence predisposing to compartment syndrome. ***(Chapter 238)***

PLATE 51

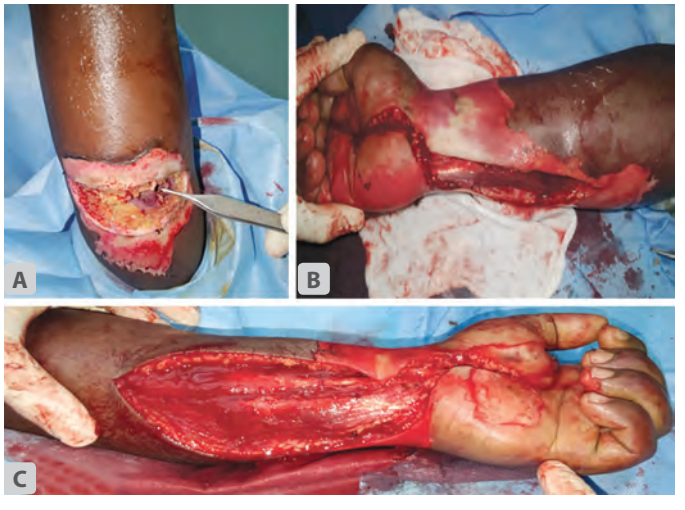
FIG. 4: Scalds due to accidental outpour of hot milk over the lower half of the face, chest, and abdomen. ***(Chapter 238)***

FIGS. 1A TO C: (A) "Flashover effect" over the posterior aspect of arm and forearm; (B) Superficial burns sustained after an electrical injury over lateral aspect of chest and abdomen; (C) Hyperpigmented skin with superficial burns. ***(Chapter 244)***

Courtesy: Dr Gaurav B Shetty.

FIGS. 2A TO C: Deep burns over posterior aspect of thigh and posterior gluteal region. ***(Chapter 244)***

Courtesy: Dr Gaurav B Shetty



FIGS. 4A TO C: S/p wound debridement of anterior aspect of forearm and posterior aspect of forearm. ***(Chapter 244)***

Courtesy: Dr Gaurav B Shetty.

FIG. 5: "Entry" site of an electrical burn, sustained from an electrical pole. ***(Chapter 244)***

Courtesy: Dr Gaurav B Shetty.

PLATE 52

FIG. 6: Checkerboard escharotomy done on a patient sustained more than 50% electrical burns. ***(Chapter 244)***

Courtesy: Dr Gaurav B Shetty.

FIGS. 2A AND B: (A) Common Indian cobra—*Naja naja*—head showing scales*;* (B) common Indian cobra—*Naja naja*—head showing hood and scales. ***(Chapter 245)***

Courtesy: Gerard Martin.

FIG. 1: Pit Viper showing pit between the nostril and eyes. ***(Chapter 245)***

FIG. 3: *Russell viper—Daboia russelii* head showing scales. ***(Chapter 245)***

Courtesy: Gerard Martin.

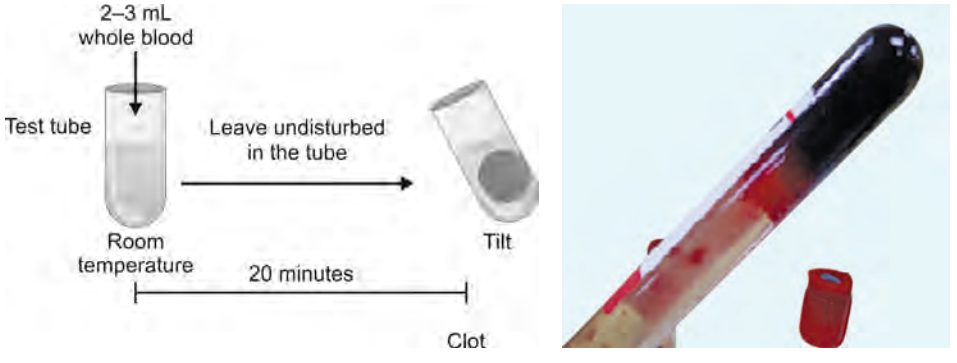


FIG. 5: Showing procedure of 20 whole blood clotting test (WBCT) to check coagulopathy in snake bite. ***(Chapter 245)***